BPS 437

Menopause and Osteoporosis

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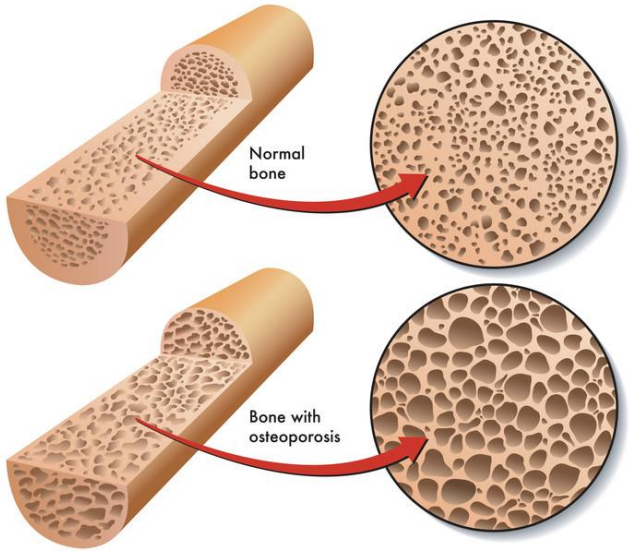
What is Osteoporosis?

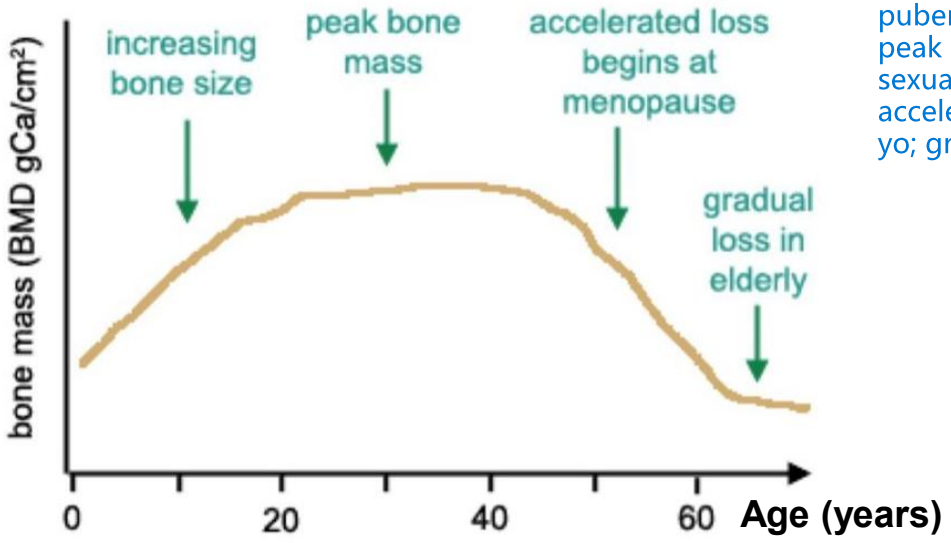
Definition: A silent disease characterized by low bone mass and structural deterioration of bone tissue with an increase in bone fragility and susceptibility to fracture



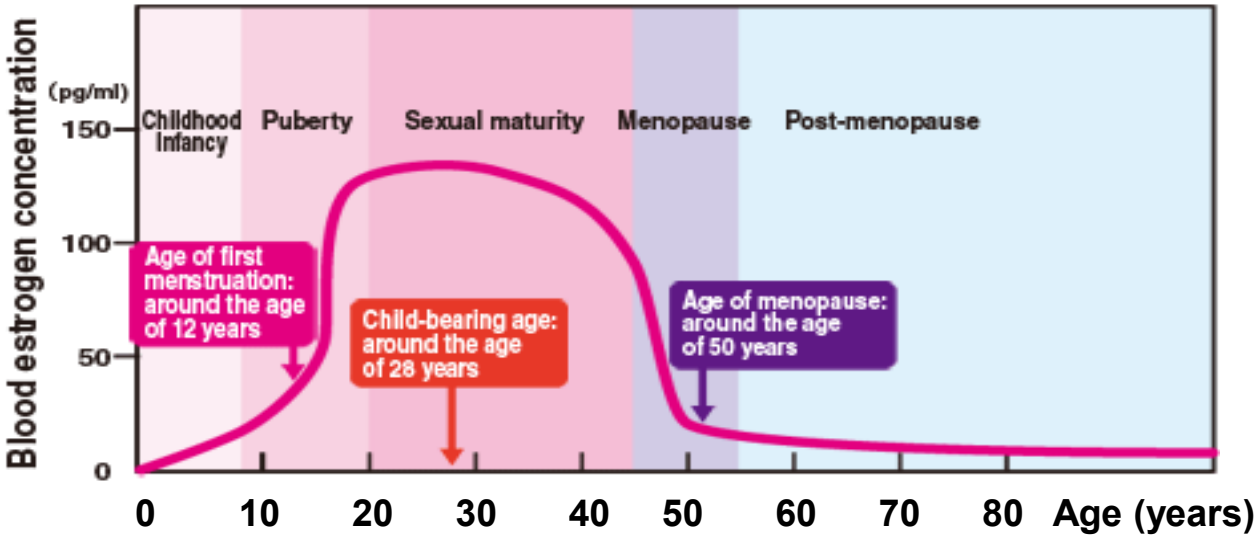
- World-wide, 1 in 3 women and 1 in 5 men are at risk of an osteoporotic fracture
- In fact, osteoporotic fracture is estimated to occur every 3 second
- The most common fractures occur at the hip, spine and wrist.

the spongy hole of bones increase in size (more porous); more susceptible to fracture

Bone Mass vs Estrogen levels during the Aging

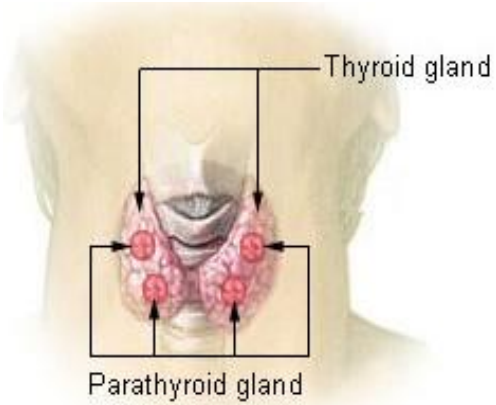


increasing bone size and childhood-puberty match
peak bone mass at ages 15-40 when sexually mature
accelerated loss begins at menopause ~50 yo; gradual loss in elderly

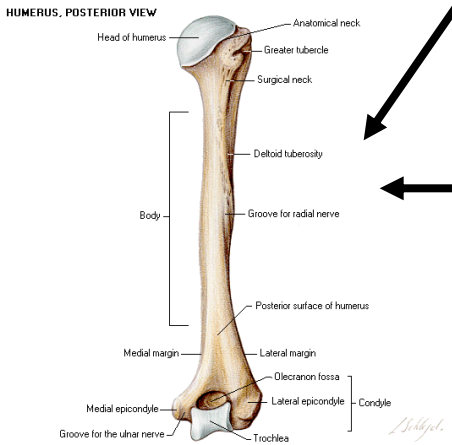


Bone, Calcium and Hormones

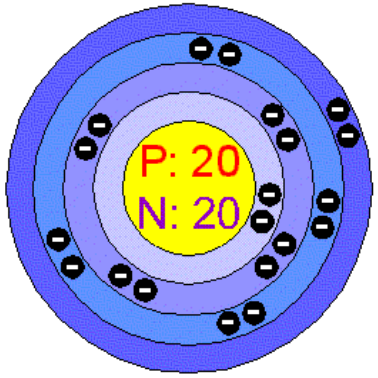
Hormones



Bone



Calcium Atom



Bone: Overview

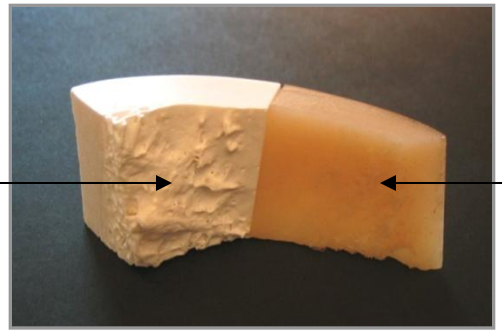
Functions:

