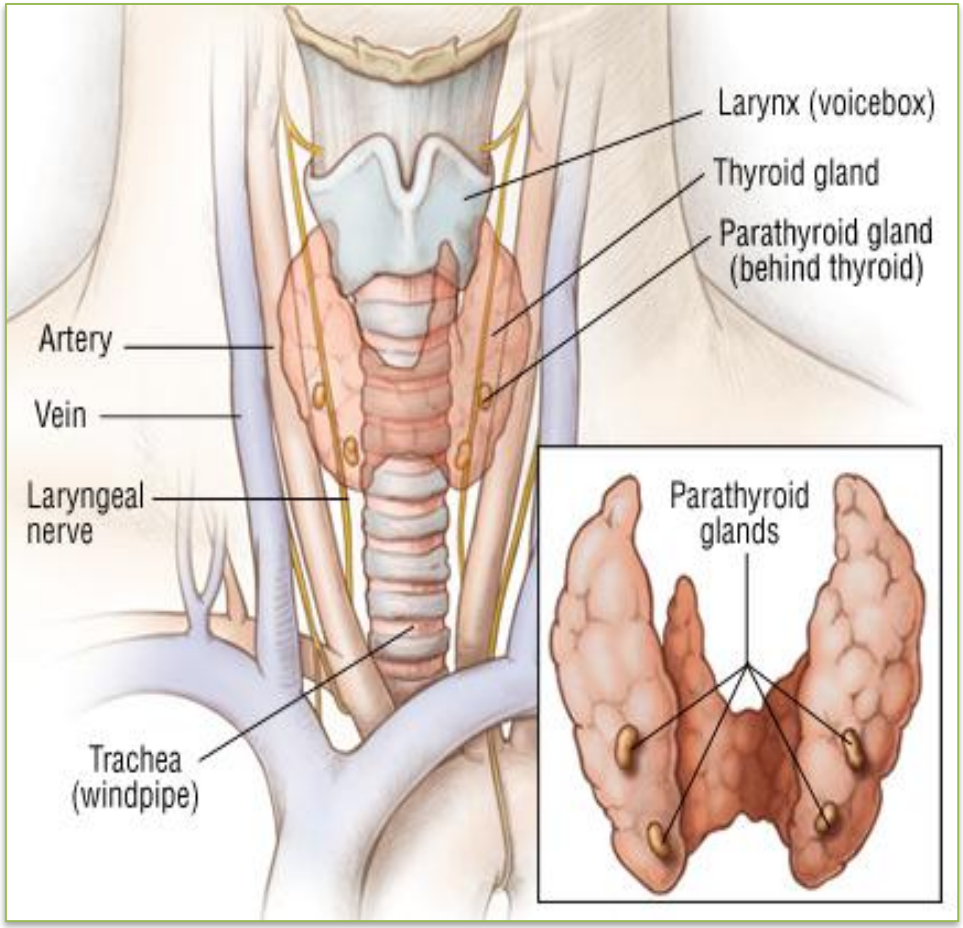
Parathyroid Glands



The parathyroid glands are 4 small masses of glandular tissue (size of grain rice) found on the posterior side of the thyroid gland.

The parathyroid glands produce the hormone parathyroid hormone (PTH), which is involved in calcium ion homeostasis.

