Physiology of calcium

The total plasma calcium, normally at a concentration of around 10 mg/dL (5 mEq/L, 2.5 mmol/L), is partly bound to protein and partly diffusible. The calcium in the plasma is present in three forms:

1. About 41 percent (1.16 mmol/L) of the calcium is combined with the plasma proteins and in this form is non-diffusible through the capillary membrane; (NON-ionized, NON-diffusible)
2. About 9 percent of the calcium (0.16 mmol/L) is diffusible through the capillary membrane but is combined with anionic substances of the plasma and interstitial fluids (citrate and phosphate, for instance) in such a manner that it is not ionized (NON-ionized, diffusible)
3. The remaining 50 percent (1.18 mmol/L) of the calcium in the plasma is both diffusible through the capillary membrane and ionized. (Ionized, diffusible)

<table>
<thead>
<tr>
<th>Total diffusible</th>
<th>1.34</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionized (Ca(^{2+}))</td>
<td>1.18</td>
</tr>
<tr>
<td>Complexed to HCO(_3^-), citrate, etc</td>
<td>0.16</td>
</tr>
<tr>
<td>Total nondiffusible (protein-bound)</td>
<td>1.16</td>
</tr>
<tr>
<td>Bound to albumin</td>
<td>0.92</td>
</tr>
<tr>
<td>Bound to globulin</td>
<td>0.24</td>
</tr>
<tr>
<td>Total plasma calcium</td>
<td>2.50</td>
</tr>
</tbody>
</table>

Thus, the plasma and interstitial fluids have a normal ionic calcium ion concentration of about 1.16 mmol/L (or 2.4 mEq/L, because it is a divalent ion), a level only one-half the total plasma calcium concentration. This ionic calcium is the form that is important for most functions of calcium in the body, including the effect of calcium on the heart, the nervous system, and bone formation.

Increases in calcium ion concentration above normal (hypercalcemia) cause:

1. progressive depression of the nervous system (depressive effects begin to appear when the blood level of calcium rises above about 12 mg/dl)
2. reflex activities of the central nervous system are sluggish;
3. decreases the QT interval of the heart
4. lack of appetite
5. constipation;

Conversely, decreases in calcium concentration (hypocalcemia) cause the nervous system to become more excited about 6 mg/dl. The result is hypocalcemic tetany, which is characterized by extensive spasms of skeletal muscle (carpopedal spasm), involving especially the muscles of the extremities. Laryngospasm can become so severe that the airway is obstructed and fatal asphyxia is produced. It is usually lethal at about 4 mg/dl.
The possible mechanism behind hypocalcemic tetany (pathophysiology):

- Hypocalcemia
  - No complete closure of Na channels at rest
  - Na leak into the cell from ECF
  - Intracellular become less negative and approaching more to threshold (more excitable)
    - So less amount of dis required to initiate depolarization
  - Slight stimuli cause action potential

The extent of Ca\(^{2+}\) binding by plasma proteins (i.e., the free Ca2+ level) is proportional to:

1. The plasma protein level,
2. Other electrolytes
3. pH.

Thus, for example, symptoms of tetany appear if the patient have higher plasma protein or hyperventilates,

- Hyperventilates
  - More wash of blood CO2
  - Alkalosis (respiratory alkalosis)
    - Plasma protein are more ionized when pH is high
    - Increase Ca binding to plasma protein
  - Hypocalcemia even though normal level of plasma protein

**Physiology of phosphate:**

Total body phosphorus is 500 to 800 g (16.1–25.8 mol) distributed as:

1. Approximately 85–90% of the body’s phosphate is stored in bones,
2. 14 to 15 percent is in the cells, and
3. less than 1 percent is in the extracellular fluid.

Total plasma phosphorus is about 12 mg/dL (because it is difficult to calculate inorganic phosphate),

1. Two-thirds of this total in organic compounds
2. Phosphate is found in ATP, cyclic adenosine monophosphate (cAMP), 2,3-diphosphoglycerate, many proteins, and other vital compounds in the body.
3. The remaining inorganic phosphorus (Pi) mostly in PO\(_4^{3-}\), HPO\(_4^{2-}\), and H\(_2\)PO\(_4^{-}\).

The amount of phosphorus normally entering bone is about 3 mg (97 μmol)/kg/d, with an equal amount leaving via reabsorption.

Phosphorylation and dephosphorylation of proteins are involved in the regulation of cell function. Therefore, it is not surprising that, like calcium, phosphate metabolism is closely regulated.
When the pH of the extracellular fluid becomes more acidic, there is a relative increase in $\text{H}_2\text{PO}_4^-$ and a decrease in $\text{HPO}_4^{2-}$, whereas the opposite occurs when the extracellular fluid becomes alkaline.

Inorganic phosphorus (Pi) in the plasma is filtered in the glomeruli, and 85–90% of the filtered Pi is reabsorbed.

