PHARMACOTHERAPY | CONTINUING PHARMACY EDUCATION

Osteoporosis

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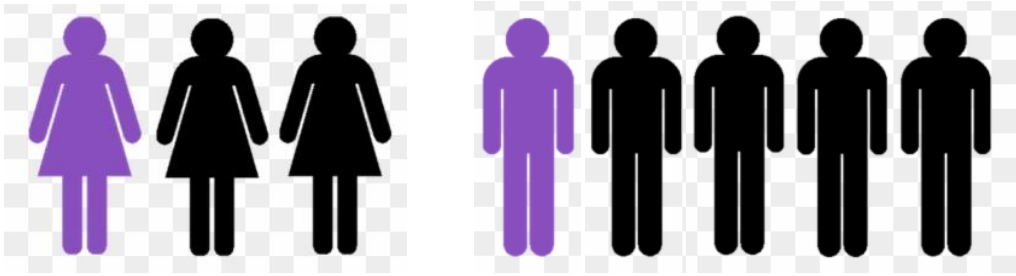
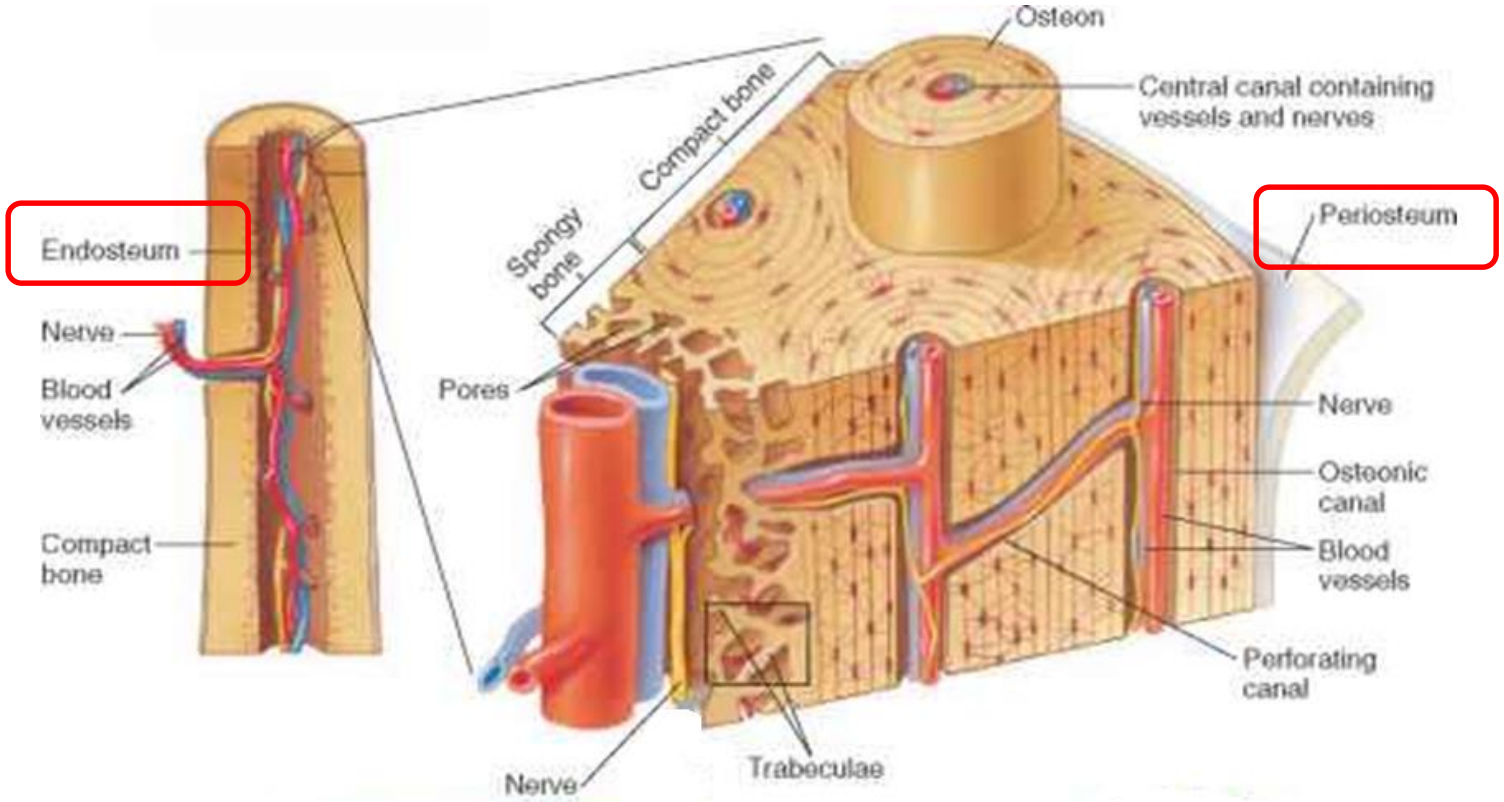
Osteoporosis

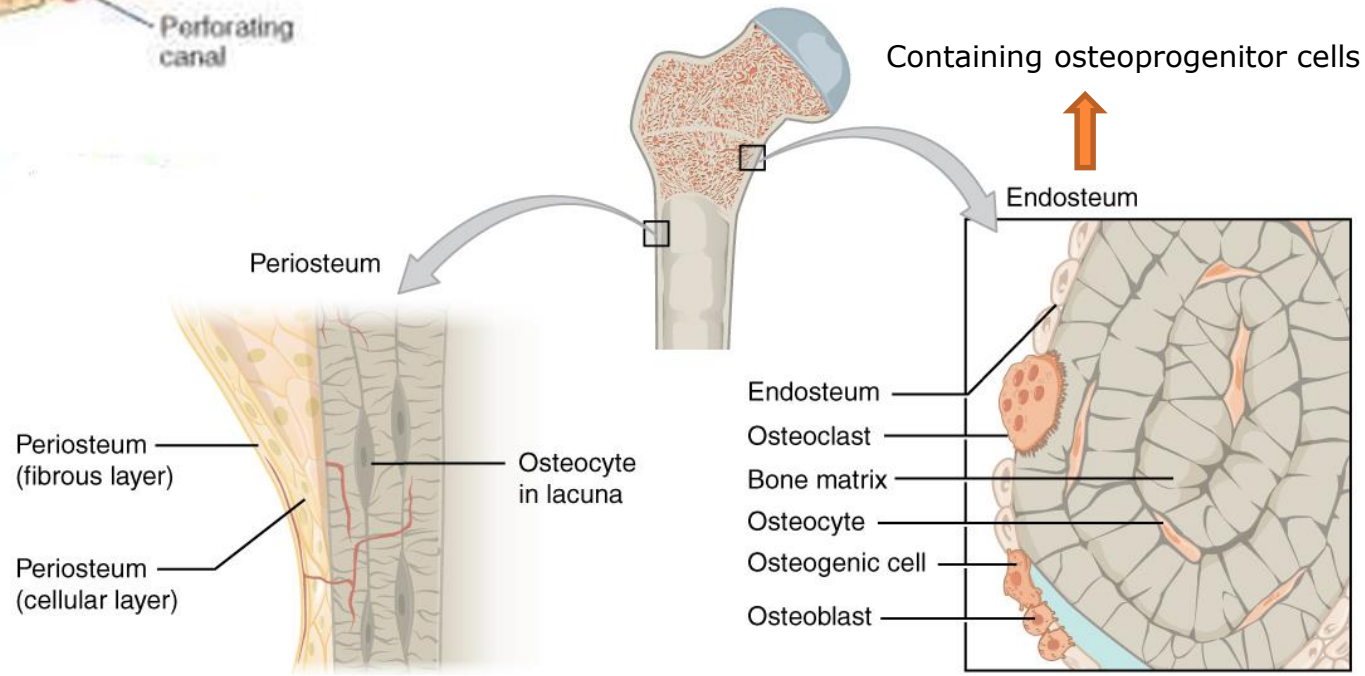
- Greek words:
  - **Osteon (bone)**
  - **Poros (pore)**