Histology of the Parathyroid Gland

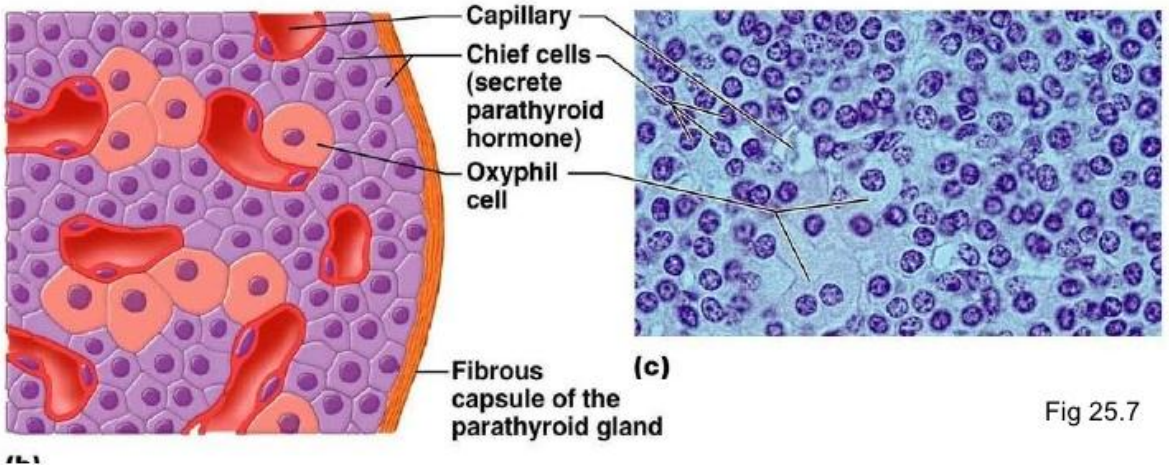


Fig 25.7

Chief cells:

- 6-8 microns, polygonal, central round nuclei, contain granules of parathyroid hormone (PTH)
- 80% of chief cells have intracellular fat
- Chief cell is most sensitive to changes in ionized calcium

Oxyphil cells:

- Slightly larger than chief cell (12 microns), acidophilic cytoplasm due to mitochondria
- No secretory granules
- First appear at puberty as single cells, then pairs, then nodules at age 40

Oxyphil cells have been shown to express parathyroid hormone-related protein (PTHrP) and calcitriol, however functions of these cells and their secretions are yet not fully understood

Endocrine Control of Calcium and Phosphate Homeostasis

Most of the physiological processes are dependent in one or other way on Ca^{2+} , thus maintain blood Ca^{2+} conc within a tight normal range is crucial or will lead to hyper /hypoclacemia

There are three major pools of calcium in the body:

Intracellular Ca^{2+}: majority of Ca^{2+} within cells is sequestered in mitochondria and ER. Intracellular free Ca^{2+} conc 100 nM -1 uM, due to release from cellular stores or influx from extracellular fluid, role in intracellular signaling, enzyme activation and muscle contractions.

Ca^{2+} in blood and extracellular fluid: half of the Ca^{2+} in blood is bound to proteins (1mM). Also, the conc of phosphorus in blood is essentially identical to that of calcium.

Bone Ca^{2+}: vast majority of body Ca^{2+} is in bone. Within bone, 99% of the Ca^{2+} is tied up in the mineral phase, but the remaining 1% is in a pool that can rapidly exchange with extracellular Ca^{2+}.

Majority of body phosphate (approximately 85%) is present in the mineral phase of bone. The remainder of body phosphate is present in a variety of inorganic and organic compounds distributed within both intracellular and extracellular compartments.

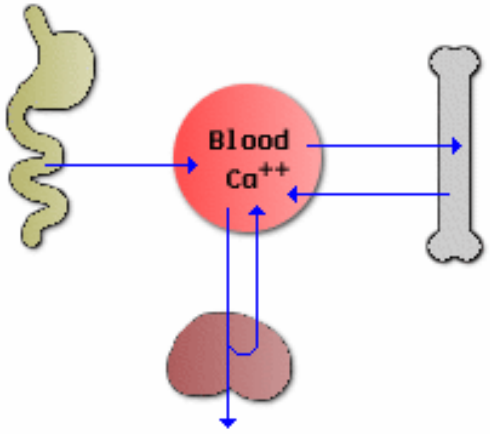
Fluxes of Calcium and Phosphate

Maintaining constant concentrations of calcium in blood requires frequent adjustments, which can be described as fluxes of Ca2+ between blood and other body compartments.

Three organs participate in supplying calcium to blood and removing it from blood when necessary:

The small intestine is the site where dietary Ca2+ is absorbed, efficient absorption of Ca2+ in the small intestine is dependent on expression of a Ca2+ -binding protein in epithelial cells.

Bone serves as a vast reservoir of calcium. Stimulating net resorption of bone mineral releases calcium and phosphate into blood, and suppressing this effect allows calcium to be deposited in bone.



The kidney is critcally important in Ca2+ homeostasis. Under normal conditions almost all of the Ca2+ that enters glomerular filtrate is reabsorbed from the tubular system back into blood, which preserves blood calcium levels.
If tubular reabsorption of Ca2+ decreases, Ca2+ is lost by excretion into urine.