**Inorganic phosphorus Active transport in the proximal tubule of the kidney:**

Inorganic phosphorus Active transport in the proximal tubule accounts for most of the reabsorption and involves two cotransporters, NaPi-IIa (1:3) and NaPi-IIc (1:2). NaPi-IIa is powerfully inhibited by parathyroid hormone, which causes its internalization and degradation and thus a reduction in renal Pi reabsorption.

**Inorganic phosphorus Active transport in the duodenum and small intestine**

Pi is absorbed in the duodenum and small intestine. Uptake occurs by a transporter related to those in the kidney, NaPi-IIb (1:2); that takes advantage of the low intracellular sodium concentration established by the Na, K ATPase on the basolateral membrane of intestinal epithelial cells to load inorganic phosphorus (Pi) against its concentration gradient. However, the pathway by which inorganic phosphorus (Pi) exits into the bloodstream is not known. Many stimuli that increase Ca$^{2+}$ absorption, including 1,25-dihydroxycholecalciferol, also increase Pi absorption via increased NaPi-IIb expression.
Bone structure:
I. Non-Cellular component (ground substance):
A. Inorganic component (Bone Salts) 65%.
The crystalline salts deposited in the organic matrix of bone are composed principally of calcium and phosphate. The formula for the major crystalline salt, known as hydroxyapatite, is as follows:

$$Ca_{10}(PO_4)_6(OH)_2$$

Each crystal is shaped like a long, or flat plate. The relative ratio of calcium to phosphorus can vary markedly under different nutritional conditions, with the calcium to phosphorus ratio on a weight basis varying between 1.3 and 2.0.
Magnesium, sodium, potassium, and carbonate ions are also present among the bone salts, although x-ray diffraction studies fail to show definite crystals formed by them. Therefore, they are believed to be conjugated to the hydroxyapatite crystals rather than organized into distinct crystals of their own. This ability of many types of ions to conjugate to bone crystals extends to many ions normally foreign to bone, such as strontium, uranium, plutonium, the other transuranic elements, lead, gold, and other heavy metals. Deposition of radioactive substances in the bone can cause prolonged irradiation of the bone tissues, and if a sufficient amount is deposited, an osteogenic sarcoma (bone cancer) may eventually develop.

B. Organic Matrix of Bone (35%).
The ground substance is composed of extracellular fluid plus
1) The protein in bone matrix is over 90% type I collagen, which is also the major structural protein in tendons and skin. This collagen, which weight for weight is as strong as steel, is made up of a triple helix of three polypeptides bound tightly together. The collagen fibers extend primarily along the lines of tensional force and give bone its powerful tensile strength.
2). Non-collagenous material: the remainder is a homogeneous gelatinous medium called ground sub-stance.
a) Proteoglycans (Proteoglycans, a family of glycosaminoglycan (GAG) conjugated proteins, consist of especially chondroitin sulfate and hyaluronic acid) such as Biglycan and decorin. The precise function of each of these proteoglycans is not known, although they do help control the deposition of calcium salts.
b) Glycosaminiglycans: since they are negatively charged so it can attract calcium
c) Calcium binding protein such as matrix gla protein osteonectin (chemo-attractant for bone cells and suppresses excess mineralization), Osteocalcin (bond hydroxyapatite to collage)
d) proteoglycans such as biglycan and decorin

**Tensile and Compressional Strength of Bone.**
Each collagen fiber of compact bone is composed of repeating periodic segments every 640 angstroms along its length; hydroxyapatite crystals lie adjacent to each segment of the fiber and are bound tightly to it. This intimate bonding prevents “shear” in the bone; that is, it prevents the crystals and collagen fibers from slipping out of place, which is essential in providing strength to the bone. In addition, the segments of adjacent collagen fibers overlap, also causing hydroxyapatite crystals to be overlapped like bricks keyed to one another in a brick wall.
The collagen fibers of bone, like those of tendons, have great tensile strength, whereas the calcium salts have great compressional strength. These combined properties plus the degree of bondage between the collagen fibers and the crystals provide a bony structure that has both extreme tensile strength and compressional strength.

**II. Cellular component**

**A. Osteoblasts:** The cells responsible for bone formation
Osteoblasts are modified fibroblasts.
Osteoblasts early development from the mesenchyme is the same as that of fibroblasts, with extensive growth factor regulation. Later, ossification specific transcription factors, such as Cbfa1/Runx2, contribute to their differentiation.

Normal osteoblasts are able to lay down type 1 collagen and form new bone.

**B. osteoclasts:** the cells responsible for bone resorption

**Mechanism of Bone Calcification.**

First step: osteoid formation

**Osteoid** is the unmineralized, organic portion of the bone matrix that forms prior to the maturation of bone tissue. Osteoid makes up about fifty percent of bone volume and forty percent of bone weight. Osteoblasts begin the process of forming bone tissue by secreting the osteoid as several specific proteins. When the osteoid becomes mineralized, it and the adjacent bone cells have developed into new bone tissue. As the osteoid is formed, some of the osteoblasts become entrapped in the osteoid and become quiescent. At this stage they are called osteocytes.