- Structural function: providing mobility, support, and protection for the body
- Reservoir function, as the storehouse for essential minerals.
- It is not a static organ, but is constantly changing particularly with calcium

Composition:

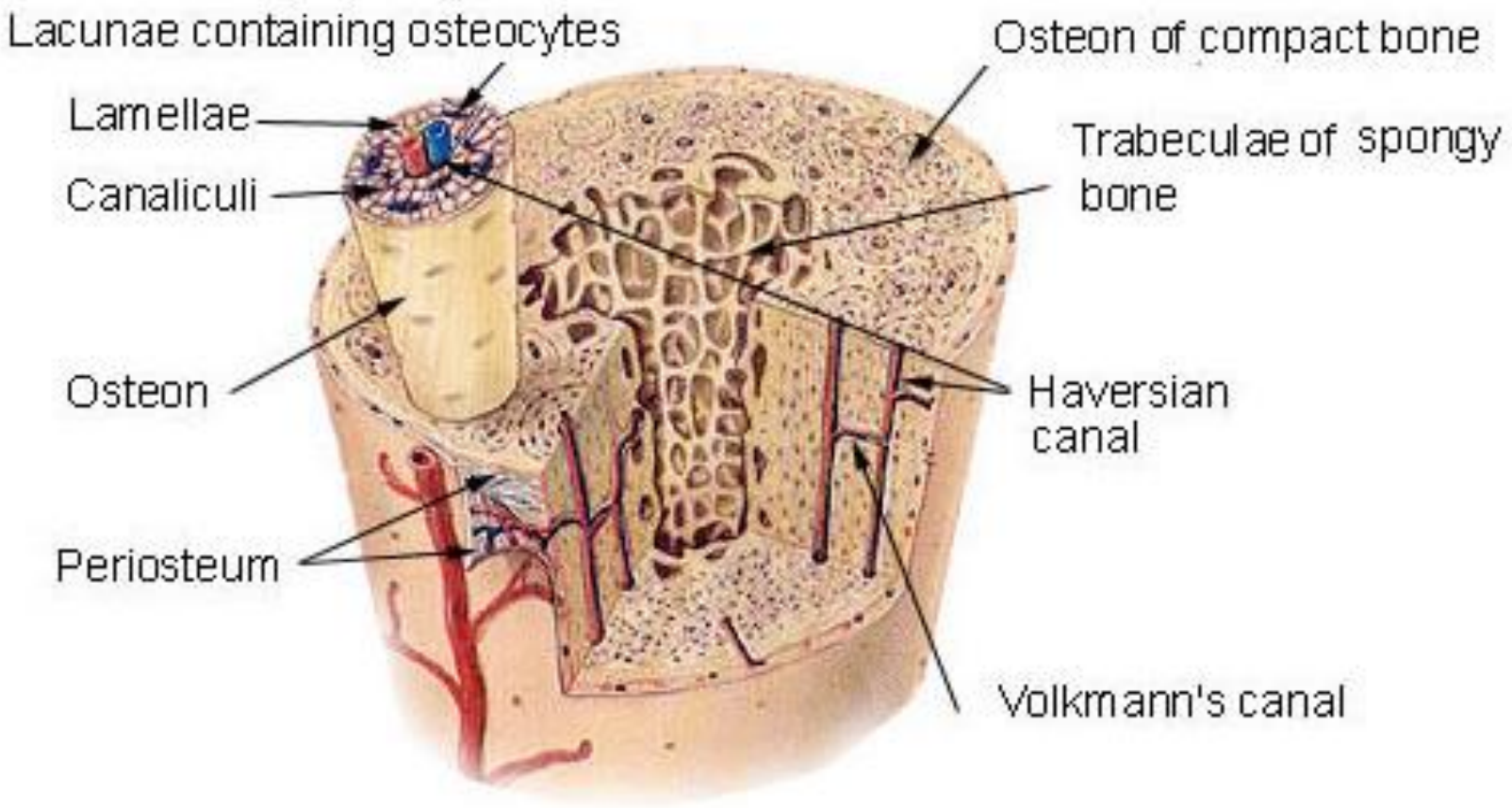
- Crystals of mineral: Calcium and Phosphorus which bind to protein.
- Protein: Mainly collagen
- Make bone have both strength and resilience (plasticity)

Treated with bleach (hypochlorite) to digest collagen, leaving mineral component intact

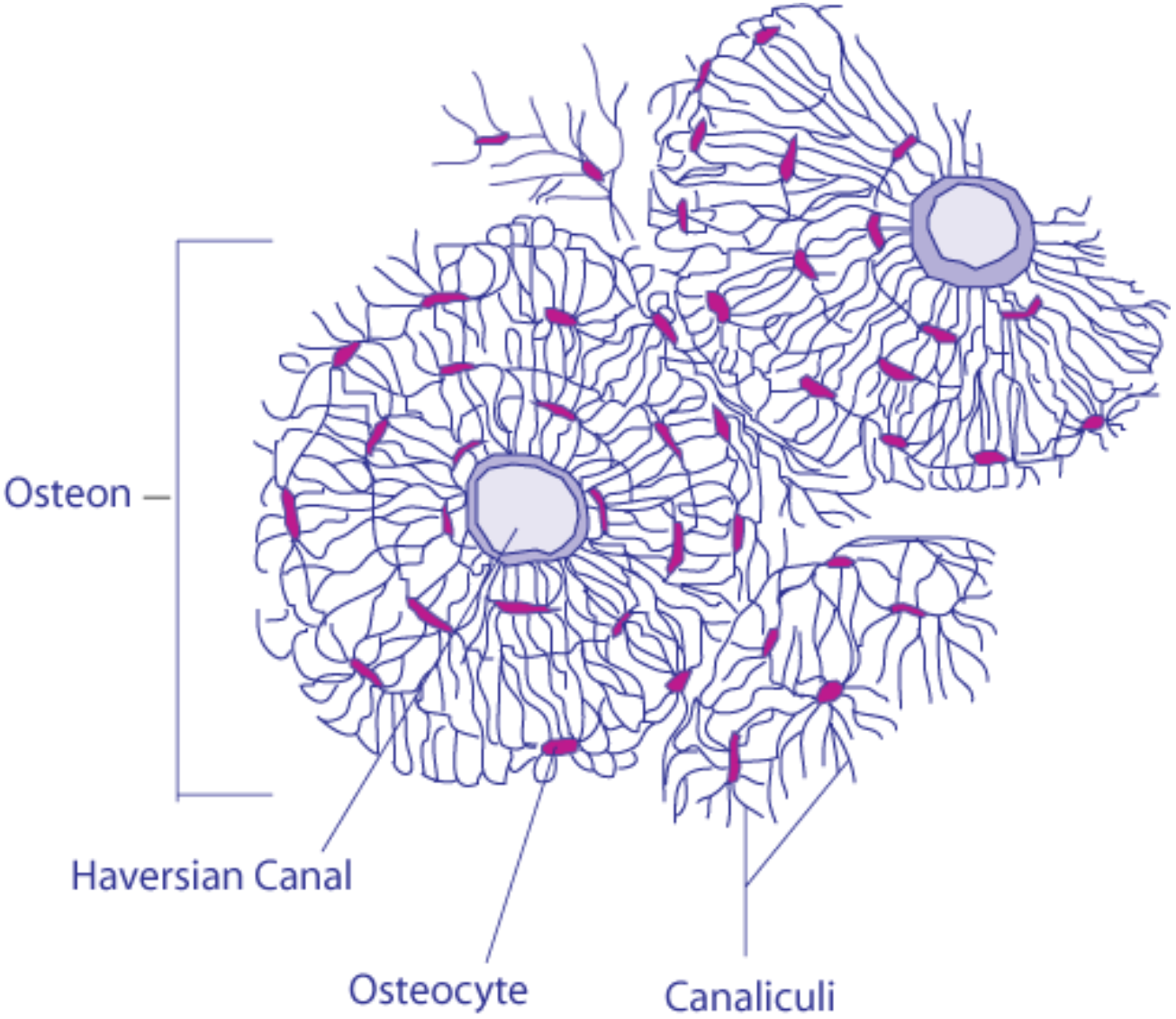


Treated with hydrochloric acid to dissolve mineral, leaving collagen component intact

