Regulators
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Introduction

KEY REGULATORS OF BONE REMODELING

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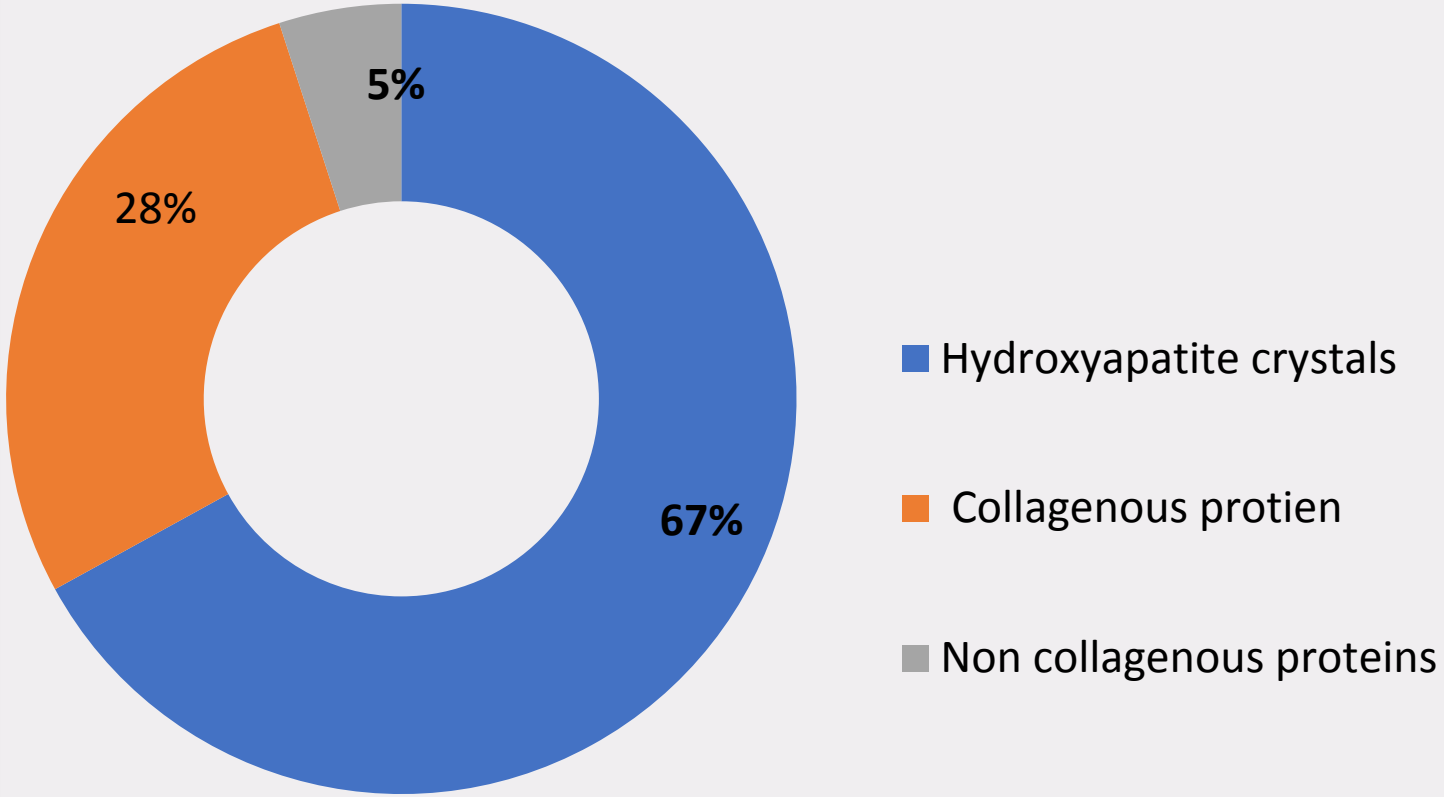
Introduction

BONE

is a living tissue, which makes up the body skeleton and is one of the hardest structures of the animal body. Posses a certain degree of toughness and elasticity.