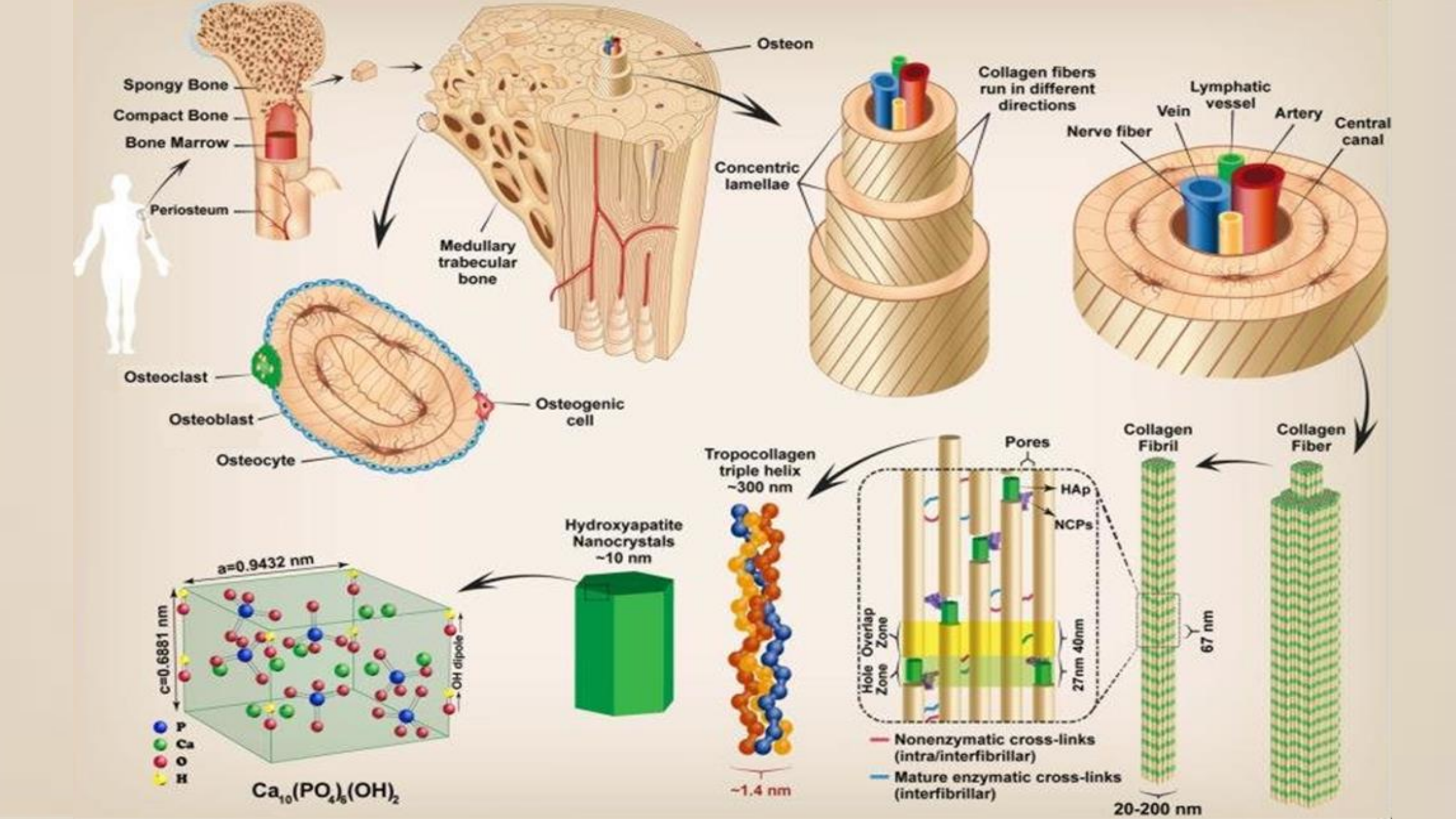
- **WHO defines Osteoporosis** as a disease
  - "Characterized by **low bone mass** & **microarchitectural deterioration of bone tissue**, leading to enhanced **bone fragility** & a consequent **increase in fracture risk**."

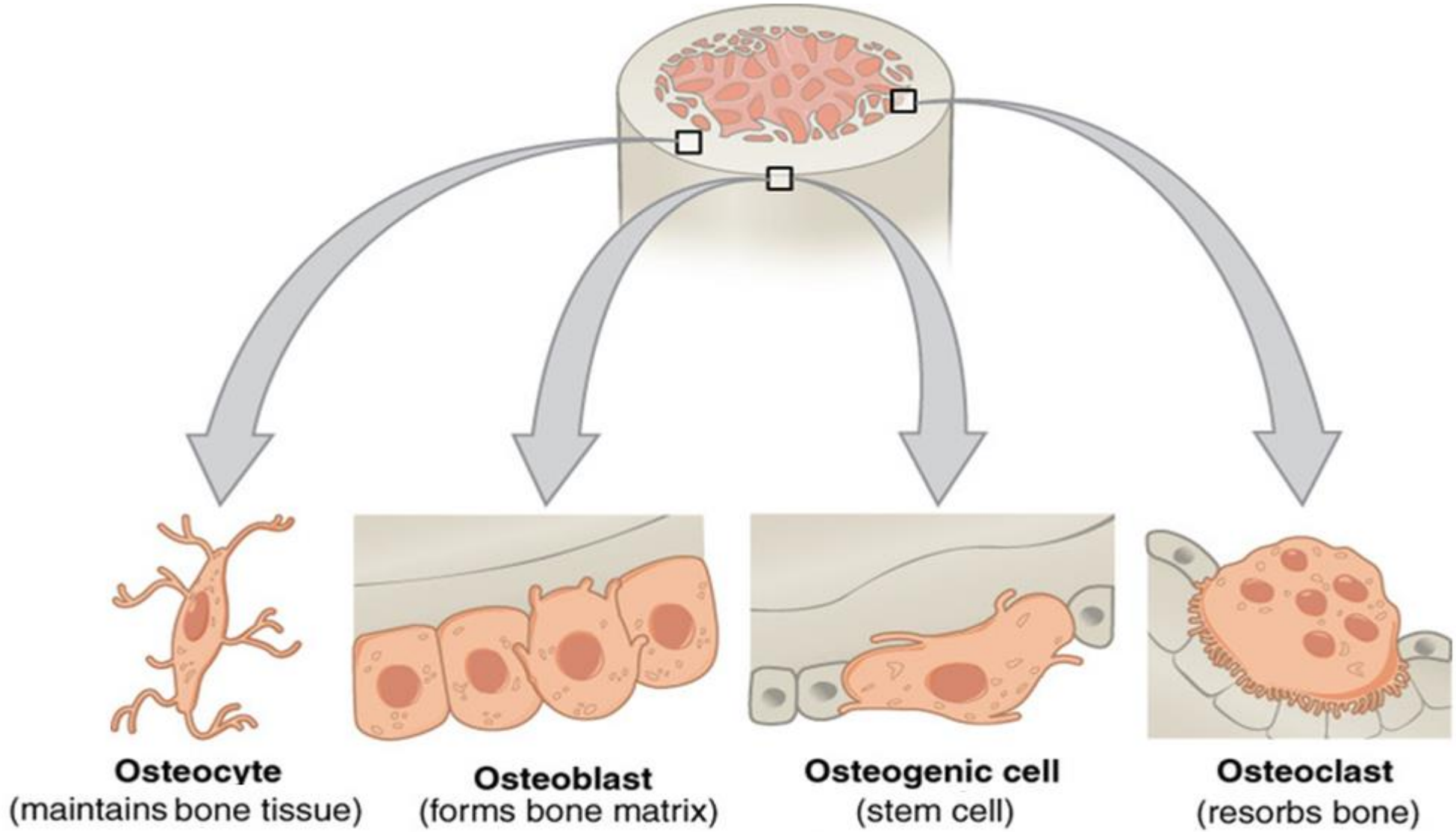
- Worldwide, **1 in 3 women & 1 in 5 men** over the age of 50 years will experience **osteoporotic fractures** in their lifetime.




Osteon
Central canal containing vessels and nerves
Compact bone
Spongy bone
Endosteum
Periosteum
Nerve
Blood vessels
Pores
Nerve
Osteonic canal
Blood vessels
Compact bone
Perforating canal
Nerve
Trabeculae


Containing osteoprogenitor cells
Endosteum
Periosteum
Periosteum (fibrous layer)
Osteocyte in lacuna
Periosteum (cellular layer)
Containing osteoprogenitor cells
Endosteum
Osteoclast
Bone matrix
Osteocyte
Osteogenic cell
Osteoblast


Spongy Bone
Compact Bone
Bone Marrow
Periosteum
Osteon
Medullary trabecular bone
Concentric lamellae
Collagen fibers run in different directions
Nerve fiber
Vein
Lymphatic vessel
Artery
Central canal
Osteoclast
Osteoblast
Osteocyte
Osteogenic cell
Collagen Fiber
Collagen Fibril
Pores
HAp
NCPs
Hole Zone
Overlap Zone
27nm 40nm
67 nm
20-200 nm
Tropocollagen triple helix ~300 nm
~1.4 nm
Nonenzymatic cross-links (intra/interfibrillar)
Mature enzymatic cross-links (interfibrillar)
Hydroxyapatite Nanocrystals ~10 nm
a=0.9432 nm
c=0.6881 nm
OH dipole
P
Ca
O
H
$Ca_{10}(PO_4)_6(OH)_2$