Bone Macro-structure



Bone Micro-structure



Bone is a Dynamic Tissue: Bone Modeling

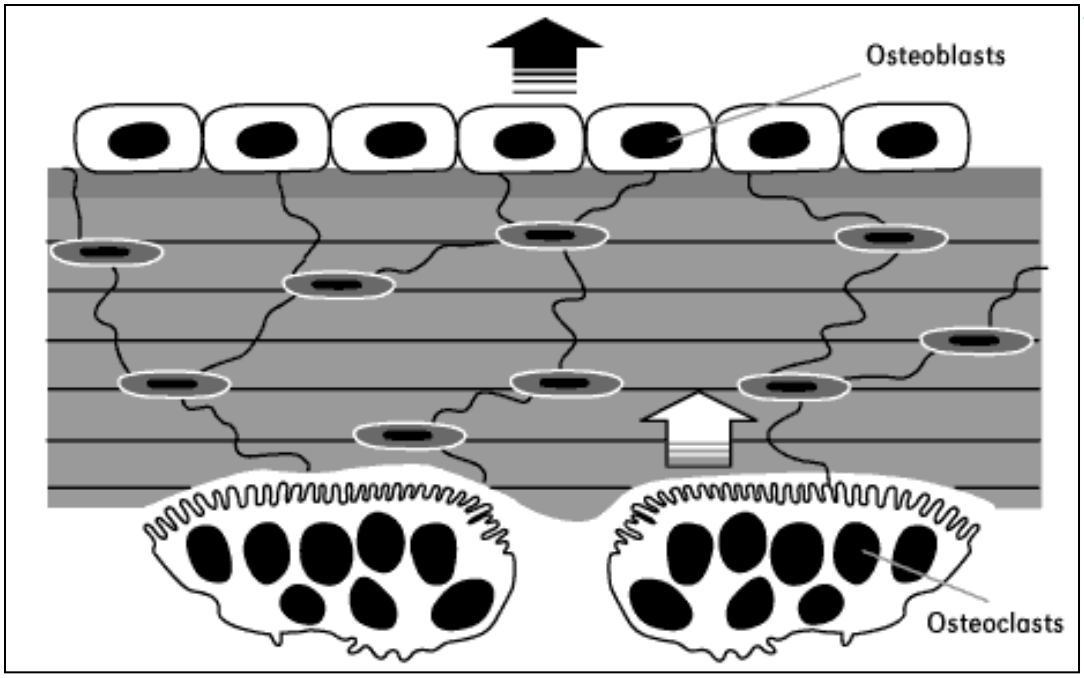
Bone Modeling

by osteoclast

- Bone growth during childhood: Resorption occurs inside the bone while formation of new bone occurs on its surface by osteoblast
- Allow bone to grow in size and to shift in space

osteoblasts create new bone from the surface, on the outside

Surface



New bone formed

Inside

Old bone dissolved

osteoclasts dissolve the bone "from inside"

Bone is Dynamic Tissue: Bone Remodeling

Bone Remodeling

- Bone goes continuous remodeling process through dissolving old bone and replacing with new bone
- Occurs throughout life and becomes the dominant process by the time that bone reaches its peak mass (typically by the early 20s).
- Such remodeling function is carried out by a team of cells, called **basic multicellular unit** (BMU)
- BMU moves on the surface of bone as remodeling continues

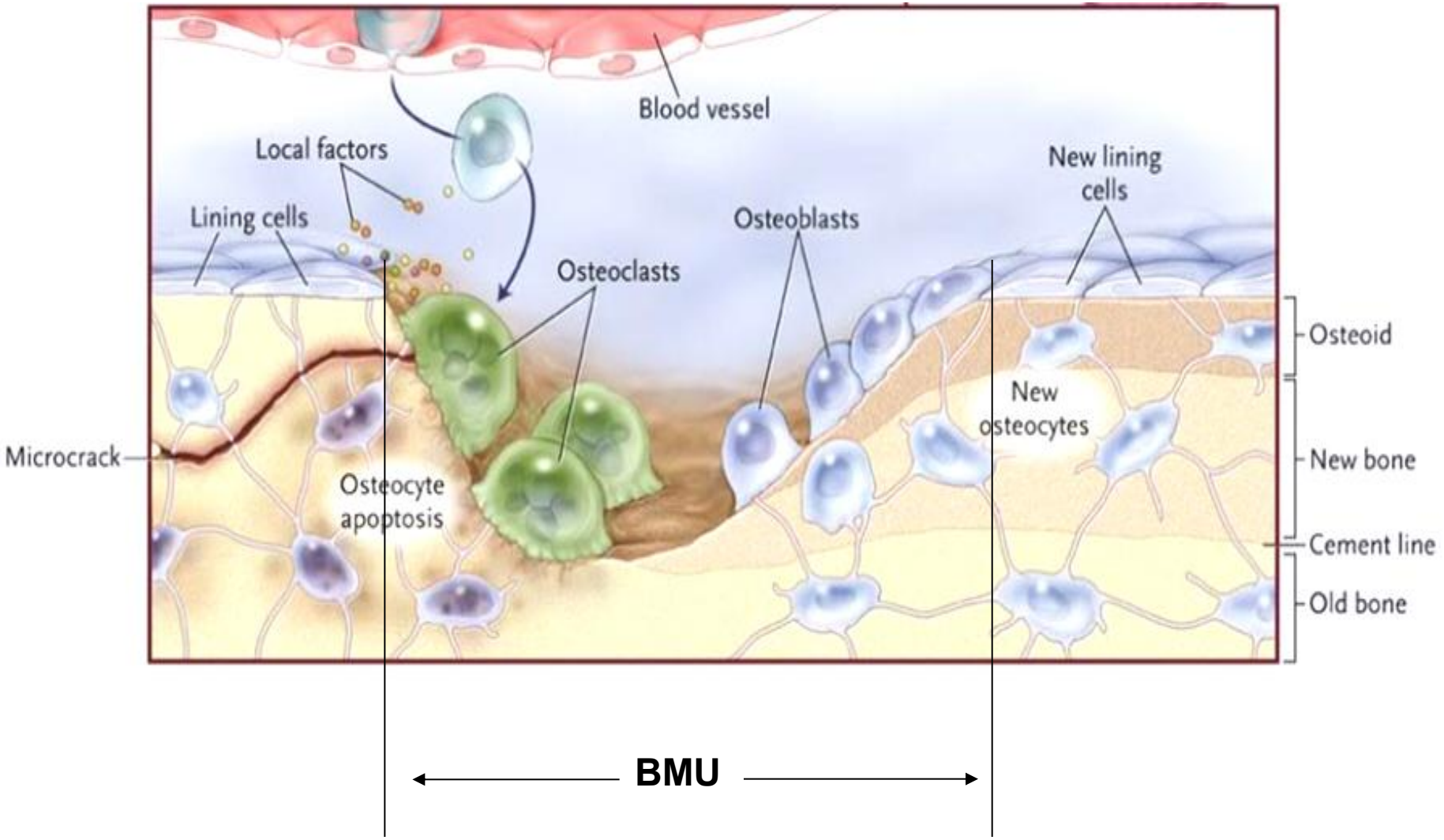
peaks at early 20 and does not grow anymore

Why Remodeling?

- Remodeling repairs the damage to the skeleton that can result from repeated stresses by replacing small cracks or deformities in areas of cell damage.
- Remodeling also prevents the accumulation of too much old bone, which can lose its resilience and become brittle.
- Remodeling is also important for the function of the skeleton as the bank for calcium and phosphorus.