Bone Composition:



Bone cells

Osteoblast

Bone forming cell

Osteoclasts

Bone degradating cells

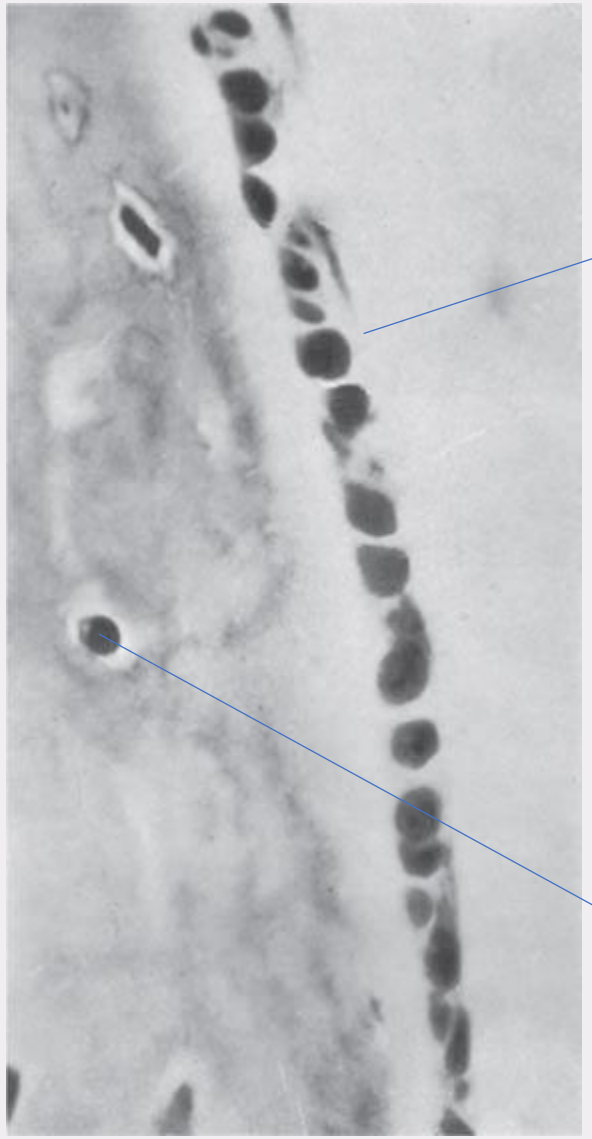
Osteocytes

Mature osteoblast

Osteoproginetor cells

Osteoblast cells

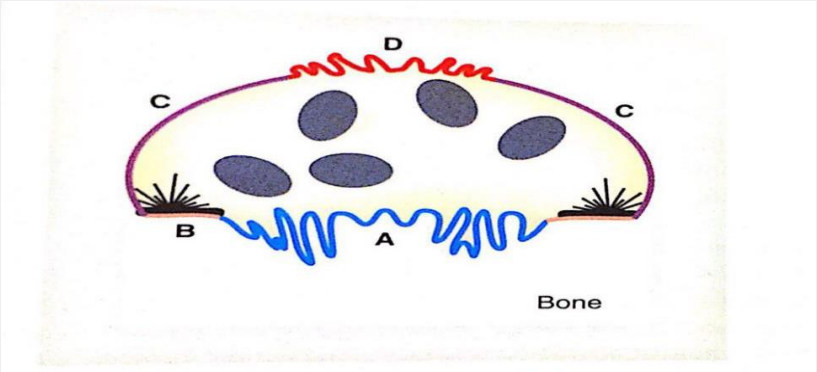
- Mononucleated cells
- Responsible for the synthesis and secretion of the macromolecular organic components of bone tissue and Control bone mineralization.
- Derived from osteoprogenitor cells of mesenchymal origin, which are present in the bone marrow and other connective tissues. In active form of osteoblast called bone lining cells



Osteocyte Cells

Osteoblasts surrounded by the products they secreted. Lies within the substance of fully formed bone
Star shape Mononucleated cells
Occupies a lacuna; and connect with each other by acanalaculi