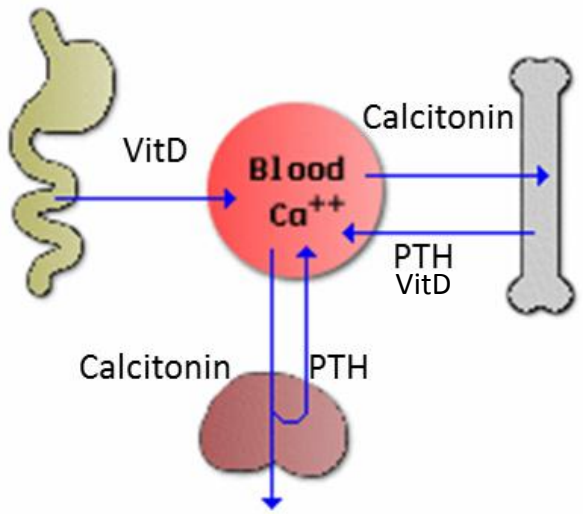
Hormonal Control Systems

Concerted action of three hormones control fluxes of calcium in and out of blood and extracellular fluid

Parathyroid hormone (Catabolic) serves to increase blood concentrations of calcium by several major effects:

- Stimulates production of the biologically-active form of vitamin D within the kidney.
- Facilitates mobilization of Ca2+ and phosphate from bone. To prevent detrimental increases in phosphate, it also has a potent effect on the kidney to eliminate phosphate (phosphaturic effect).
- Maximizes tubular reabsorption of Ca2+ within the kidney to minimize losses of Ca2+ in urine.

Vitamin D acts also to increase blood concentrations of Ca2+. It is generated through the activity of PTH within th kidney. Facilitates absorption of Ca2+ from the small intestine. In concert with PTH, vitamin D also enhances fluxes of Ca2+ out of bone.