Osteoid is composed of

A. collagen molecules (called collagen monomers)
B. ground substance: The ground substance is mostly made up of chondroitin and osteocalcin. 

Second step: mineral precipitation (mineralization) and bone hardening

The hardness and rigidity of bone is due to the presence of mineral salt in the osteoid matrix, which is a crystalline complex of calcium and phosphate (hydroxyapatite). Calcified bone contains about 25% organic matrix (2-5% of which are cells), 5% water and 70% inorganic mineral (hydroxyapatite).

1. Nucleation theory (seeding mechanism) of mineralization:
Within a few days after the osteoid is formed, calcium salts begin to precipitate on the surfaces of the collagen fibers. The precipitates first appear at intervals along each collagen fiber, forming minute nidi (single: nidus; a nest or cluster, the point of origin or focus) that rapidly multiply and grow over a period of days and weeks into the finished product, hydroxyapatite crystals.

The initial calcium salts to be deposited are not hydroxyapatite crystals but amorphous compounds (non-crystalline), a mixture of salts such as CaHPO$_4$ × 2H$_2$O, Ca$_3$(PO$_4$)$_2$ × 3H$_2$O, and others. Then, by a process of substitution and addition of atoms, or reabsorption and re-precipitation, these salts are converted into the hydroxyapatite crystals over a period of weeks or months. A few percent may remain permanently in the amorphous form, which is important because these amorphous salts can be absorbed rapidly when there is a need for extra calcium in the extracellular fluid.

2. Matrix vesicle theory of mineralization (most acceptable theory of mineralization)

Mineralization takes place in two distinct processes.

Hypertrophic chondrocytes, osteoblasts, and odontoblasts bud matrix vesicles when mineralization begins. Matrix vesicles are membrane-invested vesicles of 50–200 nm in diameter

The first step of the mineralization process occurs within the matrix vesicles, in which hydroxyapatite (Ca$_{10}$(PO$_4$)$_6$(OH)$_2$) crystals are formed.

a. Phosphate (Pi) is derived from

1. Membrane phospholipids, which are hydrolyzed by phospholipase C (PLC) to produce phosphocholine (PCho) and phosphoethanolamine (PEA). These phosphor-compounds are hydrolyzed by PHOSPO1: phosphoethanolamine/phosphocho lines phosphatase, a cytosolic phosphatase that is abundant in the matrix vesicles, to yield inorganic phosphate (Pi).
2. Another source of Pi in the matrix vesicles is Pi that is transported through the Na/Pi cotransporter Pit1 that is also abundant on the matrix vesicle membrane.

b. Calcium is incorporated into the matrix vesicles through annexin Ca^{2+} channels

Developing hydroxyapatite crystals then penetrate the matrix vesicle membrane, are elongated in the extracellular space, and eventually deposit in the spaces between collagen fibrils to complete extracellular matrix mineralization.

The concentration ratio of inorganic phosphate (Pi) to inorganic pyrophosphate (PPi) in the extracellular matrix is crucial in the second step of mineralization because PPi is an inhibitor of hydroxyapatite formation. Two mechanisms are used for inorganic pyrophosphate (PPi) formation (decrease hydroxyapatite crystals).

1. Inorganic pyrophosphate (PPi) is formed in the extracellular matrix from ATP by the matrix vesicle membrane enzyme nucleotide pyrophosphatase phosphodiesterase 1 (NPP1).
2. Inorganic pyrophosphate (PPi) is also provided through the PPi transporter anklylosis protein human (ANKH) from the cytoplasm, in which inorganic pyrophosphate (PPi) is routinely formed by cellular metabolism.

Anklylosis protein human (ANKH) is distributed on the plasma membrane of hypertrophic chondrocytes and osteoblasts.

Tissue non-specific-alkalin-ephosphatase (TNAP) on the membrane of the matrix vesicles hydrolyzes inorganic pyrophosphate (PPi) and yields inorganic phosphate (Pi), thereby reducing the levels of the PPi and promoting hydroxyapatite formation (increase hydroxyapatite crystals)

This balance between the activities of TNAP, NPP1, and ANKH is crucial for the second step of mineralization. Deficiencies of Nucleotide Pyrophosphatase Phosphodiesterase 1 (NPP1) or ANKyllosis protein Human (ANKH) cause decreased extracellular Inorganic pyrophosphate (PPi) and excessive calcification of bone, such as bone spurs, or even calcification of other tissues such as tendons and ligaments of the spine, which occurs in people with a form of arthritis called anklylosing spondylitis.