Osteoclasts

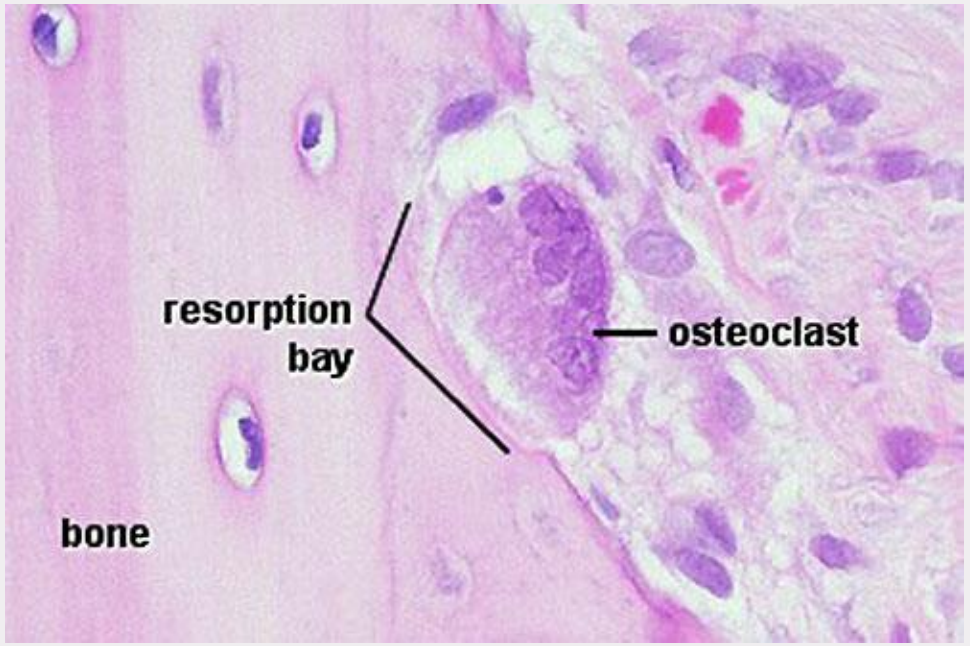


multinucleated larger cell can be identified easily under the light microscope and often are seen in clusters.

- Derive from hematopoietic progenitors in the bone marrow
- Function – *bone resorption*

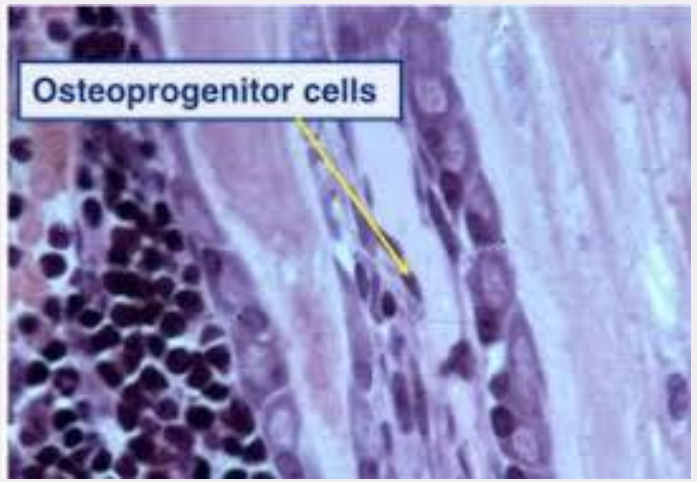
Highly specialized cytoskeletal structures

"Ruffled border"
"Sealing zone"