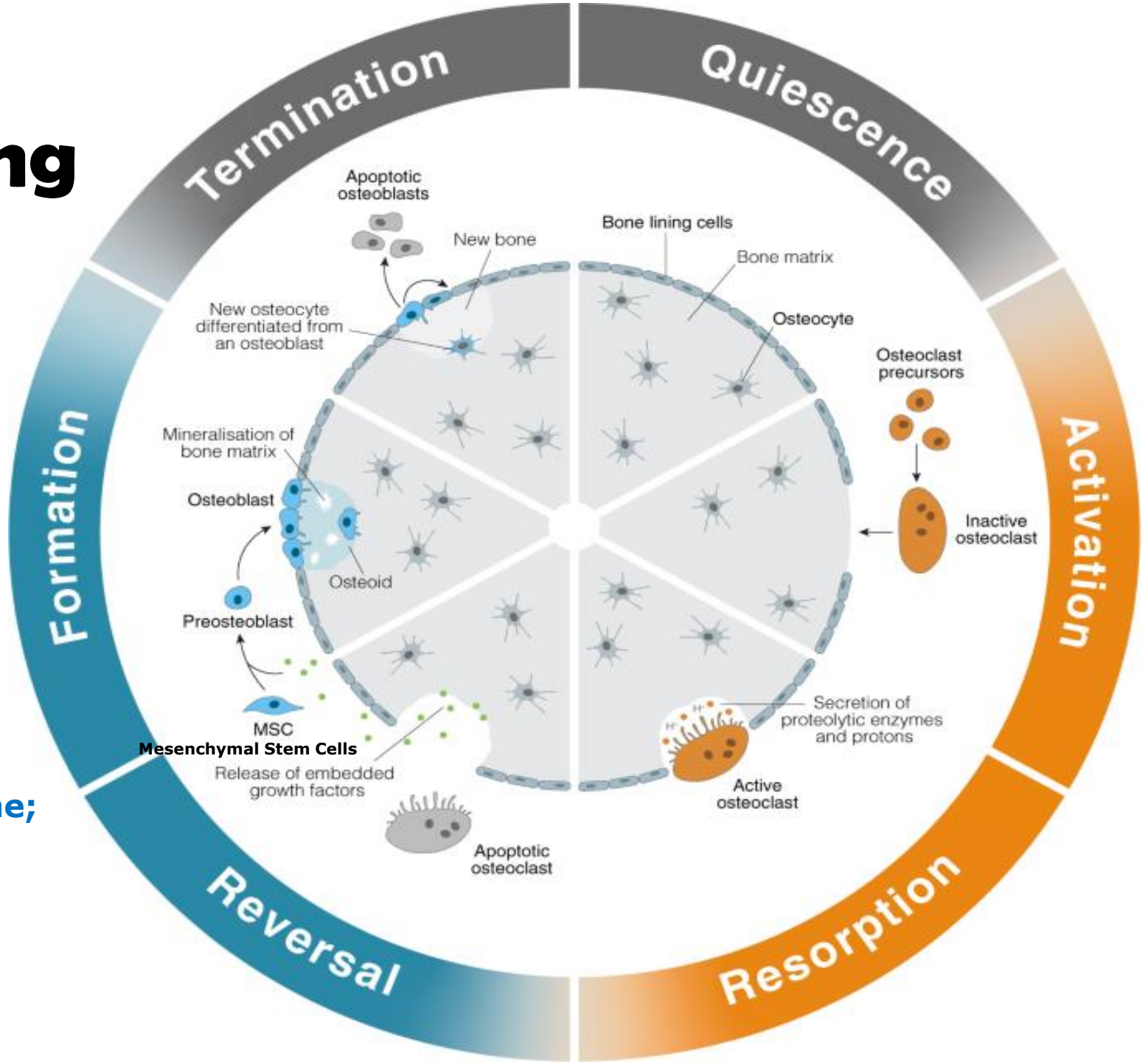

Osteocyte
(maintains bone tissue)
Osteoblast
(forms bone matrix)
Osteogenic cell
(stem cell)
Osteoclast
(resorbs bone)

Bone-Remodeling

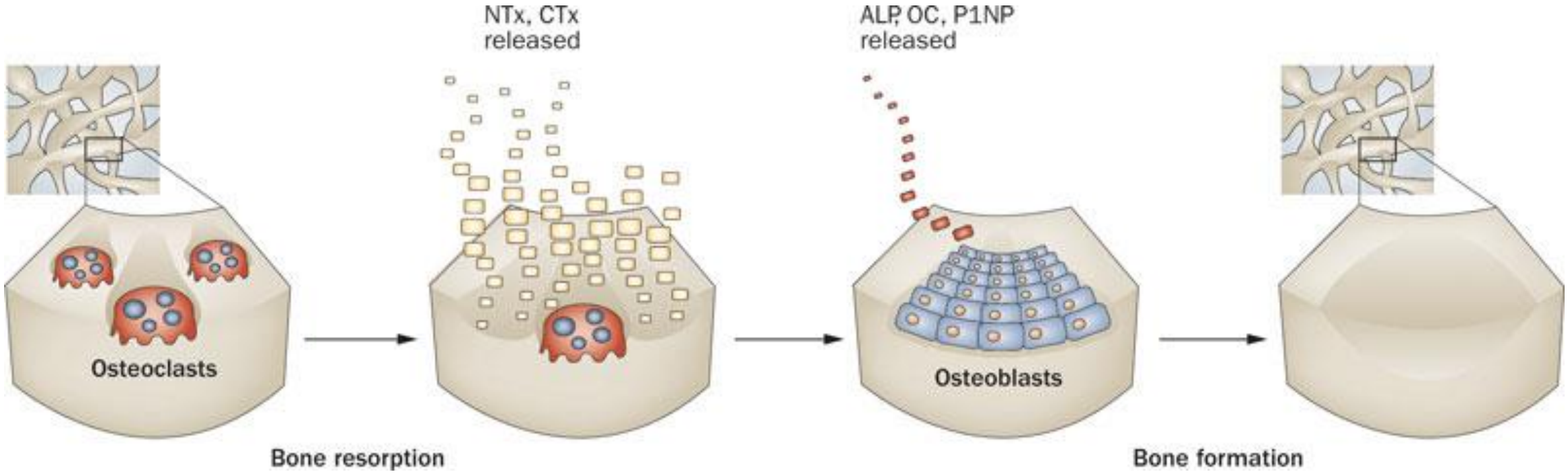
- **Bone resorption:**
  - **lasts 3-5 weeks**
- **Bone formation:**
  - **lasts 3-5 months**

- **10% of adult skeleton is remodelled each year.**

- **PTH & Glucocorticoid;**
  - Associated with **bone resorption**
- **Calcitonin, Estrogen, Testosterone;**
  - Associated with **bone formation**



Bone Turnover Markers



- NTx, aminoterminal crosslinking telopeptide of type I collagen
- CTx, carboxyterminal crosslinking telopeptide of type I collagen

- Alkaline phosphatase (ALP)
- Osteocalcin (OC)
- Procollagen type 1 aminoterminal propeptide (P1NP)

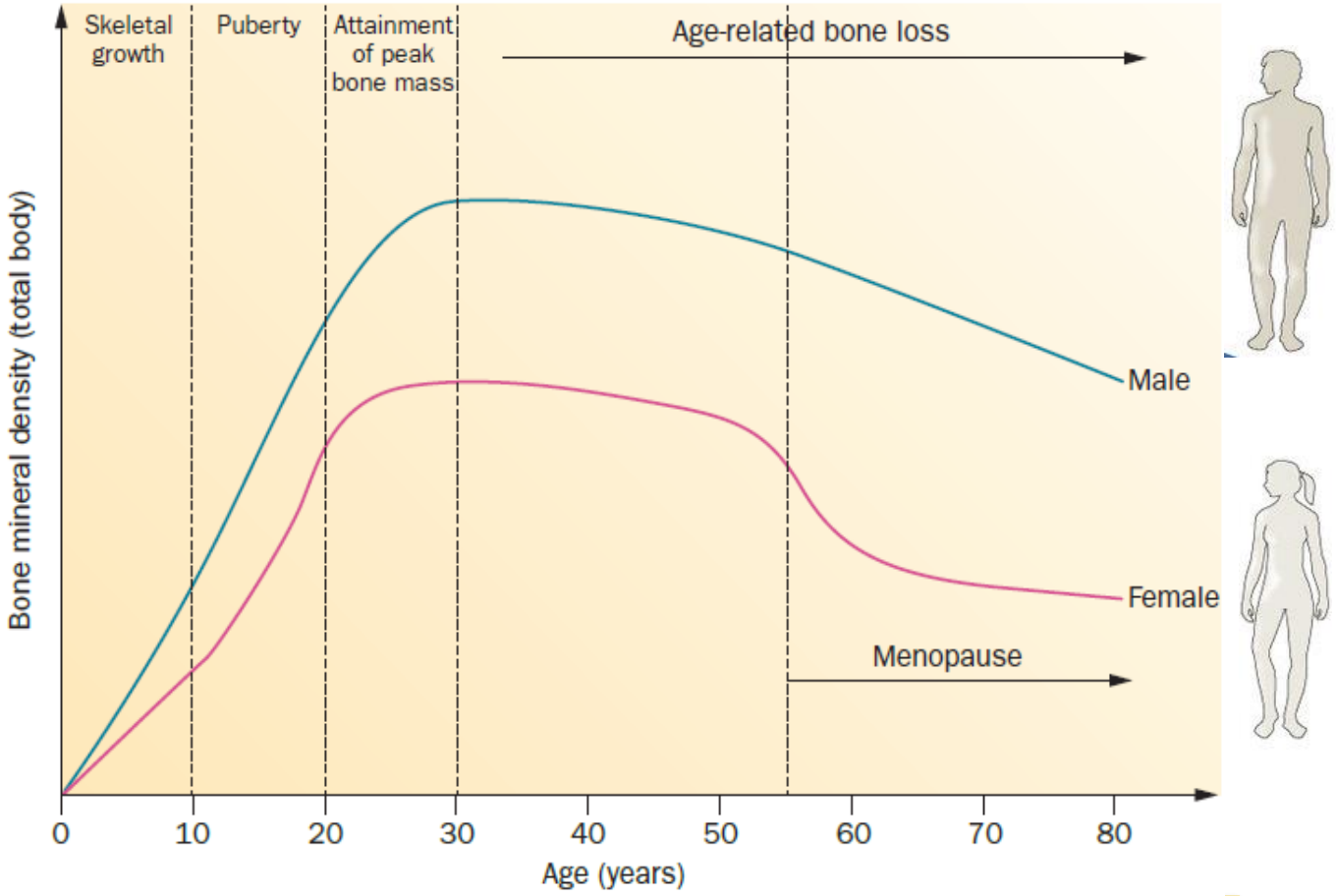
Changes in Bone Mass

❖Peak Bone Mass

- Is highly dependent on **genetic factors** that account for **60-80%** of the variability.
- The remaining **20-40%** is influenced by **modifiable factors** such as nutritional intake (e.g., calcium, vitamin D, protein), exercise, adverse lifestyle practices (e.g., smoking), hormonal status, & certain diseases & medications.