Basic Multicellular Unit (BMU)

coordination of BMU is key;
if osteoclast dissolves fast, and osteoblast does not build new bone fast enough, can lead to weak bone



Basic Multicellular Unit (BMU): Overview

Adult bone remodeling

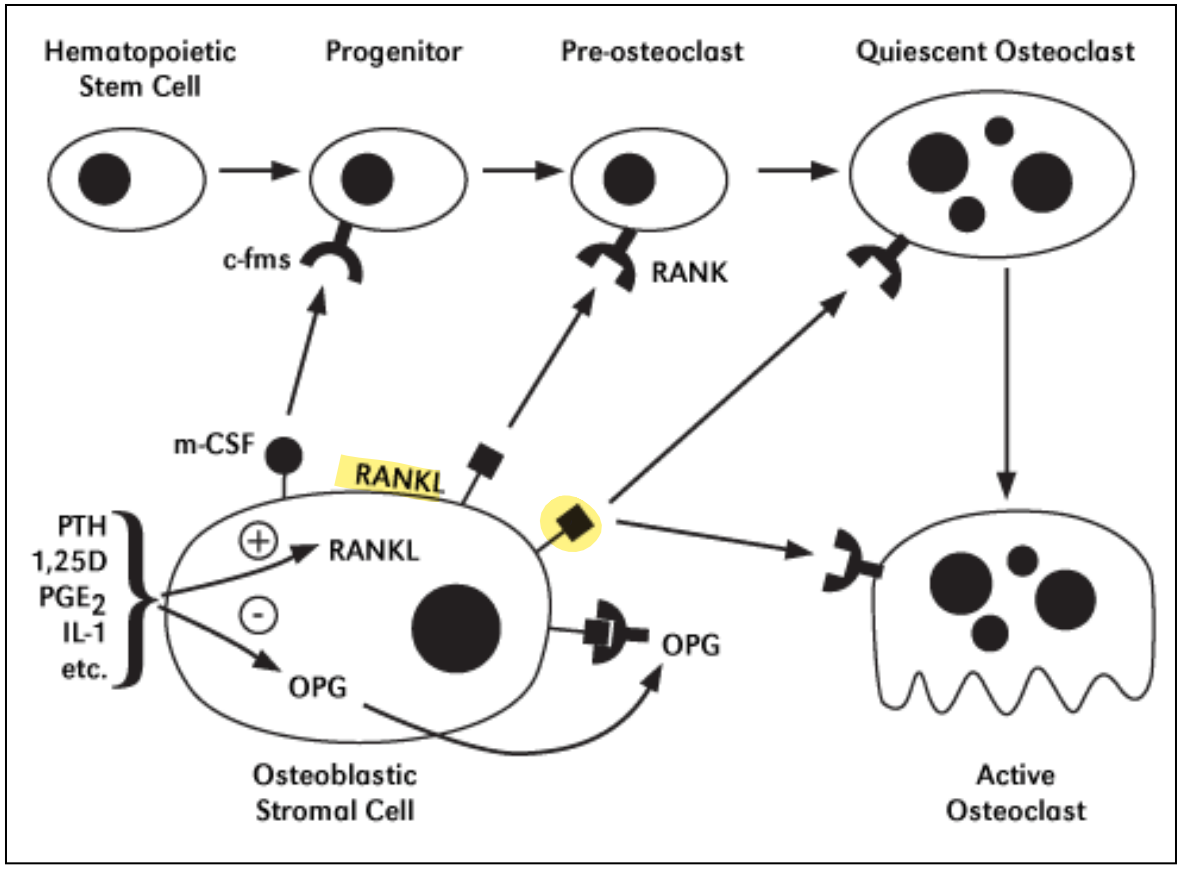
- Lifespan of BMU ~ 6-9 months
- Moving speed ~ 25 mm/day
- Interval between successive remodeling events at the same location ~ 2-5 years
- Rate of turnover of whole skeleton ~ 10% per year

Parfitt, 1993

Cells Involving in Bone Modeling and Remodeling

Osteoclasts

- Large cells that dissolve the bone.
- Formed from two or more cells that fuse together, so the osteoclasts usually have more than one nucleus.
- Derived from the bone marrow and are related to white blood cells.



OPG: Osteoprotegerin

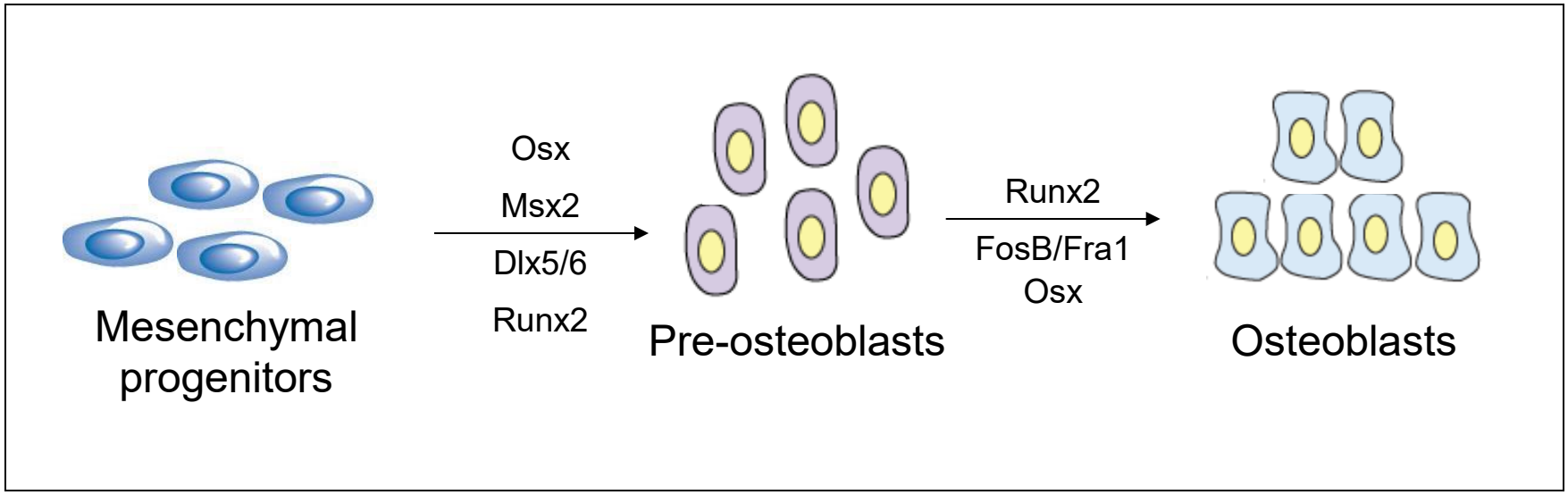
M-CSF: Macrophage colony-stimulating factor

RANK: Receptor Activator of Nuclear Factor κ B RANK ligand on osteoblast simulate osteoclast-gen

Cells Involving in Bone Modeling and Remodeling

Osteoblasts

- Cells that form new bone
- Derived from the bone marrow and are related to structural cells
- They have only one nucleus
- Producing new bone called "osteoid" which is made of bone collagen and other proteins.
- Controlling calcium and mineral deposition.



Osx: Osterix **Runx2**: Runt-related transcription factor 2 **Msx2**: msh homeobox 2 **Dlx5/6**: Drosophila distal-less gene 5/6

Cells Involving in Bone Modeling and Remodeling

Lining Cells

- Sitting on surface
- Derived from osteoblasts when new bone is formed
- Regulating passage of calcium into and out of the bone
- Responding to hormones by making special proteins that activate the osteoclasts.

Osteocytes

- Cells inside the bone.
- They also come from osteoblasts.
- Networked to each other via long cytoplasmic extensions that occupy tiny canals called canaliculi
- Sensing pressures or cracks in the bone and help to direct where osteoclasts will dissolve the bone.