3. Robinson’s alkaline phosphatase theory of mineralization (least acceptable theory): Alkaline phosphatase present in organic matrix hydrolyzes organic pyrophosphate present in plasma to organic phosphate with help of calcium to calcified the bone if it is present in excess amount. Precipitation of calcium in Non-osseous tissues under abnormal conditions.
Hydroxyapatite crystals fail to precipitate in normal tissues except in bone despite the state of super-saturation of the ions, because inhibitors are present in almost all tissues of the body, as well as in plasma, to prevent such precipitation; such inhibitor are pyrophosphate, Matrix Gla protein (MGP), Osteopontin (OPN) and Fetain. For instance,

1. They precipitate in arterial walls in arteriosclerosis and cause the arteries to become bonelike tubes.
2. Calcium salts frequently deposit in degenerating tissues (as old fibrous TB) or in old blood clots.

**Calcium exchange between bone and extra-cellular fluid:**
The calcium in bone is of two types:

1. A readily exchangeable reservoir
2. A much larger pool of stable calcium that is only slowly exchangeable.

These are two independent but interacting homeostatic systems affect the calcium in bone.

Exchangeable reservoir is the system that regulates plasma Ca2+, providing for the movement of about 500 mmol of Ca2+ per day into and out of the readily exchangeable pool in the bone. Most of the exchangeable calcium is in the bone. Exchangeable reservoir normally amounts to about 0.4 to 1 percent of the total bone calcium. This calcium is deposited in the bones in a form of readily mobilizable salt such as CaHPO4 and other amorphous calcium salts.

The importance of exchangeable calcium is that it provides a rapid buffering mechanism to keep calcium ion concentration in the extracellular fluids from rising to excessive levels or falling to low levels under transient conditions of excess or decreased availability of calcium.

A small portion of this exchangeable calcium is also the calcium found in all tissue cells, especially in highly permeable types of cells such as those of the liver and the gastrointestinal tract.

**Vitamin D**

**Vitamin D metabolism:**
The active transport of Ca2+ and PO43− from the intestine is increased by a metabolite of vitamin D. The term “vitamin D” is used to refer to a group of closely related sterols produced by the action of ultraviolet light on certain pro-vitamins.
Vitamin D₃, which is also called cholecalciferol, is produced in the skin of mammals from 7-dehydrocholesterol by the action of sunlight. The reaction involves the rapid formation of pre-vitamin D₃, which is then converted more slowly to vitamin D₃.

Vitamin D₃ and its hydroxylated derivatives are transported in the plasma bound to a globulin vitamin D binding protein (DBP).

Vitamin D₃ is also ingested in the animal diet source or ingested from plant diet source and converted to (D₂ or ergo-calciferol).

In the liver, vitamin D₃ is converted to 25-hydroxy-cholecalciferol (calcidiol, 25-OHD₃). The process is limited because the 25-hydroxycholecalciferol has a feedback inhibitory effect on the conversion reactions. This feedback effect is extremely important for two reasons.

First, the feedback mechanism precisely regulates the concentration of 25-hydroxycholecalciferol in the plasma, the intake of vitamin D₃ can increase many times and yet the concentration of 25-hydroxycholecalciferol remains nearly normal.

This high degree of feedback control prevents excessive action of vitamin D when intake of vitamin D₃ is altered over a wide range.

Second, this controlled conversion of vitamin D₃ to 25-hydroxycholecalciferol conserves the vitamin D stored in the liver for future use. Once vitamin D₃ is converted, the 25-hydroxycholecalciferol persists in the body for only a few weeks, whereas in the vitamin D form, it can be stored in the liver for many months.
The 25-hydroxy-cholecalciferol is converted in the cells of the proximal tubules of the kidneys to the more active metabolite 1,25-dihydroxycholecalciferol, which is also called calcitriol or 1,25-(OH)$_2$D$_3$ (is by far the most active form of vitamin D) effect by the presence of 1α-hydroxylase. Therefore, in the absence of the kidneys, vitamin D loses almost all its effectiveness. 1,25-Di-hydroxy-cholecalciferol is also made in the placenta, in keratinocytes in the skin, and in macrophages.

Regulation of synthesis of 1,25-dihydroxycholecalciferol (calcitriol):
Primary regulator:
1. Parathyroid hormone (PTH)
The conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol requires PTH. In the absence of PTH, almost none of the 1,25-dihydroxycholecalciferol is formed. Therefore, PTH exerts a potent influence in determining the functional effects of vitamin D in the body.
2. Calcium level:
   Hypercalcemia ➔ ↓ parathyroid hormone production ➔
a. ↓ α-hydroxylase ► decrease conversion 25-hydroxy-cholecalciferol to 1, 25 dihydroxy-cholecalciferol
b. ↑ 24-hydroxylase ► increase conversion 25-hydroxy-cholecalciferol to 24, 25 dihydroxy-cholecalciferol
3. Phosphate level:
High phosphate level has a direct on inhibit 1α-hydroxylase (so decrease production of 1,25-hydroxy-cholecalciferol). The reverse is also true.
4. 1,25-di-hydroxy-cholecalciferol
↑ 1,25-di-hydroxy-cholecalciferol ► ↓ 1α-hydroxylase ► decrease conversion 25-hydroxy-cholecalciferol to 1, 25 dihydroxy-cholecalciferol (direct negative feedback effect). The reverse is also true
Secondary regulator: Prolactin, estrogen, androgen, progesterone, insulin, growth hormone, human chorionic somatomammotropin (HCS), thyroid hormone, and calcitonin all increase 1, 25-hydroxy-cholecalciferol, while hyperthyroidism is associated with a decrease in 1,25-hydroxy-cholecalciferol.