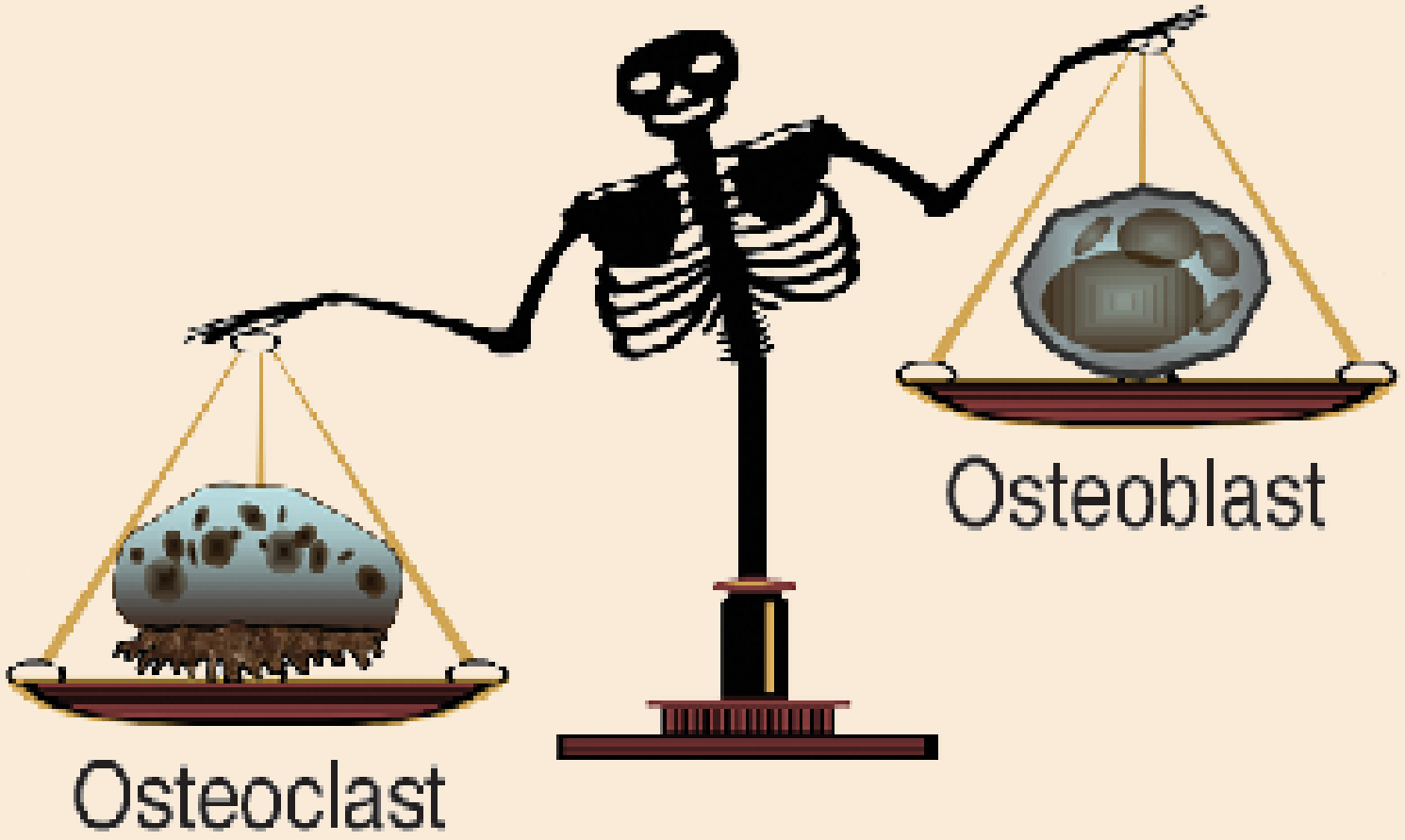
- Women experience a phase of **accelerated bone loss for 3 years after the menopause**. Afterwards this returns to the same rate as in men, i.e. **1% per year**.

- By age 70-80, 30-40% of bone mass is lost in women.