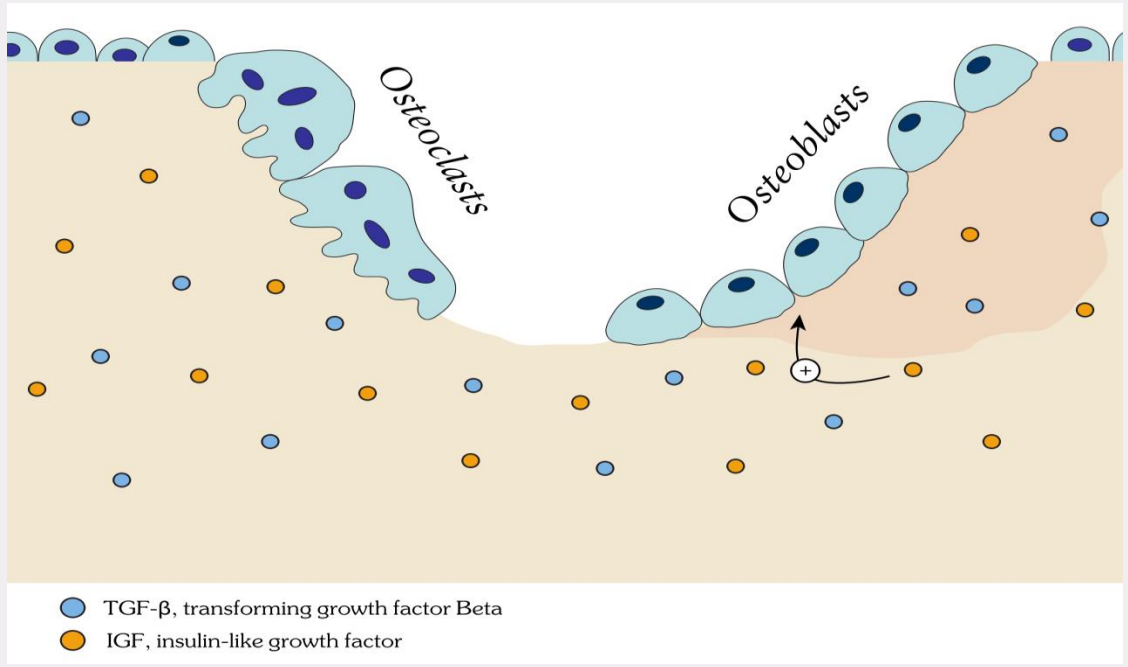
Osteoproginetor cells

Osteoprogenitor cells, also known as osteogenic cells, are **stem cells located in the bone that play a prodigal role in bone repair and growth**. These cells are the precursors to the more specialized bone cells (osteocytes and osteoblasts) and reside in the bone marrow.



Bone Remodeling

The process by which the overall size and shape of bones is established, remodeling involves the removal of mineralized bone by osteoclasts followed by the formation of bone matrix through the osteoblasts