**Intestinal Epithelia can absorb Ca^{2+} by para-cellular and trans-cellular transport.**
Passive and paracellular Ca^{2+} transport takes place across the tight junctions and is driven by the electrochemical gradient for Ca^{2+}.
The active form of vitamin D (1,25-(OH)2D3) stimulates the individual steps of trans-cellular Ca^{2+} transport by increasing the expression levels of the luminal Ca^{2+} channels, calbindins D9k, and the extrusion systems. Active and transcellular Ca^{2+} transport is carried out as a three-step process.

1. After entry of Ca^{2+} through the (hetero) tetrameric epithelial Ca^{2+} channels, TRPV5 (transient receptor potential vanilloid type 5) and TRPV6 (transient receptor potential vanilloid type 6)
2. Ca^{2+} bound to calbindin diffuses to the basolateral membrane.
3. At the basolateral membrane, Ca^{2+} is extruded via an
   a. ATP-dependent Ca^{2+}-ATPase (PMCA1b: The plasma membrane calcium pump type 1b)
   b. Na/Ca^{2+} exchanger (NCX1).

In this way, there is net Ca^{2+} absorption from the luminal space to the extracellular compartment.
Since the discovery of α-Klotho, it was found to play a role in bone metabolism, aging processes, nephrology, immunology, etc. α-Klotho is found in two forms:

A. α-Klotho transmembrane protein

The Klotho family consists of three single-pass transmembrane proteins—αKlotho, βKlotho and γKlotho. Each of them combines with fibroblast growth factor (FGF) receptors (FGFRs) to form receptor complexes for various FGFs. αKlotho is a co-receptor for physiological FGF23 signaling. FGF23 thereby

1. Kidney:
   a. Inhibits 1α-hydroxylase, reducing levels of 1,25-dihydroxycholecalciferol (Calcitriol synthesis)
   b. Decreases renal Na-dependent phosphate cotransporters (NaPi-IIa and NaPi-IIc) expression

   Increase phosphate excretion (Negative phosphate balance)

2. Parathyroid gland
   Inhibit parathyroid hormone reducing levels of 1,25-dihydroxycholecalciferol (Calcitriol synthesis)

Membrane Klotho and secreted Klotho. Membrane Klotho forms a complex with the fibroblast growth factor receptor (FGFR) to create a de novo high-affinity binding site for FGF23. Membrane Klotho is subject to ectodomain shedding by α- and β-secretases to release secreted Klotho.

b. αKlotho protein

αKlotho protein also plays a FGF23-independent role in phosphate homeostasis. Animal experimental studies and clinical observations have demonstrated that
αKlotho deficiency leads to severe hyperphosphatemia, accelerated aging, decreased bone mineral density, calcifications, and hypercalcemia;

1. moderate elevation of αKlotho reduces serum phosphate
2. extremely high αKlotho induces hypophosphatemia and high-FGF23.
αKlotho maintains circulating phosphate in a narrow range by
1. modulating intestinal phosphate absorption,
2. urinary phosphate excretion by the kidney,
3. phosphate distribution into bone rather than soft tissue in concerted interaction with other calico-phosphotropic hormones such as PTH, FGF23, calcitriol.
The role of αKlotho in maintenance of phosphate homeostasis is mediated by
1. direct suppression of Na-dependent phosphate cotransporters (NaPi-II) in target organs.
2. α-Klotho plays an important role in stabilizing the membrane localization of proteins important in calcium and phosphate (re)absorption, such as TRPV5 and Na-K ATPase.

It is already known that α-Klotho levels in blood decrease with age. Low α-klotho levels are often associated with age-related diseases.

The functions of 1,25-dihydroxycholecalciferol
• are coordinated to increase both [Ca2+] and [phosphate] in ECF to mineralize new bone.
  a. Increases intestinal Ca2+ absorption (directly or indirectly through increase PTH)
  b. Increases intestinal phosphate absorption.
  c. Increases renal re-absorption of Ca2+ and phosphate, analogous to its actions on the intestine.
The actions of vitamin D on bone will be:
  a. Small quantity of 1,25-hydroxy-cholecalciferol promote bone calcification by maintaining normal quantity of calcium and phosphate.
  b. Extreme quantity of 1,25-hydroxy-cholecalciferol causes absorption of bone.
  c. In the absence of 1,25-hydroxy-cholecalciferol, the effect of parathyroid hormone in causing bone absorption is greatly reduced.
  d. increasing osteoclast activity
When dietary calcium—and, therefore, intestinal calcium absorption—is low, 1,25(OH)2D binds to osteoblasts, thereby increasing osteoclast activity and causing the release of skeletal calcium.