Bone Disorders

Osteoporosis:

❖ **Primary**: being age-related osteoporosis, such as postmenopausal osteoporosis or unknow causes

❖ **Secondary:** the loss of bone is caused by certain lifestyle behaviors, diseases or medications. 20% to 30% of postmenopausal women and more than 50% of men with osteoporosis have a secondary cause.

•Adverse effects of drug therapy
•Endocrine disorders
•Eating disorders
•Immobilization
•Marrow-related disorders
•Disorders of the gastrointestinal or biliary tract
•Renal disease,
•Cancer
•Organ transplantation

Bone Disorders

Other Bone Disorders:

- **Primary hyperparathyroidism**: due to high levels of PTH

- **Paget's Disease**: due to defect or interfering with normal bone remodeling process (generating new bone faster than normal), the rapid remodeling produces bone that's less organized and weaker than normal bone, which can lead to bone pain, deformities and fractures

- **Renal Osteodystrophy**: a form of metabolic bone disease seen in patients with chronic renal insufficiency characterized by bone mineralization deficiency due to electrolyte and endocrine abnormalities

- **Rickets and Osteomalacia**: Rickets is a condition that affects bone development in children. It causes bone pain, poor growth and soft, weak bones that can lead to bone deformities. Adults can experience a similar condition, which is known as osteomalacia or soft bones.

- **Osteogenesis Imperfecta**: a group of genetic disorders that all result in bone that breaks easily. a problem with connective tissue due to a lack of, or poorly formed, type I collagen

Treatments for Osteoporosis

Anabolic Agents (Building bone) paradoxical building bone effect of intermittent PTH

- Parathyroid hormone (PTH): Teriparatide (Forteo)
- PTH-related protein: Abaloparatide (Tymlos)
- Romosozumab (Evenity) romosozumab dual action of building bone and reduce loss

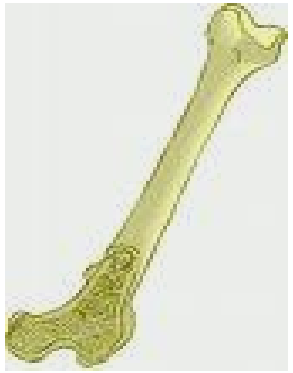
Antiresorptive Agents (Reducing bone loss)

- Bisphosphonates
- Hormone or estrogen replacement
- Selective estrogen receptor modulators (SERMs) (raloxifene)
- Calcitonin
- Denosumab (Prolia or Xgeva)
- Romosozumab (Evenity)

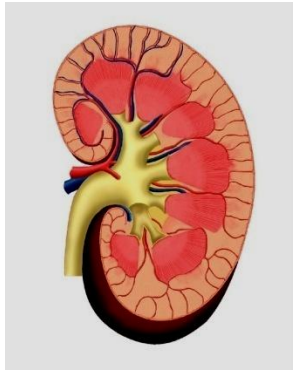
Anabolic Therapy with PTH: A Paradox

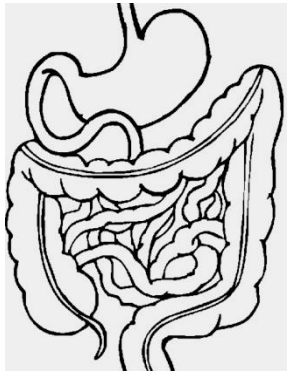
Teriparatide (Forteo)

This **paradox**—the fact that PTH secreted **continuously** can break down bone while **intermittent injections** of the same hormone actually build bone-has never been fully explained.



PTH





Increasing blood calcium levels by stimulating osteoclasts to break down bone and release calcium

Promoting calcium uptake by the kidneys

Increasing gastrointestinal calcium absorption by activating Vitamin D

Anabolic Therapy

PTH-related protein (PTHrP): Abaloparatide (Tymlos)

- Mainly made and secreted by mesenchymal stem cells
- Occasionally made and secreted by cancer cells
- Binding to the same receptor as PTH partially matching AA sequence with PTH

Intermittent injection

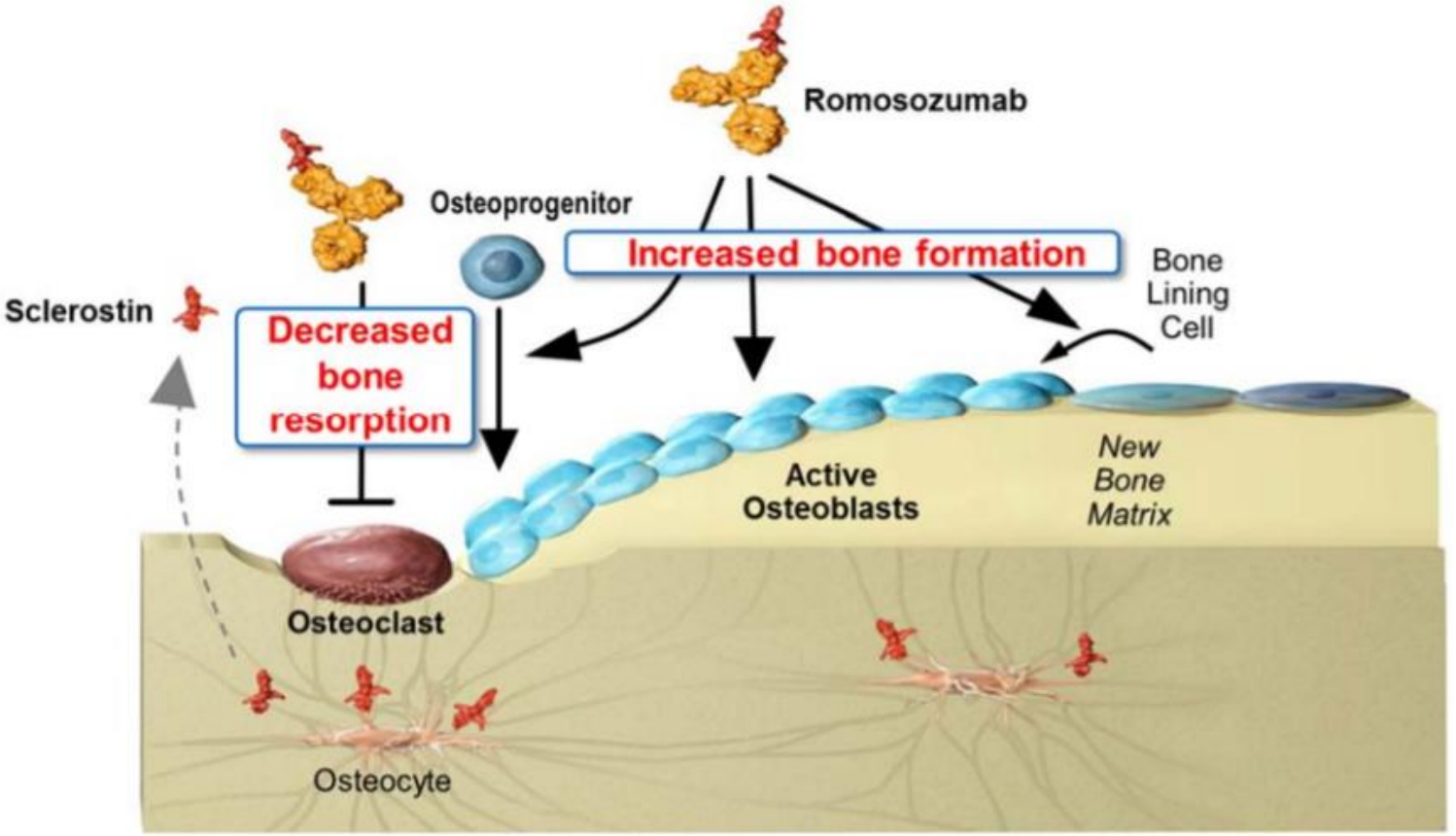
Parathyroid Hormone 1 Receptor (PTH1R)