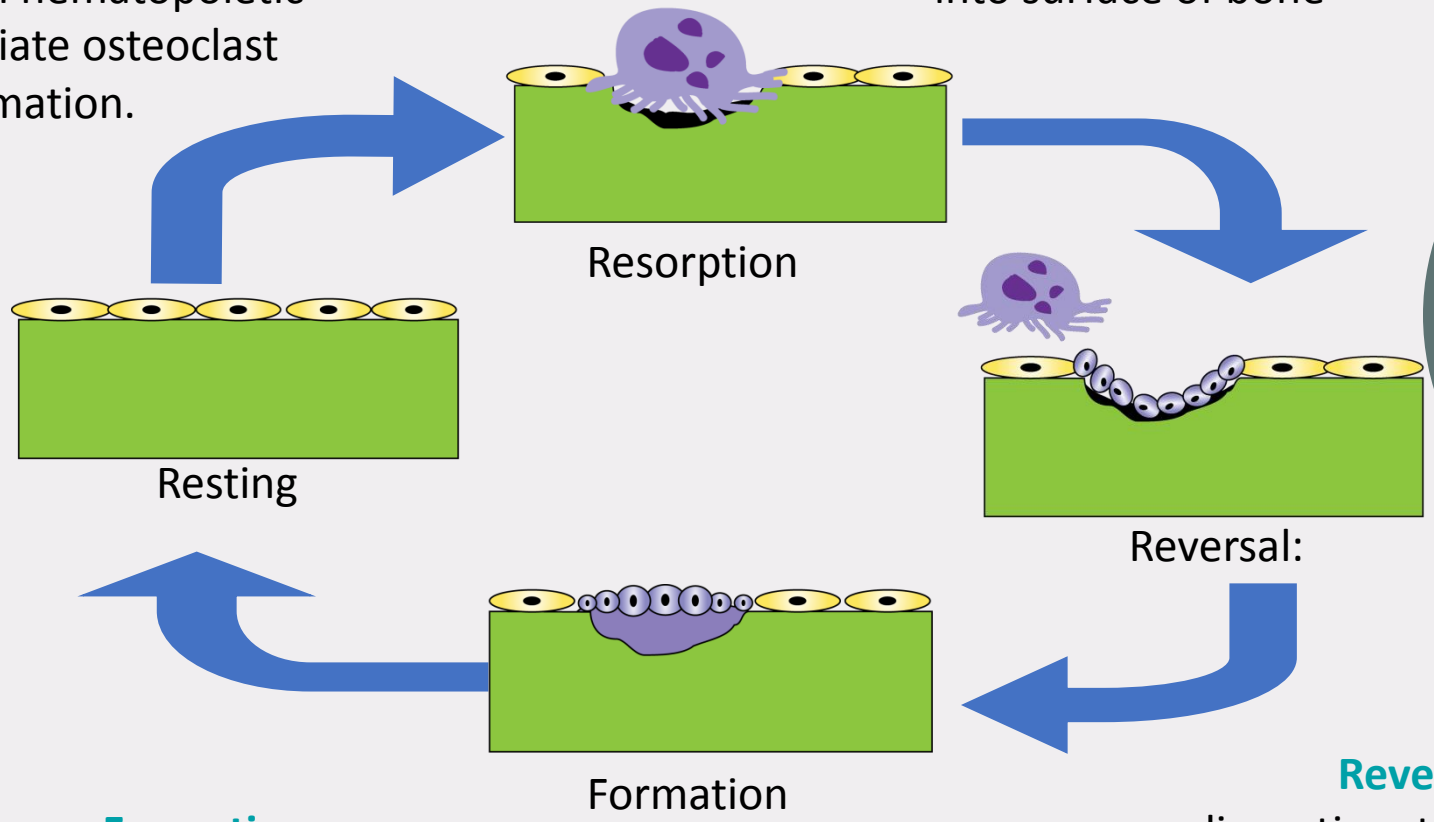
Bone Remodeling

- bone deposition is more rapid than bone resorption
- It is 30% to 100% per year in childhood, turnover doesn't stop at adulthood but continue in slow rate

Sequence of bone remodeling

Activation
The cells of the osteoblast interact with hematopoietic cells to initiate osteoclast formation.

Resorption
The osteoclasts tunnel into surface of bone



Formation
activated osteoblasts lay down new bone material

Reversal:
discontinuation of bone resorption with osteoclast apoptosis

The OPG/RANK/RANKL System

Cytokine system is essential for osteoclast biology. Various studies suggest that human metabolic bone diseases are related to alterations of this system
They belong to the tumor necrosis factor/ receptor superfamily.

OPG

Osteoprotegerin is a member of the TNF receptor family but it is secreted and acts like a cytokine
binds to RankL

Secreted by

- Stromal cells
- Osteoblast cells

Expressed on

- Osteoblasts
- Bone marrow stromal cells
- Follicular dendritic cells

inhibits osteoclastogenesis by preventing the interaction of receptor activator of nuclear factor-κB ligand (RANKL) with receptor activator of nuclear factor-κB (RANK)

RANK

RANK is a heterotrimer **C**ytokine

Formed by

- osteoblasts
- bone marrow stromal cells
- chondrocytes
- activated T lymphocytes

Expressed on

- osteoclast progenitor cells
- mature osteoclasts
- chondrocytes
- dendritic cells
- trophoblasts

Studies conducted on RANK– gene knockout animal models revealed that in these mice, osteoclastogenesis inhibition., absence of osteoclasts

RANKL

RANKL is identified to belong to the tumor necrosis factor (TNF) family and has been recognized to be the only cytokine to play an essential role in bone metabolism as it regulates the development, maintenance and activation of osteoclasts, thus plays a vital role in osteoclastogenesis

Other names

- OPG ligand (OPGL)
- Osteoclast differentiation factor (ODF)
- TNF related activation-induced cytokine (TRANCE)

Expressed on

- the plasma membrane of stromal and osteoblastic cells

Studies conducted on RANKL– gene knockout animal models revealed that in these mice, do not display osteoclastogenesis

The interaction between RANK and RANKL signals lead to **initiation of osteoclastogenesis** and activation of osteoclasts.