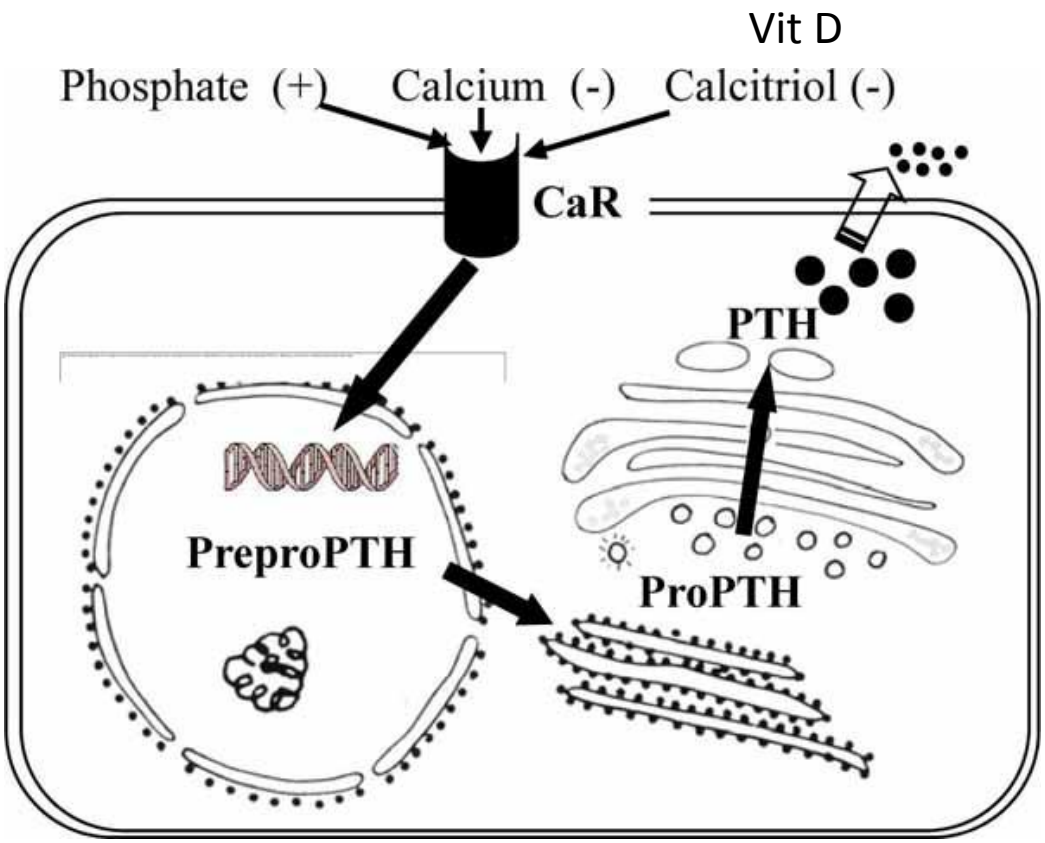


Calcitonin (anabolic) functions to reduce blood Ca2+ level secreted in response to hypercalcemia and has at least tw effects

- Suppression of renal tubular reabsorption of Ca2+.
- Inhibition of bone resorption

PTH synthesis and secretion in the parathyroid chief cell

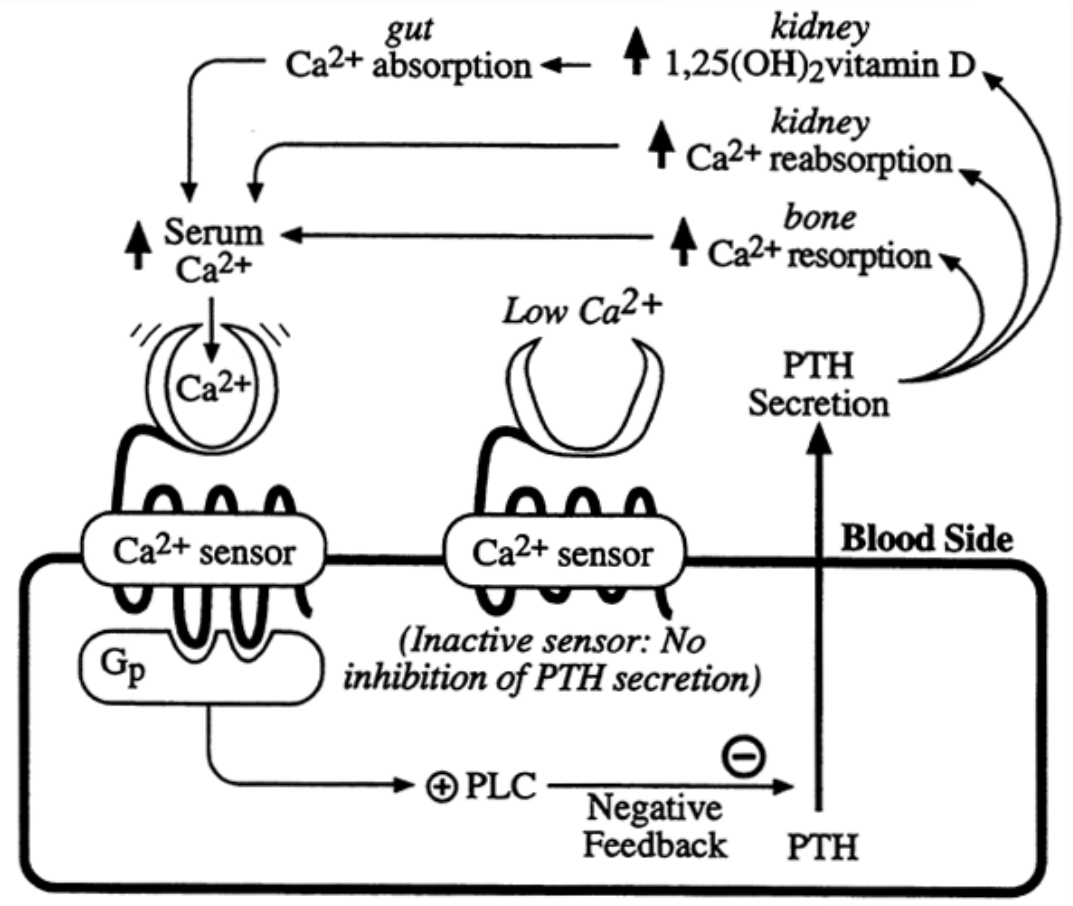
Chen et al., 2014



The deactivation of calcium-sensing receptor (CaR) stimulates synthesis of prepro PTH (115 aa), which is rapidly converted to pro PTH.