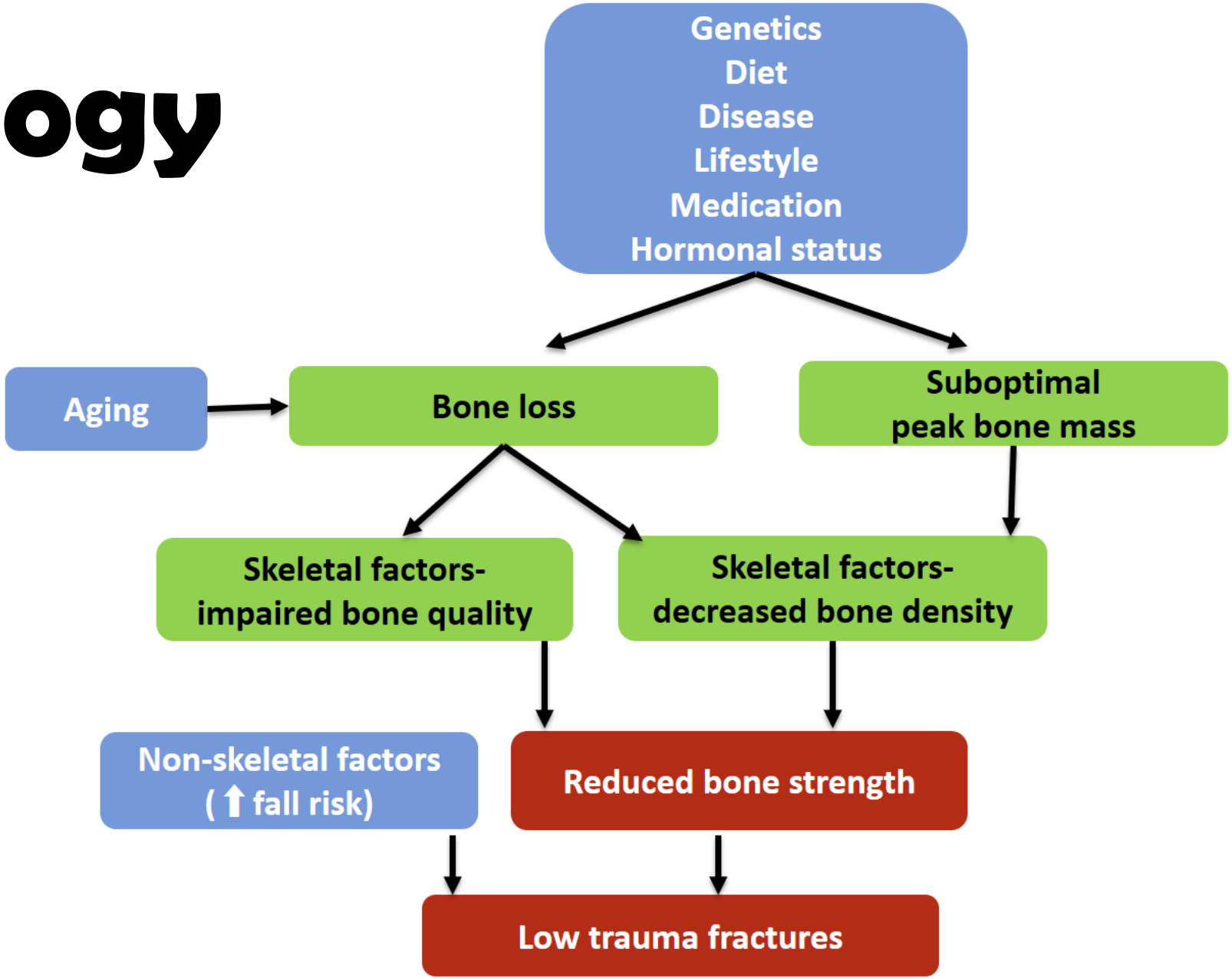


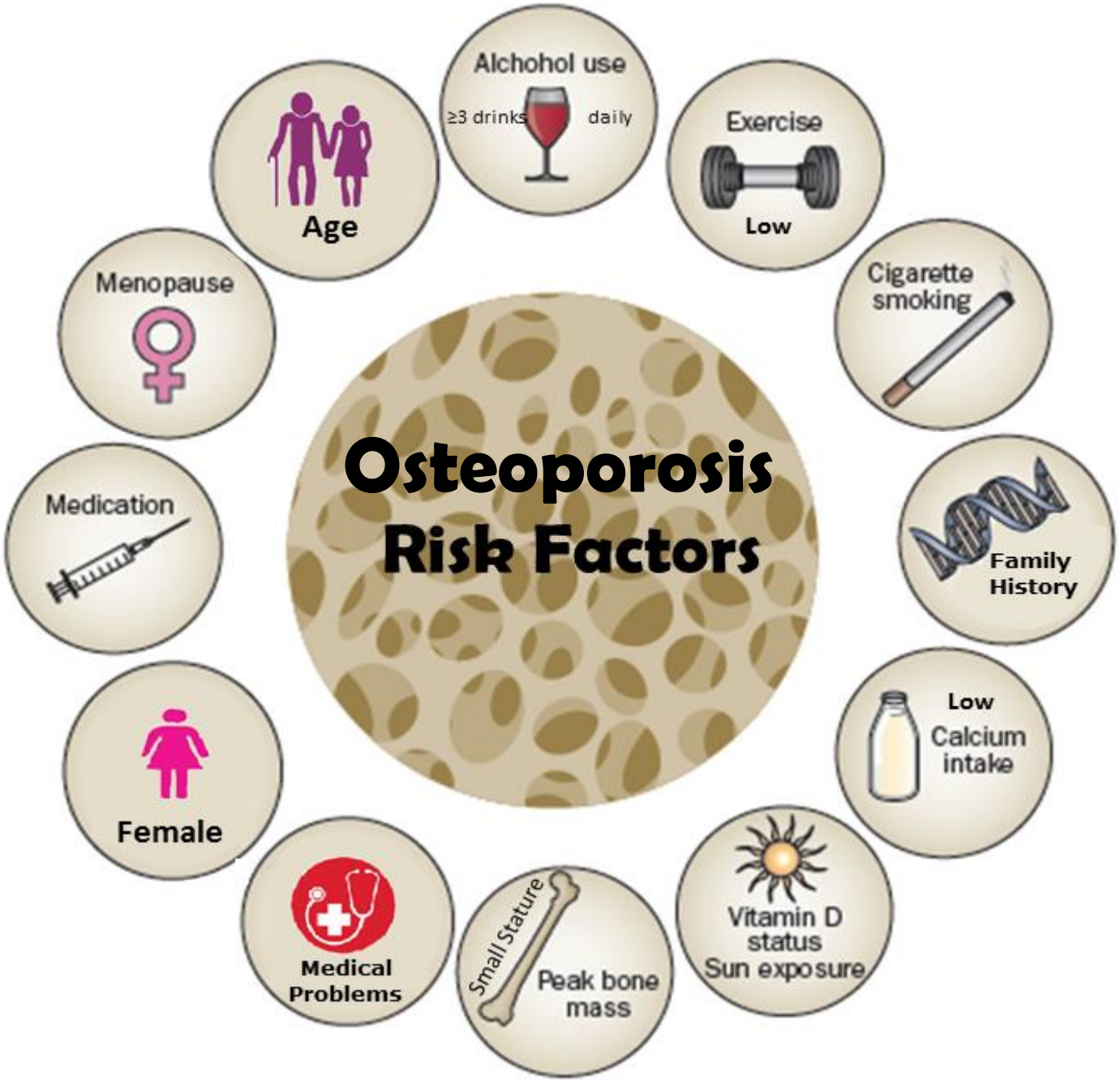
95% of peak bone mass is attained by age 18-20 years, with small gains until age 30 years.

Pathophysiology of Osteoporosis



Etiology


Genetics
Diet
Disease
Lifestyle
Medication
Hormonal status
Aging
Bone loss
Suboptimal peak bone mass
Skeletal factors- impaired bone quality
Skeletal factors- decreased bone density
Non-skeletal factors (⬆ fall risk)
Reduced bone strength
Low trauma fractures


Osteoporosis
Risk Factors
Alchohol use
≥3 drinks
daily
Exercise
Low
Cigarette smoking
Family History
Low
Calcium intake
Vitamin D status
Sun exposure
Peak bone mass
Small Stature
Medical Problems
Female
Medication
Menopause
Age

Calcium & Vitamin D Intakes

Life Stage Group	RDA Calcium	RDA Vitamin D
Males		
19–50 years	1,000 mg	600 IU (15 mcg)
51–70 years		
>70 years	1,200 mg	
Females (Nonpregnant)		
19–50 years	1,000 mg	600 IU (15 mcg)[a]
51–70 years	1,200 mg	
>70 years		800 IU (20 mcg)[a]

[a]NOF recommends vitamin D 800 to 1,000 IU in patients ≥ 50 years.

IU, International Unit; RDA, Recommended Dietary Allowance.

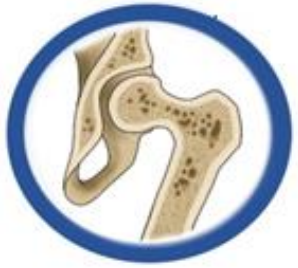
Vitamin D conversions: 1 mcg = 40 IU

Selected Medications Associated with ⬆ Bone Loss &/or Fracture Risk

Anticonvulsants (phenytoin, carbamazepine, phenobarbital, valproic acid)	↓BMD & ↑fracture risk; **↑vitamin D metabolism**
Aromatase inhibitors (letrozole, anastrozole)	↓BMD & ↑fracture risk; **↓ estrogen concentrations**
Furosemide	↑fracture risk; **↑calcium renal elimination**
Glucocorticoids	↓BMD & ↑fracture risk; dose & duration dependent
GnRH analogs (leuprolide, goserelin)	↓BMD & ↑fracture risk; **↓ sex hormone production**
Heparin or LMWH	↓BMD & ↑fracture risk (UFH >>> LMWH) with long-term use (e.g., >6 mo); **↓ osteoblast function & ↑ osteoclast function**
Medroxyprogesterone acetate depot	↓BMD; **↓ estrogen concentrations**
PPI therapy (long-term therapy)	↑vertebral & hip fracture risk; possible **calcium malabsorption** secondary to acid suppression for carbonate salts
SSRIs	↑hip fracture risk; **↓osteoblast activity**
SGLT2 Inhibitors	↓BMD & ↑fracture risk; **alteration in Ca & P hemostasis; ↑ osteoclast function**
Thiazolidinediones (pioglitazone)	↓BMD & ↑fracture risk; **↓ osteoblast function**
Excessive thyroid supplementation	↓BMD & ↑fracture risk (> in men); risk ↑ with TSH concentration <0.1 µIU/mL (<0.1 mIU/L); possible **increase in bone resorption**

Osteoporosis Diagnosis

- Based on measurement of **bone mineral density (BMD)** by **dual energy X-ray absorptiometry (DEXA)** at either **femur neck region of hip or lumbar spine**.



Proximal femur

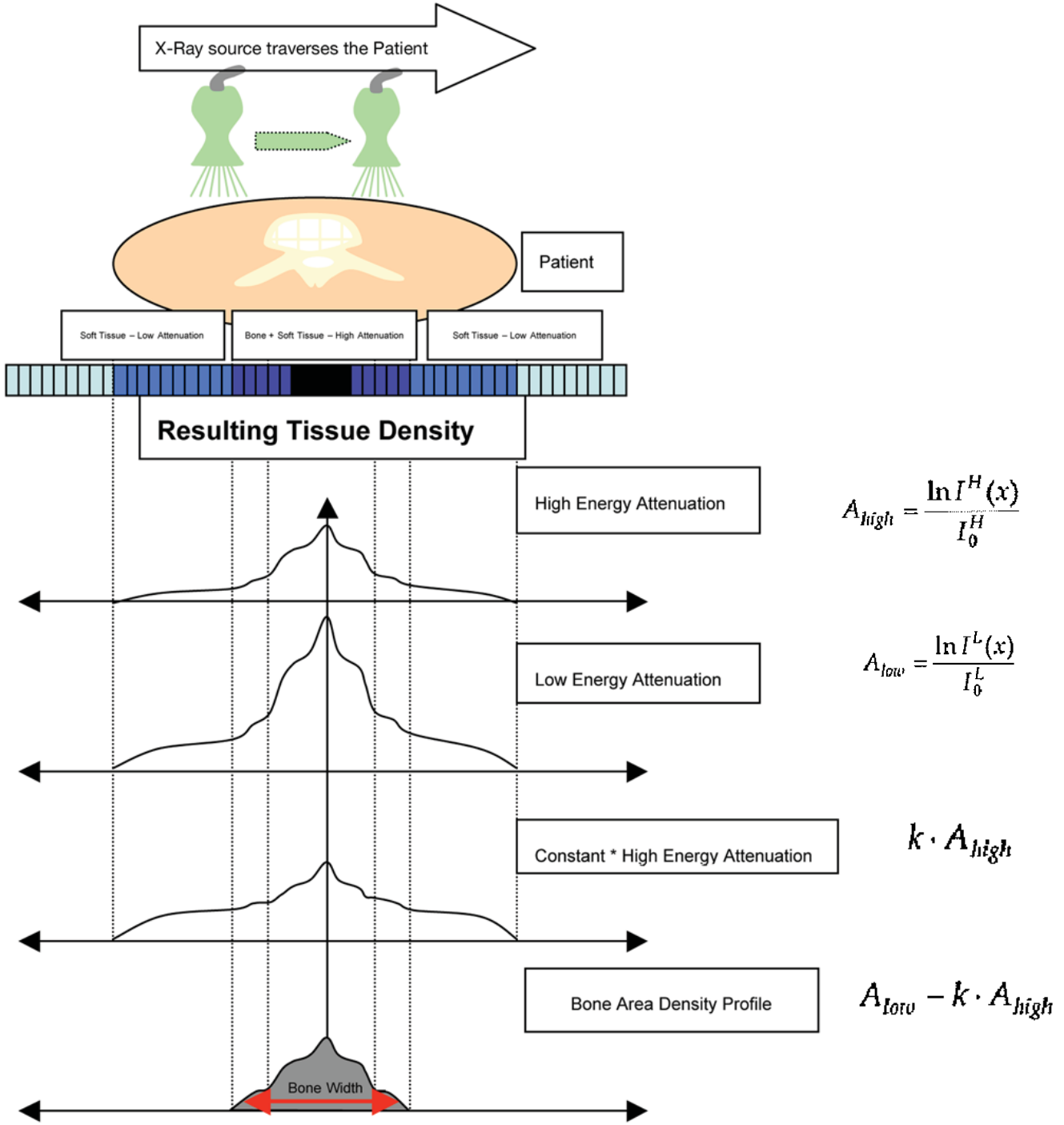
Lumbar spine

Forearm

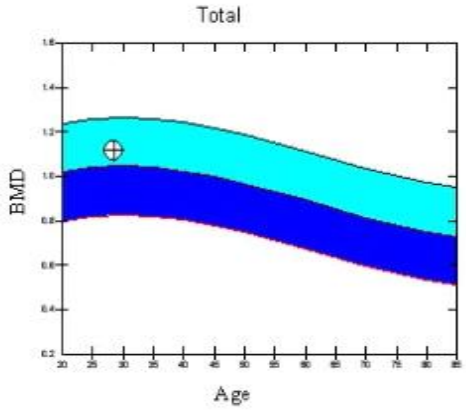
- **BMD test** measures the **amount of mineral (Calcium)** in a specific area of the bone. The more mineral in the bone measured, the greater is the bone density or bone mass.