RANKL is also a ligand for the soluble receptor OPG and this interaction **blocks osteoclastogenesis** via RANKL

Thus, RANKL has a dual antagonistic type action on osteoclastogenesis, depending on the type of **receptor** it interacts with: RANK or OPG. RANKL thus plays a key role in activation of osteoclasts, thereby influencing bone resorption.

Systemic regulators

- Parathyroid hormone
- Calcitonin
- vitamin D3
- Insulin
- Estrogen
- Androgens

Local regulators

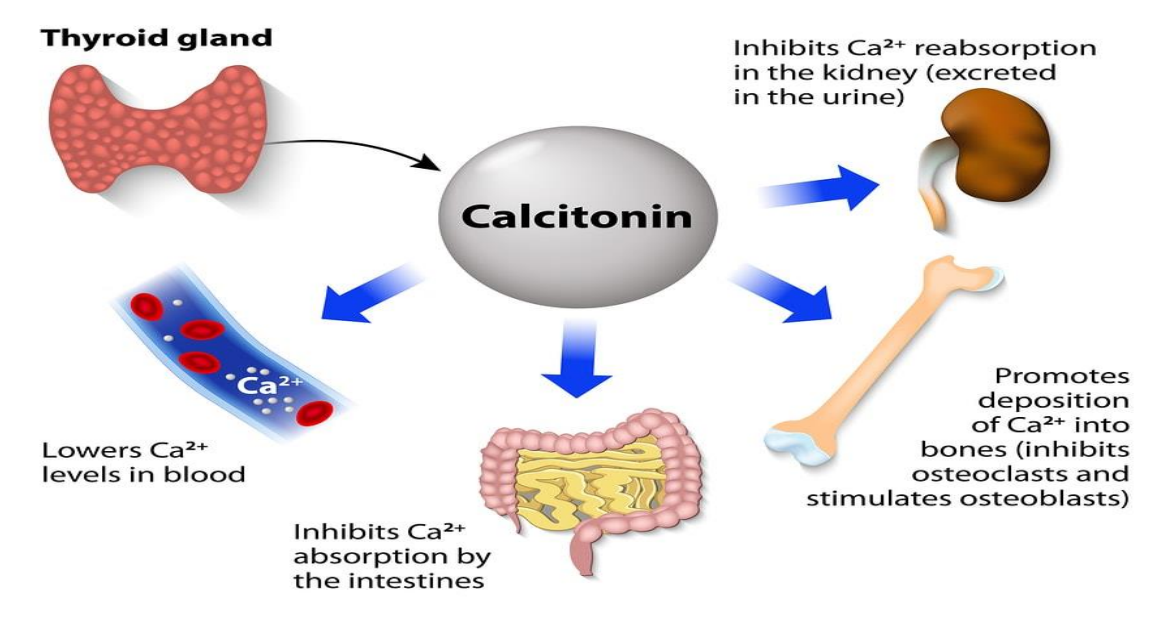
- Runx2
- Osterix
- M-CSF (Macrophage colony-
- stimulating factor)
- (bone morphogenetic protein)
- (insulin like growth factors)
- transforming growth factor-β
- Interleukin (IL-6)
- Interleukin(IL-1)

Parathyroid hormone

- Synthesized and secreted by the parathyroid glands
- Function of PTH is to maintain blood calcium homeostasis.
- It stimulates bone resorption through the synthesis of RANKL on the part of the osteoblastic cells, also induces the synthesis of IGF-1 to stimulate osteoblast proliferation and differentiation