Enhancing new bone building

Romosozumab: Function and Mechanism

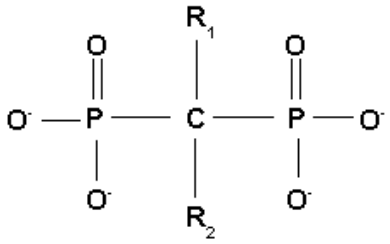
- A humanized monoclonal antibody
- Specifically targets to sclerostin, an inhibitor of Wnt pathway signaling
- Increasing bone formation and decreasing bone resorption.
- Approved by FDA in 2019

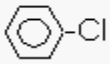
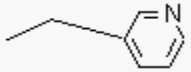
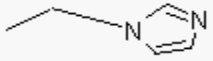
sclerostin's dual effect of promoting osteoclast and inhibiting osteoblast; thus intercepting sclerostin allow increase bone formation and decrease breakdown



Antiresorptive Agents: Bisphosphonates

All bisphosphonate drugs share a common P-C-P "backbone



Agent	R_1 side chain	R_2 side chain
Etidronate	-OH	$-CH_3$
Clodronate	-Cl	-Cl
Tiludronate	-H	-S-  -Cl
Pamidronate	-OH	$-CH_2-CH_2-NH_2$
Neridronate	-OH	$-(CH_2)_5-NH_2$
Olpadronate	-OH	$-(CH_2)_2N(CH_3)_2$
Alendronate	-OH	$-(CH_2)_3-NH_2$
Ibandronate	-OH	$-CH_2-CH_2N$ (CH_3, $(CH_2)_4-CH_3$)
Risedronate	-OH	
Zoledronate	-OH	

Non-N-containing bisphosphonates

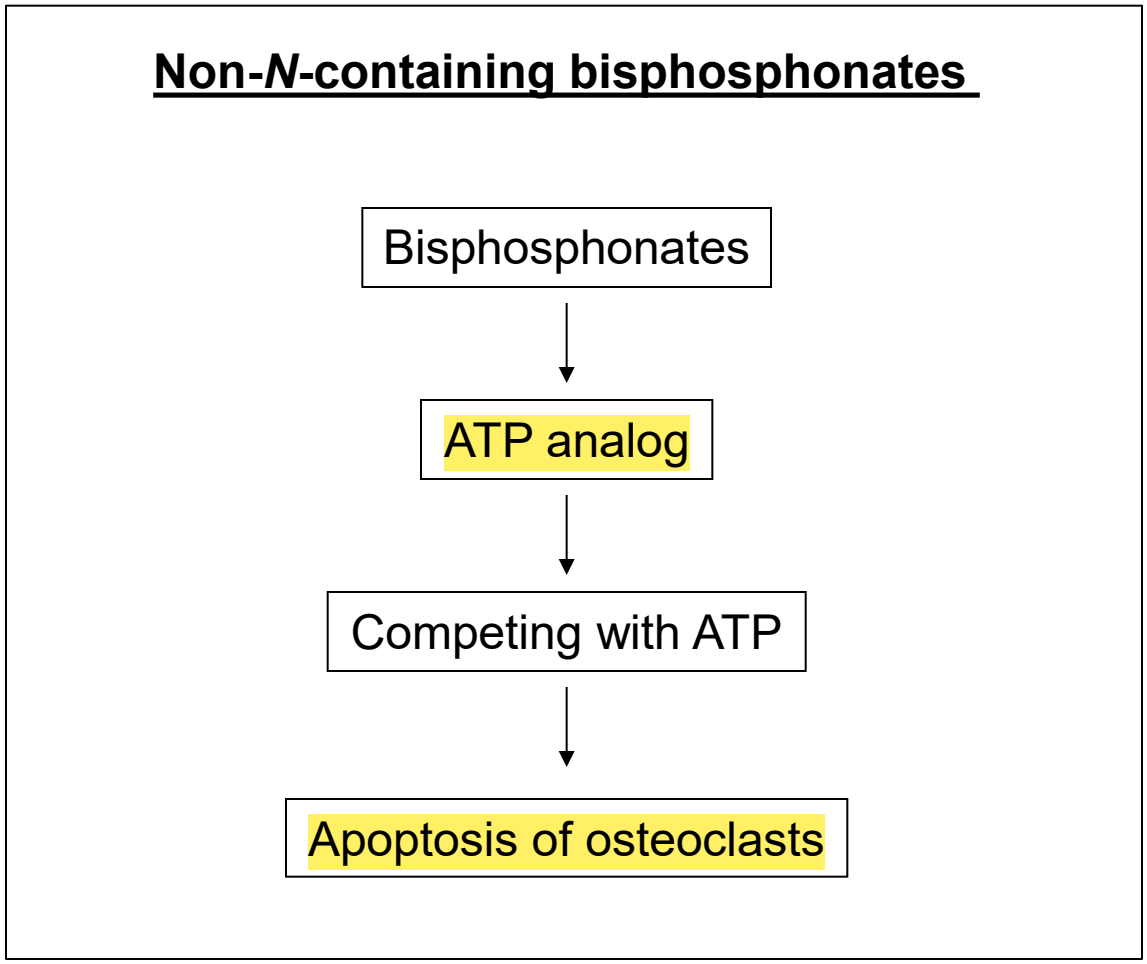
- Etidronate - 1 (relative potency)
- Clodronate - 10
- Tiludronate - 10

N-containing bisphosphonates

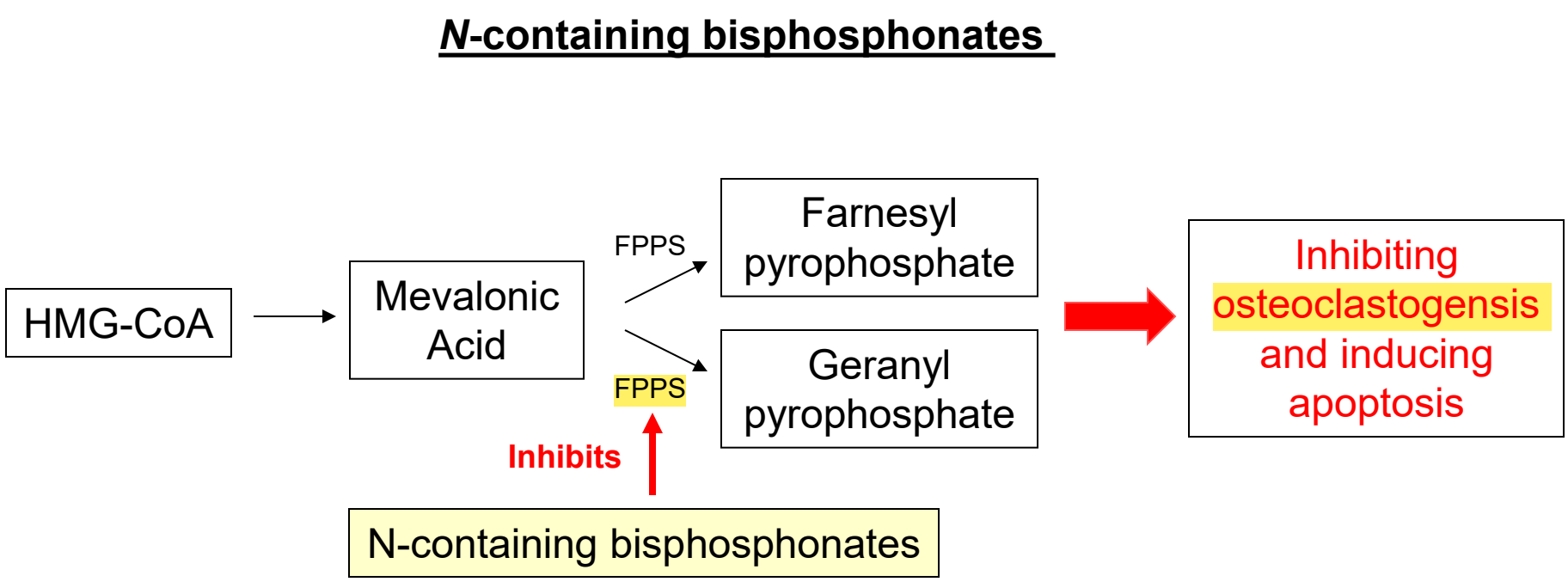
- Pamidronate - 100
- Neridronate - 100
- Olpadronate - 500
- Alendronate - 500
- Ibandronate - 1000
- Risedronate - 2000
- Zoledronate - 10000