Other effects of Vitamin D
1. Vitamin D exhibits local (paracrine) effects on cell proliferation and differentation and immune function.
Research has shown that vitamin D might play an important role in regulating mood and warding off depression.

Most cells in the body express vitamin D receptor (VDR) and 1α-hydroxylase, thereby permitting local production of 1,25(OH)2D, which has therapeutic implications. For example, Topical 1,25 (OH)2D is used to treat psoriasis.

Ongoing studies are aiming to clarify the role of 1,25(OH)2D in the treatment of cancer and immune disorders, including rheumatoid arthritis (RA).

**Failure of skin synthesis of vitamin D can be caused by:**
1. Aging (synthesis is reduced by 75% at age 70)
2. Skin pigmentation (melanin absorb UV photon and prolong exposure time require for synthesis)
3. Body fat (excess body fat takes up and store newly synthesized Vitamin D)
4. Regular sunscreen, clothing, atmospheric pollution, sun avoidance all decrease amount of exposure to sun

**Parathyroid hormone (PTH)**

Parathyroid hormone has a molecular weight of about 9500.

Smaller compounds with as few as 34 amino acids adjacent to the N terminus of the molecule have also been isolated from the parathyroid glands that exhibit full PTH activity. In fact, because the kidneys rapidly remove the whole 84–amino acid hormone within minutes but fail to remove many of the fragments for hours, a large share of the hormonal activity is caused by the fragments. The half-life of PTH is approximately 10 min.

**Parathyroid hormone (PTH) effects:**

1. PTH acts directly on bone to increase bone resorption and mobilize Ca\(^{2+}\) and phosphate.

   PTH has two effects to mobilize calcium and phosphate from bone.
One is a rapid phase that begins in minutes and increases progressively for several hours. This phase results from activation of the already existing bone cells (mainly the osteocytes) to promote calcium and phosphate release.

The second phase is a much slower one, requiring several days or even weeks to become fully developed. On a longer time scale, PTH stimulates both osteoblasts and osteoclasts.

PTH results from proliferation of the osteoclasts, followed by greatly increased osteoclastic resorption of the bone itself, not merely release of the calcium and phosphate salts from the bone.

PTH increases phosphate excretion in the urine and thereby depresses plasma phosphate levels. This phosphaturic action is due to a decrease in reabsorption of phosphate via effects on NaPi-IIa in the proximal tubules, as discussed previously. The decline in phosphate concentration is caused by a strong effect of PTH to increase renal phosphate excretion, an effect that is usually great enough to override increased phosphate absorption from the bone.

PTH also increases renal tubular reabsorption of calcium at the same time that it diminishes phosphate reabsorption.

The increased calcium reabsorption occurs mainly in the late distal tubules, the early collecting ducts, and possibly the ascending loop of Henle to a lesser extent.

Although Ca2+ excretion in the urine is often increased in hyperparathyroidism because the increase in the load of filtered calcium overwhelms the effect on reabsorption, Plasma Ca2+ is filtered in the kidneys, but 98–99% of the filtered Ca2+ is reabsorbed. About 60% of the reabsorption occur in the proximal tubules and the remainder in the ascending limb of the loop of Henle and the distal tubule.
osteoporosis, and skin atrophy). Cytosolic calcium is immediately bound by calbindin-D28K, which shuttles calcium to the basolateral aspect of the distal tubules cell, where it can be transported out by the type 1 sodium calcium exchanger (NCX1) or calcium ATPases. These processes are tightly regulated by hormones, such as parathyroid hormone and vitamin D.

4 PTH also increases the formation of 1,25-dihydroxycholecalciferol, and this increases both calcium and phosphate absorption from the intestine.

5 PTH increases reabsorption of magnesium ions and hydrogen ions while it decreases reabsorption of sodium, potassium, and amino acid ions in much the same way that it affects phosphate.

**Control of parathyroid secretion by calcium ion concentration**

Even the slightest decrease in calcium ion concentration in the extracellular fluid causes the parathyroid glands to increase their rate of secretion within minutes; if the decreased calcium concentration persists, the glands will hypertrophy, sometimes fivefold or more.

The parathyroid glands become greatly enlarged in persons with:

1. rickets,
2. pregnancy,
3. lactation

The parathyroid glands become greatly depressed in persons with:

1. excess quantities of calcium in the diet,
2. increased vitamin D in the diet
3. bone resorption caused by factors other than PTH (e.g., disuse of the bones)

Changes in extracellular fluid calcium ion concentration are detected by a calcium-sensing receptor in parathyroid cell membranes.

Mild decreases in serum [Mg\textsuperscript{2+}] stimulate PTH secretion.

Severe decreases in serum [Mg\textsuperscript{2+}] inhibit PTH secretion and produce symptoms of hypo-parathyroidism (e.g., hypocalcemia).