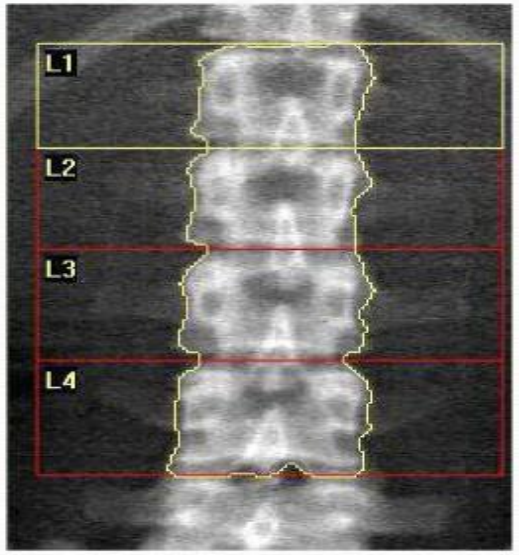
- **DEXA machine** sends a thin beam of low-dose X-rays with **two distinct energy peaks** through the bones being examined. One peak is absorbed mainly by soft tissue & the other by bone. The soft tissue amount can be subtracted from the total & what remains is a patient's bone mineral density.

- **BMD refers to the amount or weight of bone mass per area & is measured in g/cm².**

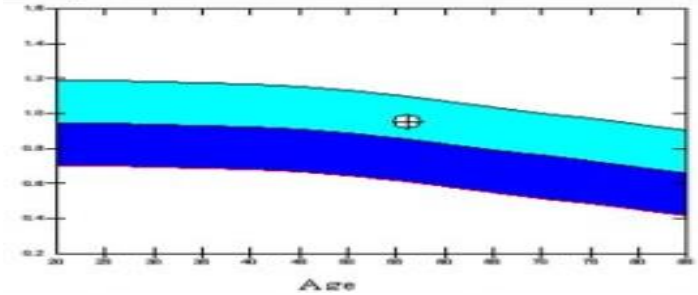


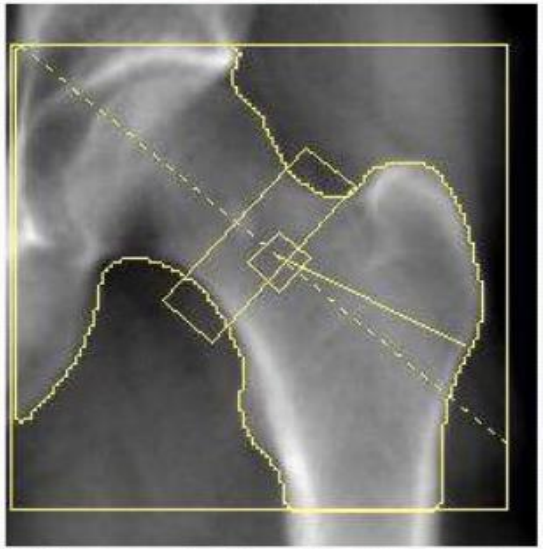
Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T - Score	Z - Score
L1	12.11	12.01	0.992	0.6	0.6
L2	12.29	14.22	1.157	1.2	1.2
L3	14.27	16.18	1.134	0.5	0.5
L4	15.72	18.28	1.163	0.4	0.4
Total	**54.39**	**60.70**	**1.116**	**0.6**	**0.6**



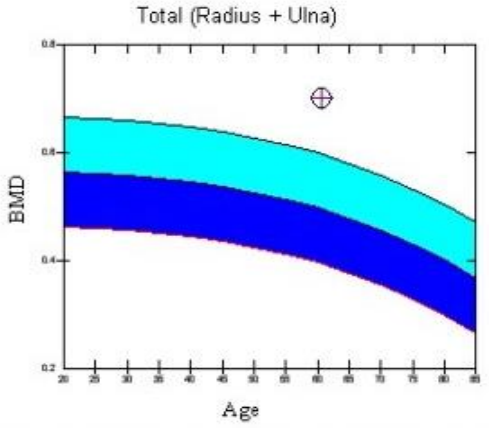


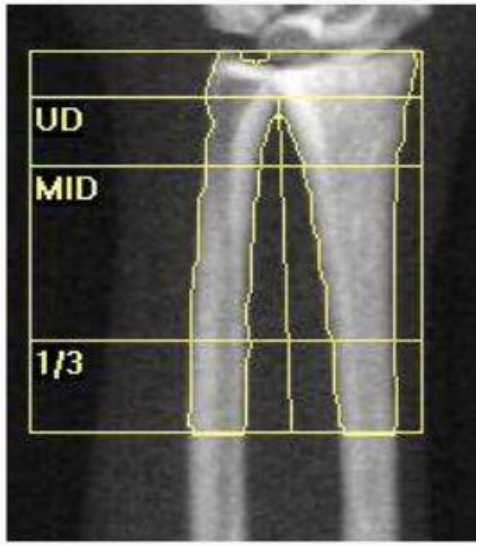
Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T - Score	Z - Score
Neck	5.45	4.82	0.884	0.3	1.4
Troch	12.25	9.04	0.738	0.3	1.1
Inter	21.94	23.90	1.089	-0.1	0.4
Total	**39.64**	**37.75**	**0.952**	**0.1**	**0.8**
Ward's	1.13	0.82	0.722	-0.1	1.7





Radius + Ulna	Area (cm²)	BMC (g)	BMD (g/cm²)	T - Score	Z - Score
UD	4.73	3.71	0.785	7.3	8.3
MID	10.70	7.23	0.676	1.7	3.1
1/3	4.16	2.76	0.664	-0.4	1.0
Total	**19.58**	**13.70**	**0.700**	**2.7**	**4.0**





- **T-score** shows how much your bone mass differs from the bone mass of an average **healthy 30 year old adult matched for gender**.

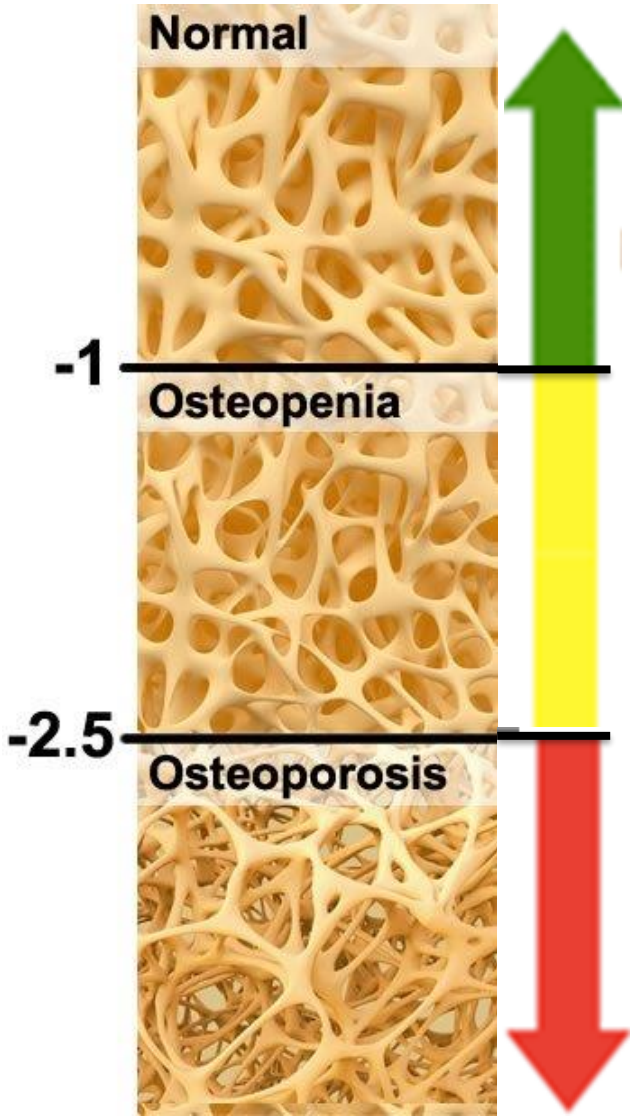
$$\text{T-score} = \frac{\text{Measured BMD} - \text{Young adult mean BMD}}{\text{Young adult population SD}}$$