Bisphosphonates: Mechanisms of Action

Bisphosphonates have high affinity with bone and when attached to bone tissue, they are "ingested" by osteoclasts



Bisphosphonates: Mechanisms of Action

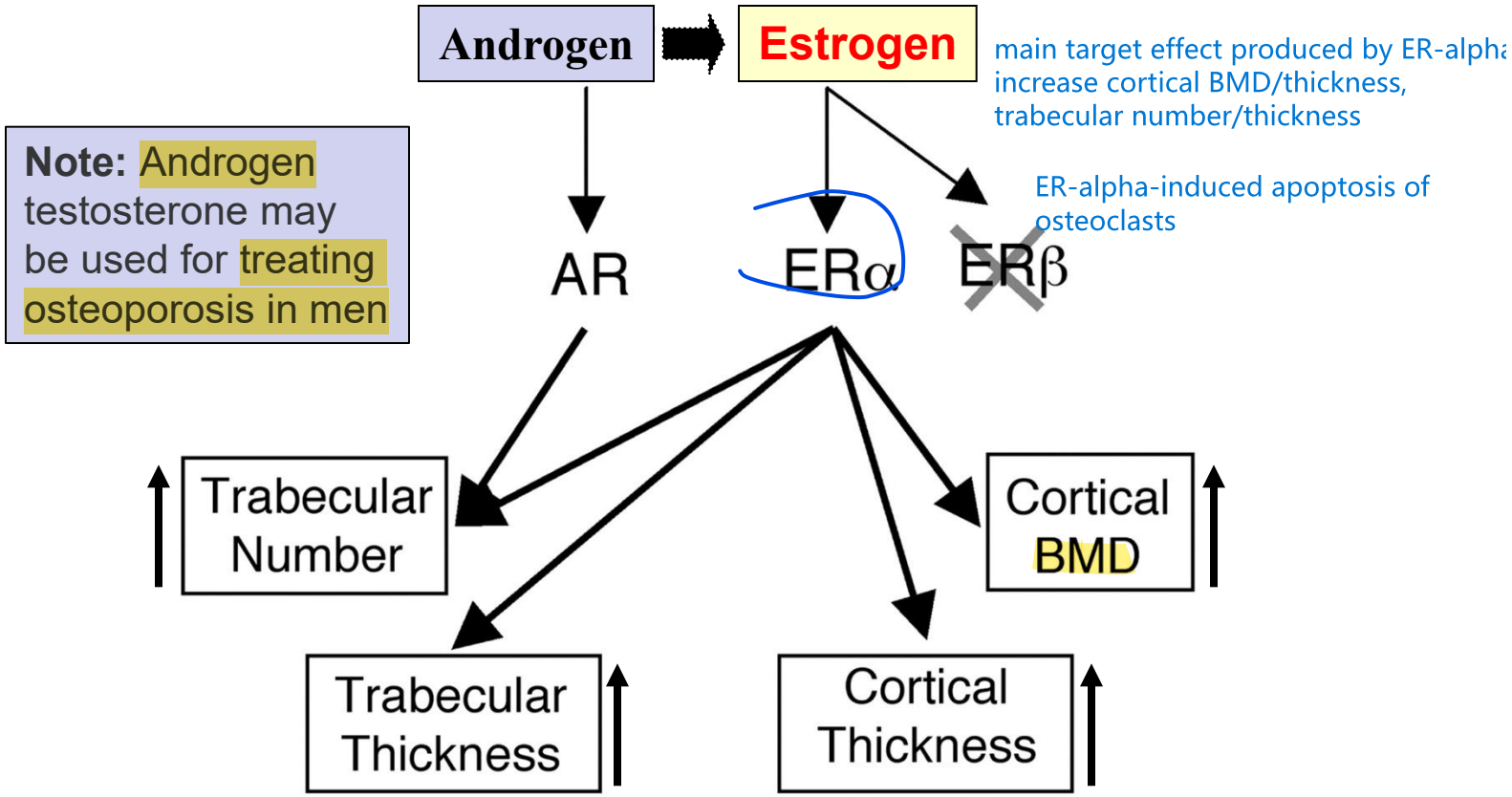


HMG-CoA: 3-hydroxy-3-methyl-glutaryl-CoA reductase

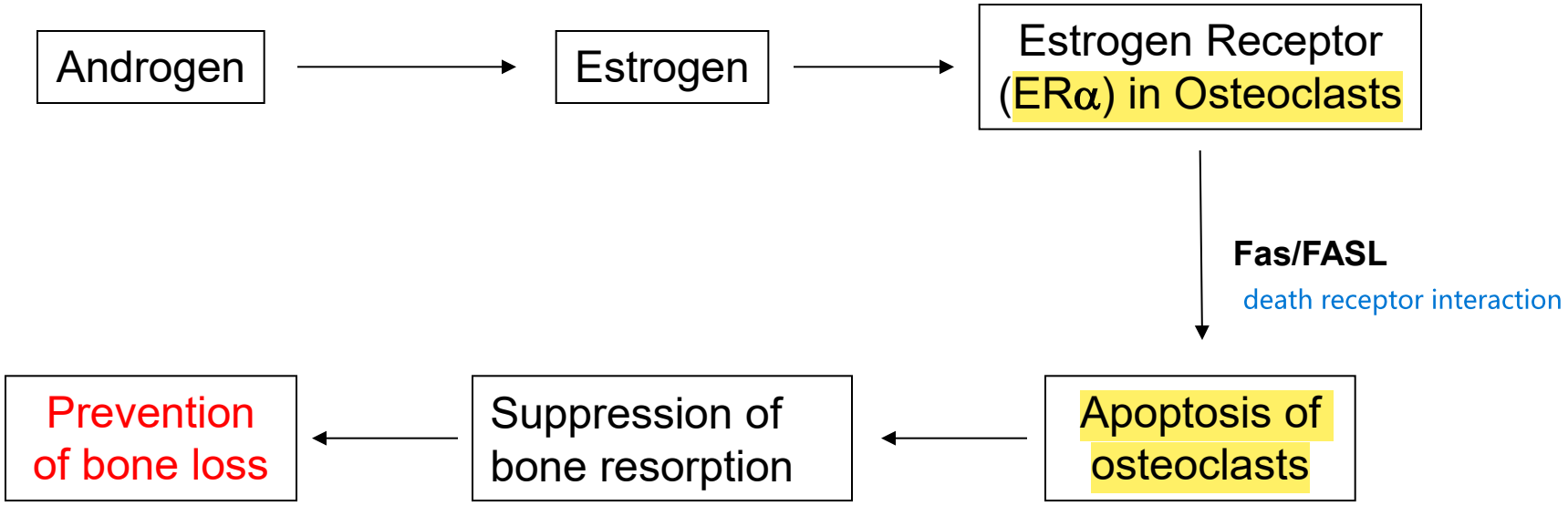
FPPS: farnesyl diphosphate synthase

Antiresorptive Agents:Hormone Replacement Therapy (HRT)