Pro PTH is transported from endoplasmic reticulum to Golgi complex, where it is converted to active PTH (84aa) and packaged into secretory granules.

Under certain conditions such as low extracellular calcium concentration PTH is released to extracellular space.



Parathyroid Hormone:

i) functions to raise plasma calcium via bone resorption and renal calcium reabsorption

ii) stimulates the metabolism of Vitamin D to its active hormonal form, $1,25(OH)_2D_3$

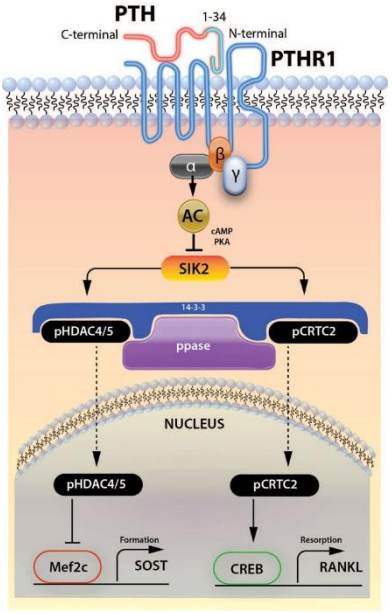
$1,25(OH)_2D_3$ enhances PO_4^{3-} and Ca^{2+} absorption which in turn elicits bone mineralization preventing Rickets in children and bone remodeling / strengthening in adults

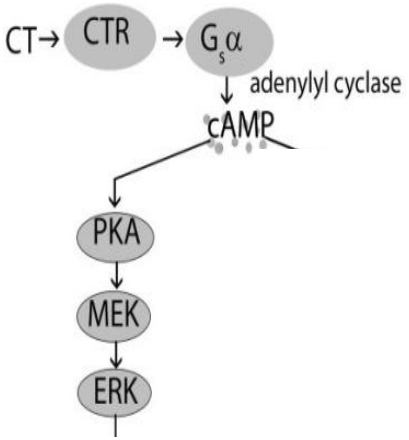
MOA of PTH and calcitonin

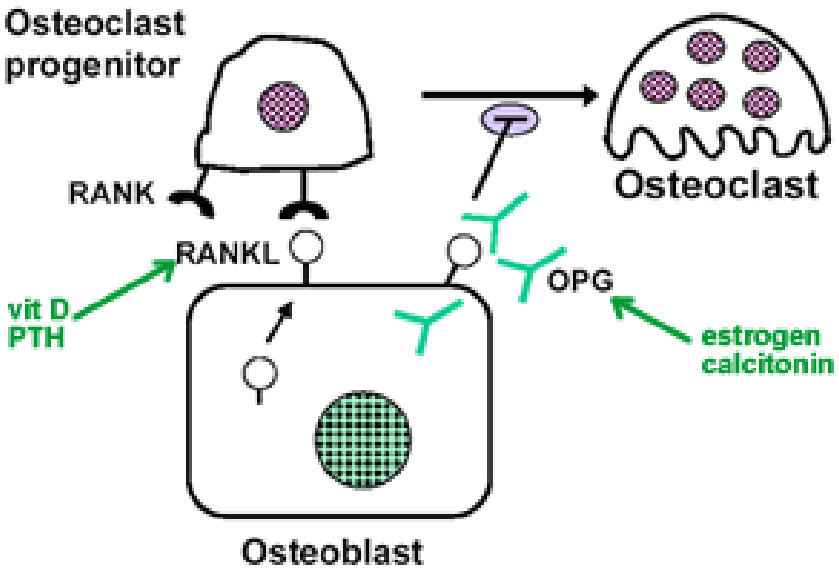
PTH/Vit D binds to PTHR1 on osteoblast and stimulates expression of RANKL which binds to RANK (receptor activator of NF-kB)present on the Osteoclast progenitor cells.