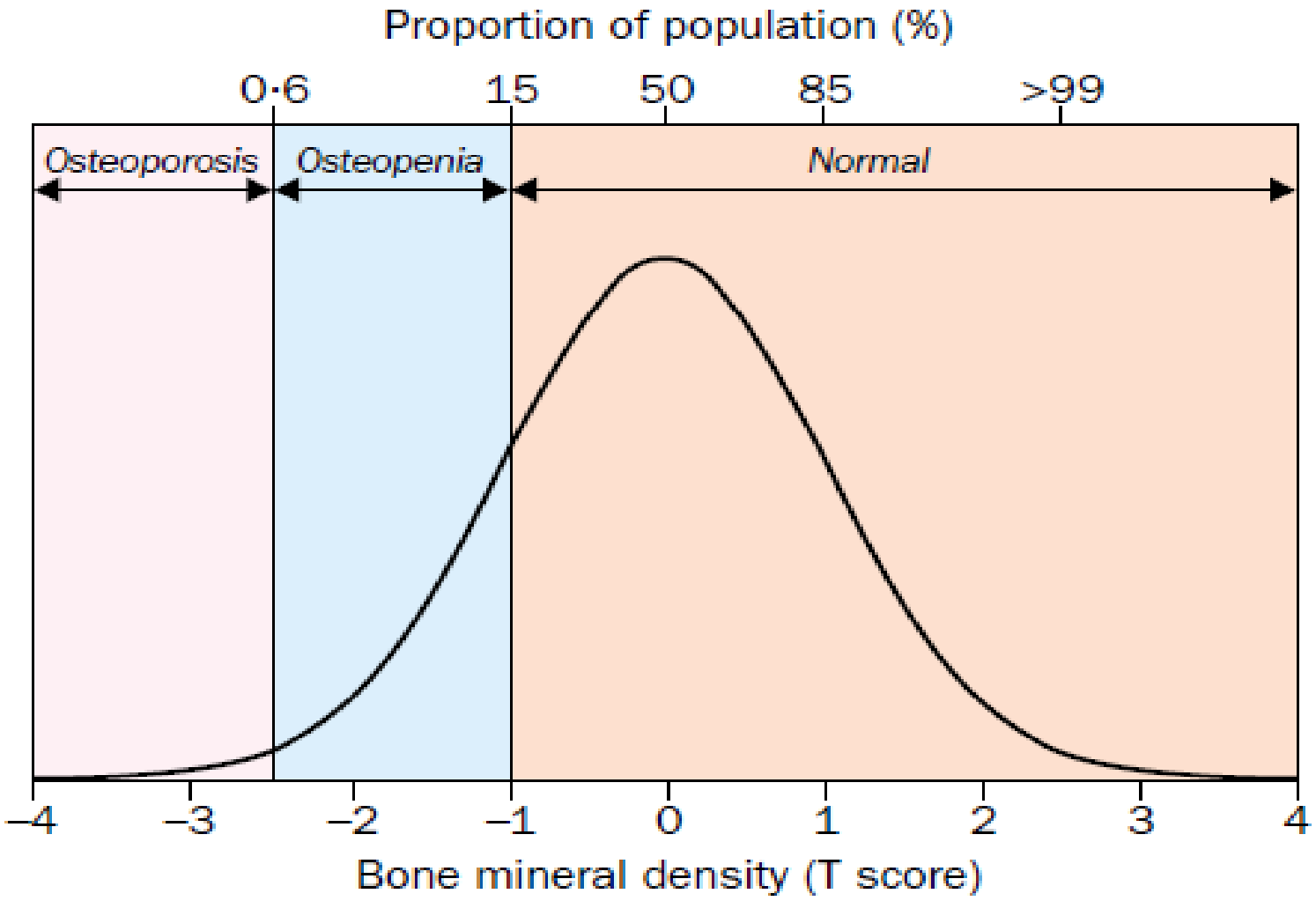
- **Z-score** compares your bone density to the average bone density of people **your own age & gender**.

$$\text{Z-score} = \frac{\text{Measured BMD} - \text{Age-matched mean BMD}}{\text{Age-matched population SD}}$$

Z-score is helpful in diagnosing **secondary osteoporosis &** is always used for **children, young adults, women who are pre-menopausal, & men under age 50**.

Classification	T-score
Normal	−1.0 or higher
Low bone mass (osteopenia)	Between −1.0 and −2.5
Osteoporosis	−2.5 or lower
Severe osteoporosis	−2.5 or lower and personal history of fragility fracture

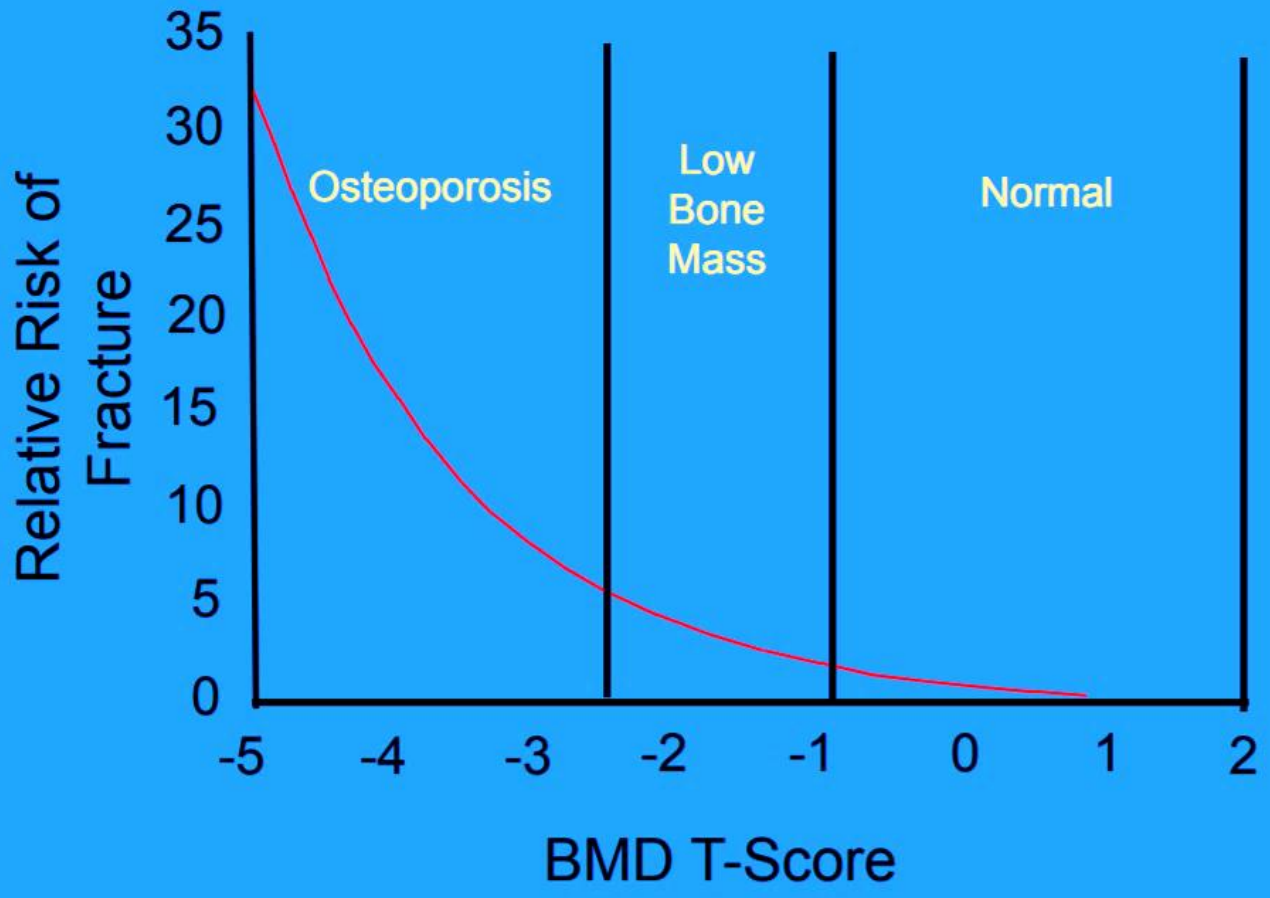




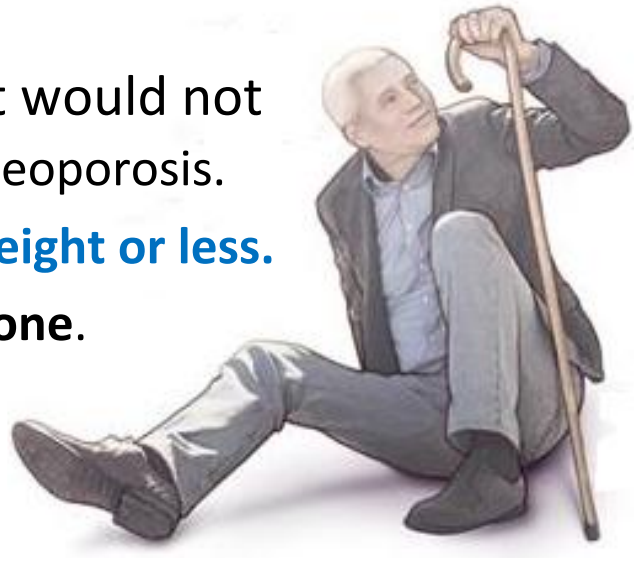
Distribution of bone mineral density in healthy women aged 30–40 years

In the young healthy population, 15% of women have a T score of < –1 & thus have low bone mass or osteopenia.
Because of the normal distribution for BMD, **about 0·5% of women fall into the osteoporotic range, with a T score of –2·5 or less.**

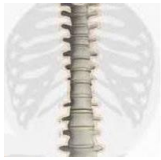
Every SD decrease in BMD in women represents a 10% decrease in bone mass & a 1.5- to 3-fold increase in fracture risk.