Estrogen alone or a combination of estrogen and progestin



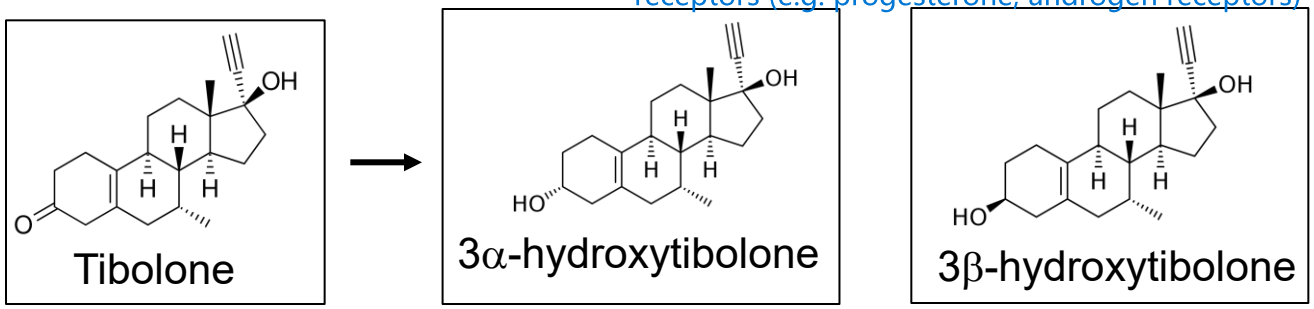
Sex Steroids and Bone: Mechanism



Antiresorptive Agents: Tibolone

A selective tissue estrogenic activity regulator (STEAR)

different to estrogen receptor modulator because this "Regulator" can also have pleiotropic effects on other receptors (e.g. progesterone, androgen receptors)



Estrogen receptor alpha (ERα)

Reducing bone loss
Maintaining healthy bone

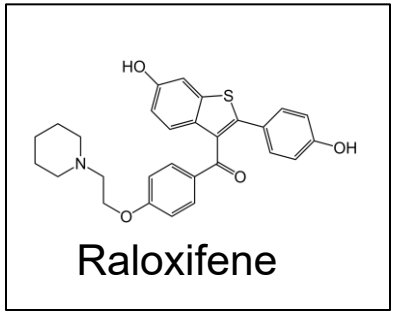
Note: Other tibolone metabolites have agonistic activity to progesterone and androgen receptor.

Antiresorptive Agents: Selective Estrogen Receptor Modulators (SERMs)

modulator specific to estrogen receptor, no affinity to other receptors such as progesterone androgen unlike regulator

Raloxifene

simultaneous dual mechanism depending on tissue type;
agonistic on bone, but antagonistic in breast/uterus (reduced risk of breast/endometrial cancer)



Raloxifene

Antagonistic activity

ERα in breast and uterus

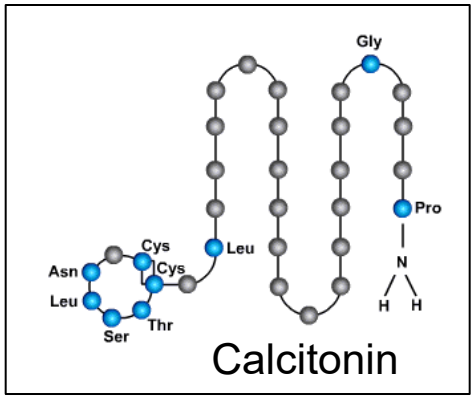
Reduced side effects in those tissues

Agonistic activity

Estrogen receptor alpha (ERα) in bone

Reducing bone loss
Maintaining healthy bone

Antiresorptive Agents: Calcitonin



Calcitonin

Note: This drug is safer but less effective than other osteoporosis medications. For that reason, it's considered to be one of the last treatment options.

not as potent; so reserved as last line, not responding to previous agents

Calcitonin receptor
A GPCR with $G\alpha_s$

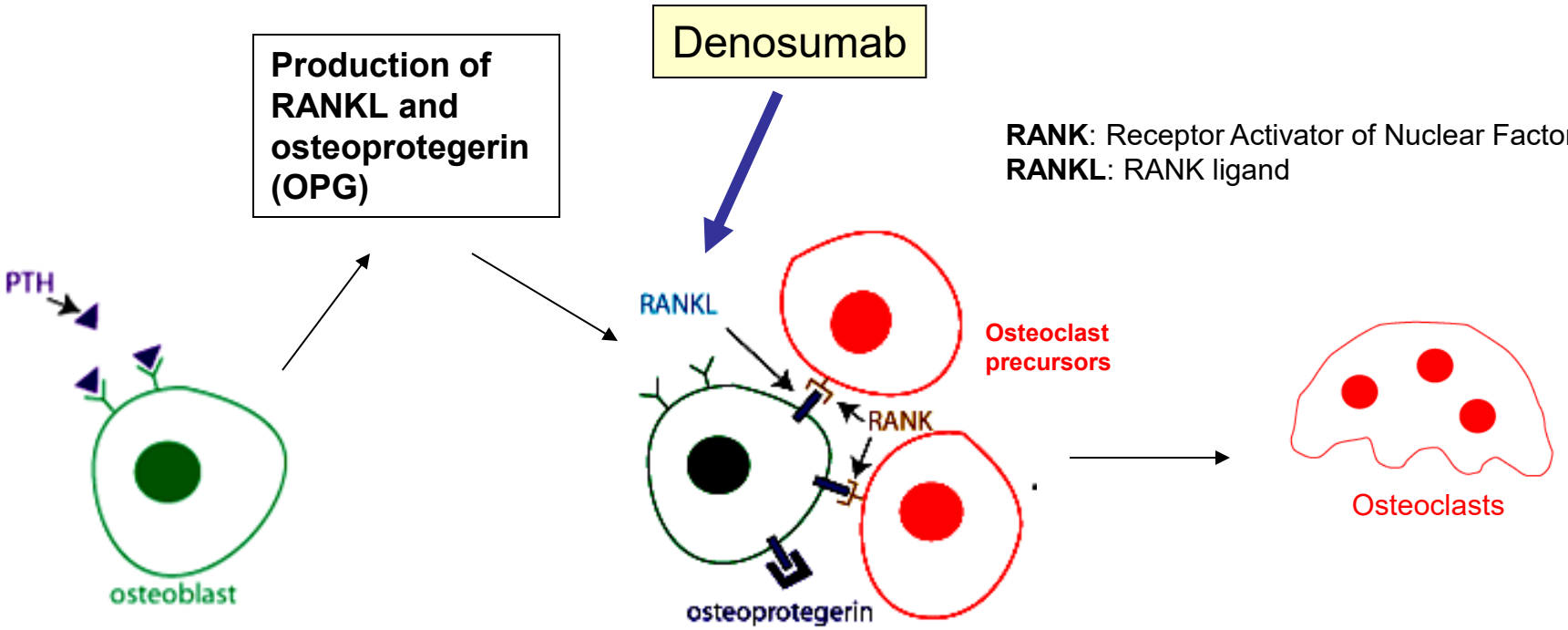
Activating AC/cAMP signaling pathway

Inhibits osteoclast activity and slow bone breakdown

Denosumab: Function and Mechanism

- Formerly known as AMG 162
- A fully-humanized monoclonal antibody
- Specifically targets to RANKL to block the osteoclastogenesis

block the RANK ligand signaling by osteoblasts; prevent activation of osteoclast precursors



Nonpharmacological management of osteoporosis

- Adequate calcium supplement
- Vitamin D intake
- Weight-bearing exercise
- Smoking cessation
- Limitation of alcohol/caffeine consumption associated reduce calcium uptake from the diet
- Fall-prevention techniques.

Treatment of Other Bone Disorders

Primary hyperparathyroidism
- Removal of parathyroid adenoma(s) by surgery
- Hormone therapy
- Bisphosphonates

Renal osteodystrophy (bone disease from kidney failure)
- Treatment of kidney problem (dialysis, transplantation)
- Special diets
- Calcitriol

Paget's disease of bone
- Bisphosphonates (alendronate, risedronate, tiludronate, etidronate)

Osteogenesis imperfecta
- Rehabilitation
- Physical therapy
- Bisphosphonates

Rickets and Osteomalacia
- Vitamin D
- Calcium

Combination Therapies

Drugs with different mechanisms of action are combined as combinational therapies

combination of anabolic + anti-reabsorptive therapy

- Bisphosphonates with hormone therapy
- Anti-absorptive Agents with anabolic PTH
- Drug therapy with calcium and Vitamin D
- Therapy with Dietary supplements

note: dual action of romosozumab