Calcitonin

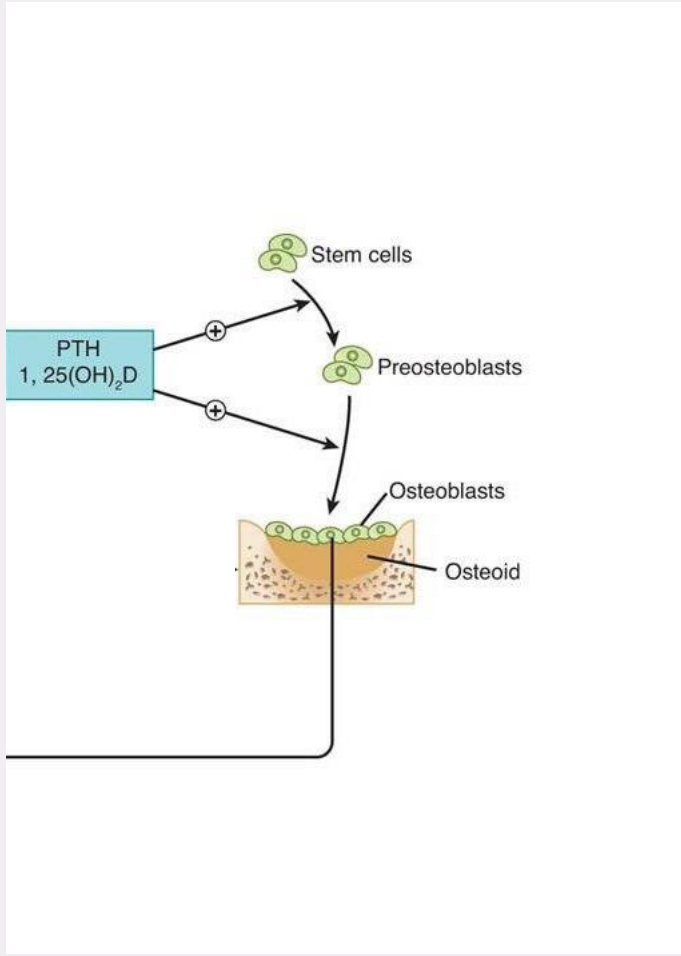
It is secreted by the thyroid C cells
.It mediates its actions through the CTR (calcitonin receptor)
. It increase bone formation by increases the extracellular level of insulin-like growth factors (IGF-1 and IGF 2) in cultures of human osteoblast like cells .
In addition, CT may also prevent osteoblast and osteocyte apoptosis



vitamin D3

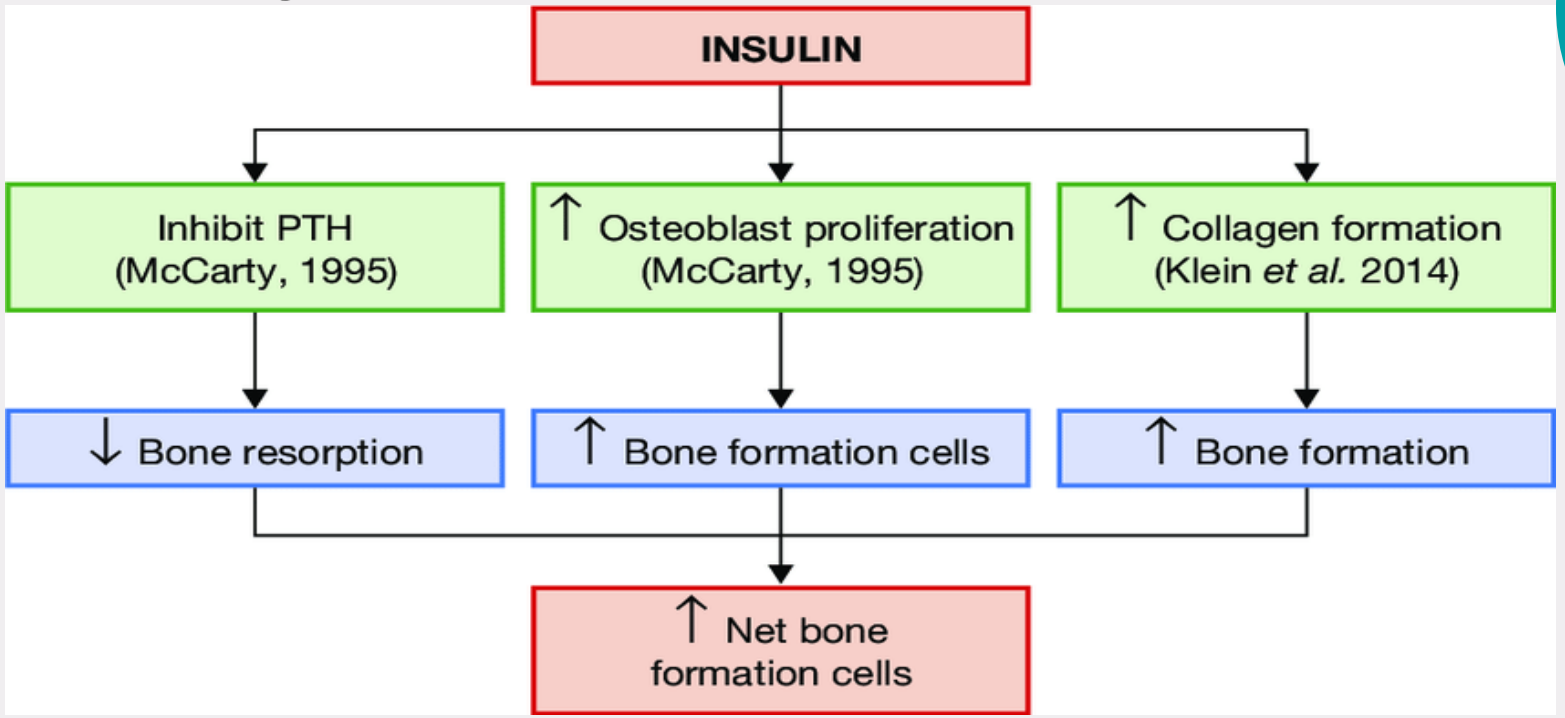
is essential for normal development and maintenance of the skeleton