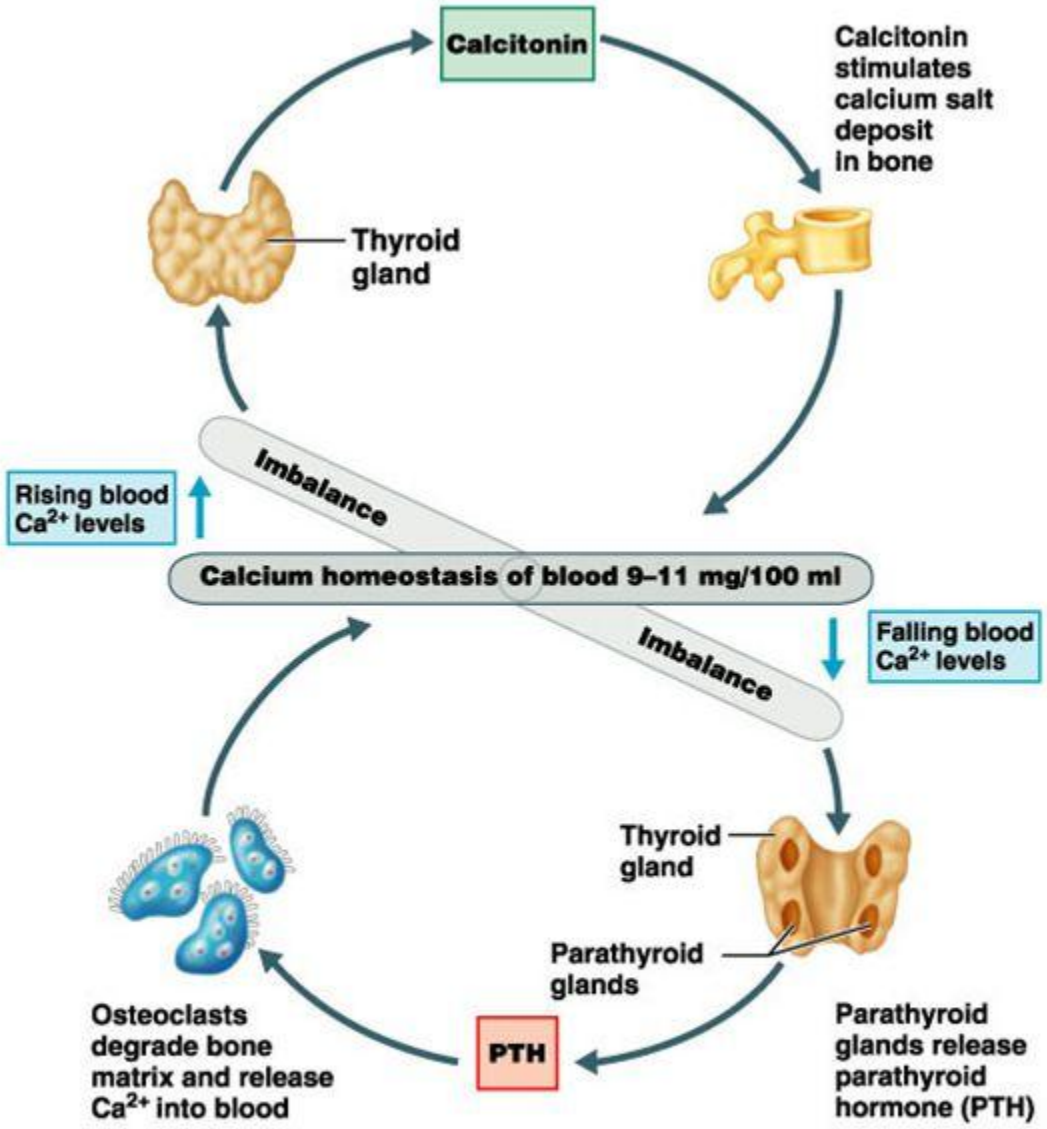
Activation of the RANK receptor leads to differentiation of osteoclasts. RANKL signals through the Ras/MEKK/JNK/Jun pathway.

Where as Calcitonin and estrogen stimulates expression of osteoprotegerin (OPG), which binds RANKL and prevents its binding to RANK, thus acts as an inhibitor of osteoclast formation and function.









- Regulation
  - Feedback loops (Whether and when)
    - Calcium homeostasis in the blood
    - Parathyroid hormone (PTH)
      - Elevates blood calcium concentration by increasing resorption
    - Calcitonin
      - Increase calcium deposition by osteoblasts

PTH related Protein (PTHrP) is homologus to PTH.