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**Parathyroid hormone-related protein (PTHrP),**

Parathyroid hormone related protein (PTHrP), is produced by many different tissues in the body.

Parathyroid hormone related protein has 140 amino acid residues

Parathyroid hormone related protein bind the same receptor of PTH this why it has same activates of PTH

Parathyroid hormone related protein actions

1. Parathyroid hormone related protein has a marked effect on the growth and development of cartilage in utero
Parathyroid hormone related protein stimulated cartilage cells proliferate and their terminal differentiation is inhibited.

Parathyroid hormone related protein expressed in the brain, where evidence indicates that it inhibits excitotoxic damage to developing neurons.

Parathyroid hormone related protein is involved in Ca2+ transport in the placenta.

Parathyroid hormone related protein is also found in keratinocytes in the skin, in smooth muscle, and in the teeth, where it is present in the enamel epithelium that caps each tooth.

In the absence of Parathyroid hormone related protein teeth cannot erupt.

Parathyroid hormone related protein play a role of hypercalcemia in malignancy such as lung cancer.

Calcitonin

In mammals, calcitonin is produced by the para-follicular cells of the thyroid gland, which are also known as the clear or C cells. Human calcitonin has a molecular weight of 3500 and contains 32 amino acid residues.

Calcitonin gene-related peptide (CGRP: is a polypeptide that exists in two forms in humans: CGRP α and CGRPβ) and the calcium-lowering hormone calcitonin are both products of the calcitonin gene.

In the thyroid gland, splicing produces the mRNA that codes for calcitonin, whereas in the brain, alternative splicing produces the mRNA that codes for CGRP α where it act as neurotransmitter.

CGRP has little effect on Ca2+ metabolism, and calcitonin is only a weak vasodilator.

Secretion of calcitonin is increased when the thyroid gland is exposed to plasma calcium level of approximately 9.5 mg/dL.

Above this level, plasma calcitonin is directly proportionate to plasma calcium. β-adrenergic agonists, dopamine, and estrogens also stimulate calcitonin secretion.

Gastrin, cholecystokinin (CCK), glucagon, and secretin have all been reported to stimulate calcitonin secretion, with gastrin being the most potent stimulus. Thus, the plasma calcitonin level is elevated in Zollinger–Ellison syndrome and in pernicious anemia. However, the dose of gastrin needed to stimulate calcitonin secretion is supra-physiological and not seen after eating in normal individuals, so dietary calcium in the intestine probably does not induce secretion of a calcium lowering hormone prior to the calcium being absorbed. In any event, the actions of calcitonin are short-lived because it has a half-life of less than 10 min in humans.
Calcitonin actions:
Calcitonin exact physiologic role is uncertain.
Calcitonin receptors are found in bones and the kidneys.
Calcitonin lowers circulating calcium levels.
Calcitonin exerts its calcium-lowering effect by inhibiting bone resorption. This action is direct, and calcitonin inhibits the activity of osteoclasts in vitro.
Calcitonin increases Ca2+ excretion in the urine.
Calcitonin content of the human thyroid is low.
After thyroidectomy, bone density and plasma Ca2+ level are normal as long as the parathyroid glands are intact. In addition, there are only transient abnormalities of Ca2+ metabolism when a Ca2+ load is injected after thyroidectomy. This may be explained in part by secretion of calcitonin from tissues other than the thyroid. However, there is general agreement that the hormone has little long term effect on the plasma Ca2+ level in adult animals and humans. Further, unlike PTH and 1, 25-dihydroxycholecalciferol, calcitonin does not appear to be involved in phosphate homeostasis. Moreover, patients with medullary carcinoma of the thyroid have a very high circulating calcitonin level but no symptoms directly attributable to the hormone, and their bones are essentially normal.

No syndrome due to calcitonin deficiency has been described.
More Calcitonin is secreted in young individuals, and Calcitonin may play a role in skeletal development.
Calcitonin may protect the bones of the mother from excess calcium loss during pregnancy.
Bone formation in the infant and lactation are major drains on Ca2+ stores, and plasma concentrations of 1, 25-dihydroxycholecalciferol are elevated in pregnancy. They would cause bone loss in the mother if bone resorption were not simultaneously inhibited by an increase in the plasma calcitonin level.

SUMMARY

1. **PTH** increases plasma Ca2+ by mobilizing this ion from bone.
   PTH increases Ca2+ reabsorption in the kidney, but this may be offset by the increase in filtered Ca2+.
   PTH also increases the formation of 1,25-dihydroxycholecalciferol.
2. 1,25-Dihydroxycholecalciferol increases Ca2+ absorption from the intestine
   1,25-Dihydroxycholecalciferol increases Ca2+ reabsorption in the kidneys.
3. Calcitonin inhibits bone resorption and
   Calcitonin increases the amount of Ca2+ in the urine.