. It plays a central role in calcium and bone homeostasis through binding to the vitamin D receptor (VDR) present mainly in intestine, bone, kidney, and parathyroid gland In contrast.



Insulin

- directly stimulates bone matrix formation and mineralization
- indirectly affects bone formation through stimulation of IGF-I (insulin like growth factor)



Estrogen

Estrogen is the one of the major hormonal regulators of bone metabolism in both women and men.

It attenuate osteoclastogenesis and stimulate osteoclast apoptosis. In osteoclasts, estrogen blocks RANKL/M-CSF. In addition, estrogen has also been shown to modulate the production of a number of bone-resorbing cytokines, including IL-1, IL-6, TNF, and prostaglandins

Androgens

Androgen is a well-known and intensely studied hormonal regulator of postmenopausal bone health in women. It can indirectly inhibit osteoclast activity and bone resorption via effects on osteoblasts/osteocytes and the RANKL/RANK/OPG system

Runx2

acts as a master regulatory switch that mediates the temporal activation of cell as osteoblasts progress through stages of differentiation. bone matrix proteins ,osteopontin, osteocalcin, and collagen type I, and it seems to control the maturation of osteoblasts and their transition into osteocytes.

Osterix

may play an important role in directing precursor cells away from the chondrocyte lineage and toward osteoblast lineage.

Both genes are critical for bone formation; mice that do not express Runx2 or Osterix show a complete absence of intramembranous and endochondral ossification

M-CSF

Macrophage colony-stimulating factor is promotes the migration of mature osteoclasts. M-CSF is produced by osteoblasts and osteoblast precursors, osteocytes. M-CSF is present in two distinct biologically active forms, a membrane-bound and a secreted form. Osteocytes, osteoblasts, and stromal cells express both forms

IGF-I and II

(insulin like growth factors) The primary function of IGF-1 in the bone matrix is to maintain bone mass and skeletal homeostasis during bone remodeling .Furthermore, IGF-1 promotes osteoclast differentiation

TGF-β

(transforming growth factor-β is to recruit and stimulate osteoprogenitor cells to proliferate, providing a pool of early osteoblasts. In contrast, during later stages of osteoblast differentiation, TGF-β blocks differentiation and mineralization. inhibit proliferation and differentiation of committed precursors into mature osteoclasts. TGF-β also promotes apoptosis of osteoclasts

Inter leukin (IL-6)

Is an anti-inflammatory produced by stromal or osteoblast cells in response to PTH and vitamin D3 and on stimulation by IL-1. IL-6 alone or in concert with other agents stimulates osteoclastogenesis.

Inter leukin(IL-1)

does not have direct action on the osteoclast, but like PTH acts via the osteoblast. It has a direct promotional effect on osteoclast formation. It inhibits the apoptosis of osteoclasts.

THANK YOU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