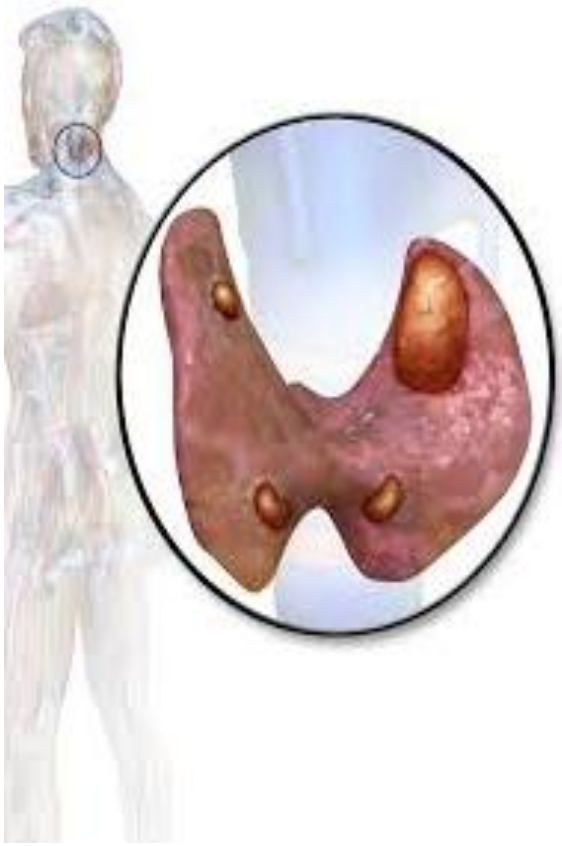
It shares the same N-terminal end as PTH and can bind to the PTHR1. can simulate most of the actions of PTH including increases in bone resorption and distal tubular calcium reabsorption, does not stimulate 1,25-dihydroxyvitamin D production, and thus does not increase intestinal calcium absorption.

PTHrP is produced in low concentrations by virtually all tissues and in higher concentrations by cancer cells. It acts as a paracrine and autocrine factor to regulate cellular growth, differentiation, development and cell death as well as epithelial calcium transport in cartilage, bone, mammary glands, and a variety of other tissues.

HYPERPARATHYROIDISM/OSTEITIS FIBROSA CYSTICA

- Primary hyperparathyroidism is characterized by increased parathyroid cell proliferation and PTH secretion which is independent of calcium levels.

- Etiology unknown, but radiation exposure,and lithium implicated, associated with MEN1, and MEN 2A (multiple endocrine neoplasia- tumors of parathyroid, thyroid etc)



HYPOPARATHYROIDISM/TETANY

- Hypocalcemia occurs when there is inadequate response of the Vitamin D-PTH axis to hypocalcemic stimuli
- Hypocalcemia is often multifactorial
- Hypocalcemia is invariably associated with hypoparathyroidism
- PTH-deficient hypoparathyroidism
  - Reduced or absent synthesis of PTH
  - Often due to inadvertent removal of excessive parathyroid tissue during thyroid or parathyroid surgery
- PTH-ineffective hypoparathyroidism
  - Synthesis of biologically inactive PTH

Osteoporosis

➢A disorder characterized by compromised bone strength which increases risk of fragility fractures.

➢ Osteoporosis typically occurs in a state of negative skeletal balance in which bone resorption exceeds bone formation.

➢A patient with osteoporosis may have a lifetime fracture risk as high as 40%. Osteoporotic fractures impair mobility, independence and quality of life; fractures of the hip also increase mortality by up to 20% . Bone mineral density (BMD) as assessed by dual x-ray absorptiometry (DXA) is the most reliable test available to estimate bone strength .

➢The most commonly used medications for treatment of osteoporosis are antiresorptive agents, including the bisphosphonates, estrogen, selective estrogen receptor modulators and denosumab. In contrast to the antiresorptive agents, anabolic agents can directly stimulate osteoblastic formation of new bone.

PTH hormone analogue like PTH 1-34 and PTH 1-84 are used in the treatment of hypoparathyroidism