**Effects of other hormones and humoral agents on calcium metabolisms**

1. **Growth hormone**
   Increases calcium excretion in the urine
   Increases intestinal absorption of Ca2+, and this effect may be greater than the effect on excretion, with a resultant positive calcium balance.
   Insulin-like growth factor I (IGF-I) generated by the action of growth hormone stimulates protein synthesis in bone.
2. **Thyroid hormones** may cause hypercalcemia, hypercalciuria, and, in some instances, osteoporosis.
3. **Estrogens** prevent osteoporosis by inhibiting the stimulatory effects of certain cytokines on osteoclasts.
4. **Insulin** increases bone formation, and there is significant bone loss in untreated diabetes.
5. **Glucocorticoids**
Lower plasma Ca^{2+} levels by inhibiting osteoclast formation and activity, over long periods they cause osteoporosis by decreasing bone formation and increasing bone resorption. They decrease bone formation by inhibiting protein synthesis in osteoblasts. They also decrease the absorption of Ca^{2+} and PO_{4}^{3-} from the intestine and increase the renal excretion of these ions. The decrease in plasma Ca^{2+} concentration also increases the secretion of PTH, and bone resorption is facilitated.

**Physiology of the teeth:**

**Function of different parts of the teeth:**
The tooth can be divided into crown (which is the portion that protrudes out from the gum into the mouth), and the root (which is the portion within the bony socket of the jaw). The collar between the crown and the root where the tooth is surrounded by the gum is called the neck. The inside parts of the tooth are:
Enamel:
- It forms the outer surface of the tooth
- It is formed by special epithelial cells called ameloblast.
- It is formed before tooth eruption, once the tooth is erupted, no more enamel is formed.
- It is composed of very large and very dense crystals of hydroxyapatite with adsorbed carbonate, magnesium, sodium, potassium, and other ions imbedded in the fine meshwork of strong and almost insoluble protein fibers that are similar in physical characteristics (but not chemically identical) to the keratin of hair.
- Crystalline structure of salts makes the enamel extremely hard.
- The special protein fiber meshwork, although constituting only about 1% of the enamel mass, makes enamel resistant to acids, enzymes, and other corrosive agents because this protein is one of the most insoluble and resistant proteins known.

Dentin:
- It is made up principally of hydroxyapatite crystals similar to those in the bone but much denser. These crystals are imbedded in strong meshwork of collagen fibers (i.e., the principle constituent of dentin is much the same as that of bone).
- Dentin does not contain any osteoblast, osteocytes, osteoclasts, or spaces for blood vessels or nerves.
- Dentin nourishment is by a layer of cells called odontoblast, which lines the inner surface along the wall of the pulp cavity.
- The calcium salts in dentin make it extremely resistant to compression force and the collagen fibers make it tough and resistant to tensional force.

Cementum:
- It is bony substance secreted by cells of the periodontal membrane, which lines the tooth socket.
- Many collagen fibers pass directly from the bone of the jaw, through the periodontal membrane, and then into the cementum (periodontal ligament). These collagen fibers and the cementum hold the tooth in place.
- The cementum becomes thicker and stronger with age and with exposure to excessive strain causing the teeth to become more firmly seated in the jaws.
Pulp:

😊 It is the tooth cavity which is composed of connective tissue with abundant supply of nerve fibers, blood vessels and lymphatic.

😊 The cell lining the surface of the pulp cavity are the odontoblast, which, during the formative years of the tooth, lay down the dentin but at the same time encroach more and more on the pulp cavity, make it smaller. In later life, the dentin stops growing and the pulp cavity remains essentially constant in size.

😊 The odontoblast send projections into small dentinal tubules that penetrate all the way through the dentin: they are important for exchange of calcium, phosphate with the dentin.

Dentition:

Human develop two sets of teeth during a lifetime. The first teeth are called the (deciduous teeth, or milk teeth), and they number 20 in human. They erupt between the 7th month and the 2nd year of life, and they last until the 6th to the 13th year. After each deciduous tooth is lost, a permanent tooth replaces it and additional 8 to 12 molars appear posteriorly in the jaws, making the total number of permanent teeth 28 to 32, depending on whether the four wisdom teeth finally appear.

Mineral exchange in teeth:

🪚 The salts of teeth, like those of bone, are composed of hydroxyapatite with adsorbed carbonates and various cations bound together in a heard crystalline substance. New salt are constantly being deposited while old salts are being reabsorbed from the teeth, as occurs in bone.

🪚 Deposition and reabsorption occur mainly in the dentin and cementum and to a very limited extent in the enamel. In the enamel, these processes occur mostly by diffusion exchange of mineral with saliva instead of with the fluid of the pulp cavity.

🪚 The rate of absorption and deposition of minerals in the cementum is about equal to that in the surrounding bone of the jaw, whereas the rate of deposition and absorption of minerals in dentin is only 1/3 that of bone.

🪚 The cementum has characteristics almost identical to those of usual bone, including the presence of osteoblast and osteoclast, whereas dentin does not have these characteristics.