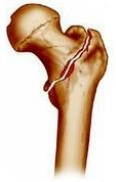


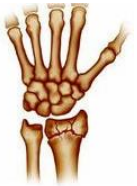
Fragility fracture



- A fragility fracture is a low-trauma fracture, i.e. mechanical forces that would not ordinarily result in fracture. They are the clinically relevant outcome of osteoporosis.
  - **WHO has quantified this as forces equivalent to a fall from a standing height or less.**
- Osteoporotic fractures typically occur where there is significant **trabecular bone**.
- The most common sites of fragility fractures are:
  - **Spine (vertebrae)**
  - **Hip (proximal femur)**
  - **Wrist (distal radius)**

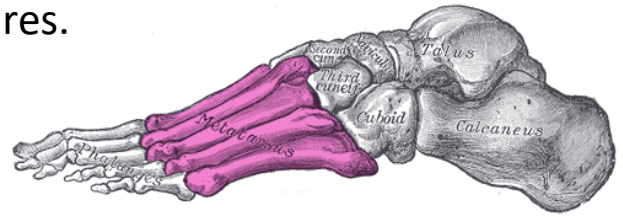


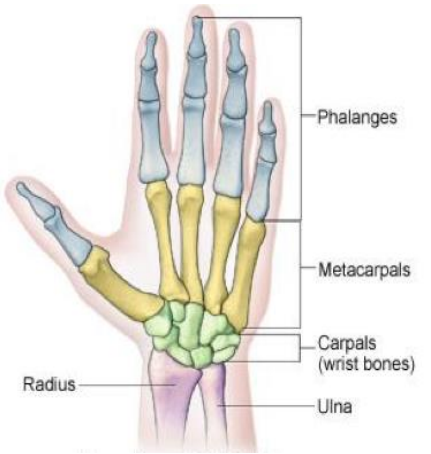




- They also occur in the arm (humerus), pelvis, ribs, & other bones.

- Fractures of the hands & feet (e.g. metacarpal & metatarsal fractures) are not generally regarded as osteoporotic fragility fractures.

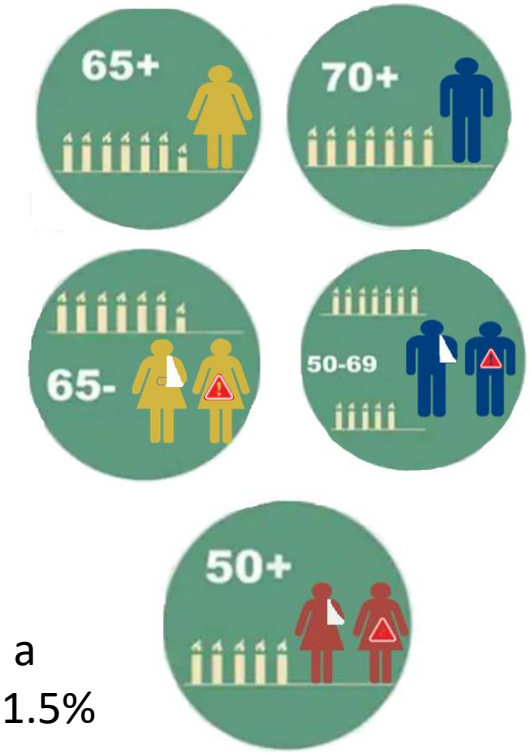




BMD Measurement

❖ NOF recommends BMD testing for:

1. **Women age ≥65 years,** regardless of clinical risk factors
2. **Men age ≥70 years,** regardless of clinical risk factors
3. Menopausal women or women in menopausal transition who are < 65 & at ⬆ risk of osteoporosis or who suffered a low impact fracture
4. **Men ages 50-69** who have suffered a low impact fracture or who are at risk for fracture
5. Nonmenopausal women > 50 who have suffered a low impact fracture or who are at risk for fracture
6. Adults with a condition or who take medication that is associated with low bone mass.



❖ For postmenopausal women who are not receiving medications for osteoporosis prevention, a DEXA may be useful no more frequently than **every 2 -5 years** because rate of bone loss is 1-1.5% per year.

Prevention

: Premenopausal Women

- **Adequate intake of calcium & vitamin D**
  - 1,000 mg Daily/ 600 IU Daily
- **Weight-bearing & strengthening exercise**
  - at least 30 min most days of week (weight-bearing)
  - at least twice per week for 20-30 min (strengthening)
  - Maintain BMI between 20-25 kg/m2
- **Reduced alcohol consumption**
  - No more than 1 drink
- **Smoking cessation**

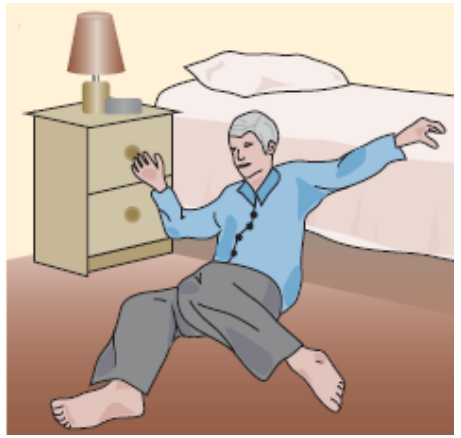
Postmenopausal Women (Age >50 years)

- **Adequate intake of calcium & vitamin D**
  - 1,200 mg Daily/ 1,000-2,000 IU Daily
- **Weight-bearing & strengthening exercise**
  - Same as Premenopausal Women
- **Reduced alcohol consumption**
  - Same as Premenopausal Women
- **Smoking cessation**
- **Pharmacologic Prevention**
  - **Estrogen, Bisphosphonates, Raloxifene**

Treatment

Dietary Intake

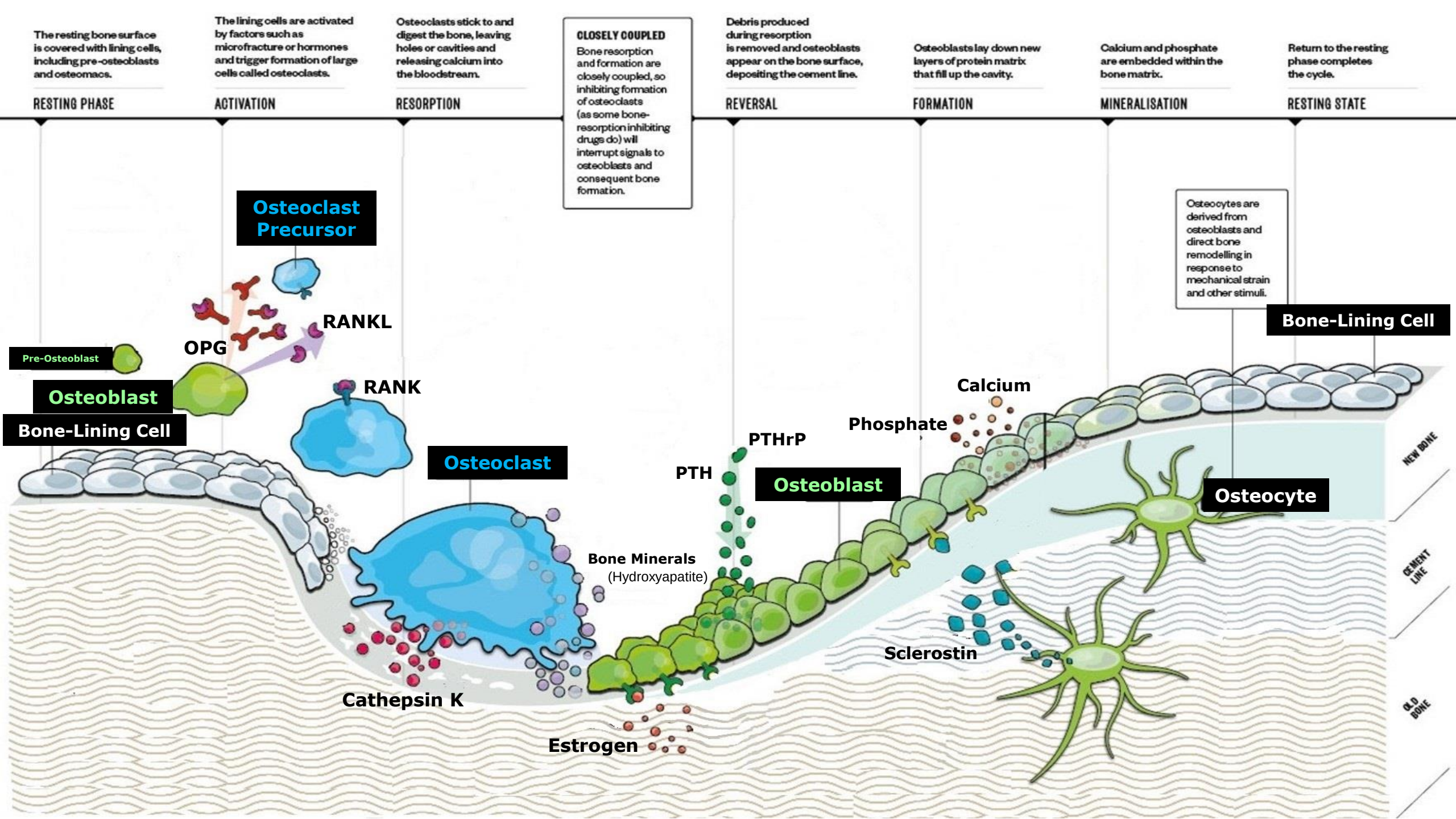
- Calcium: at least 1,200 mg/day
- Vitamin D: Maintaining **serum 25OHD levels >30 ng/mL**

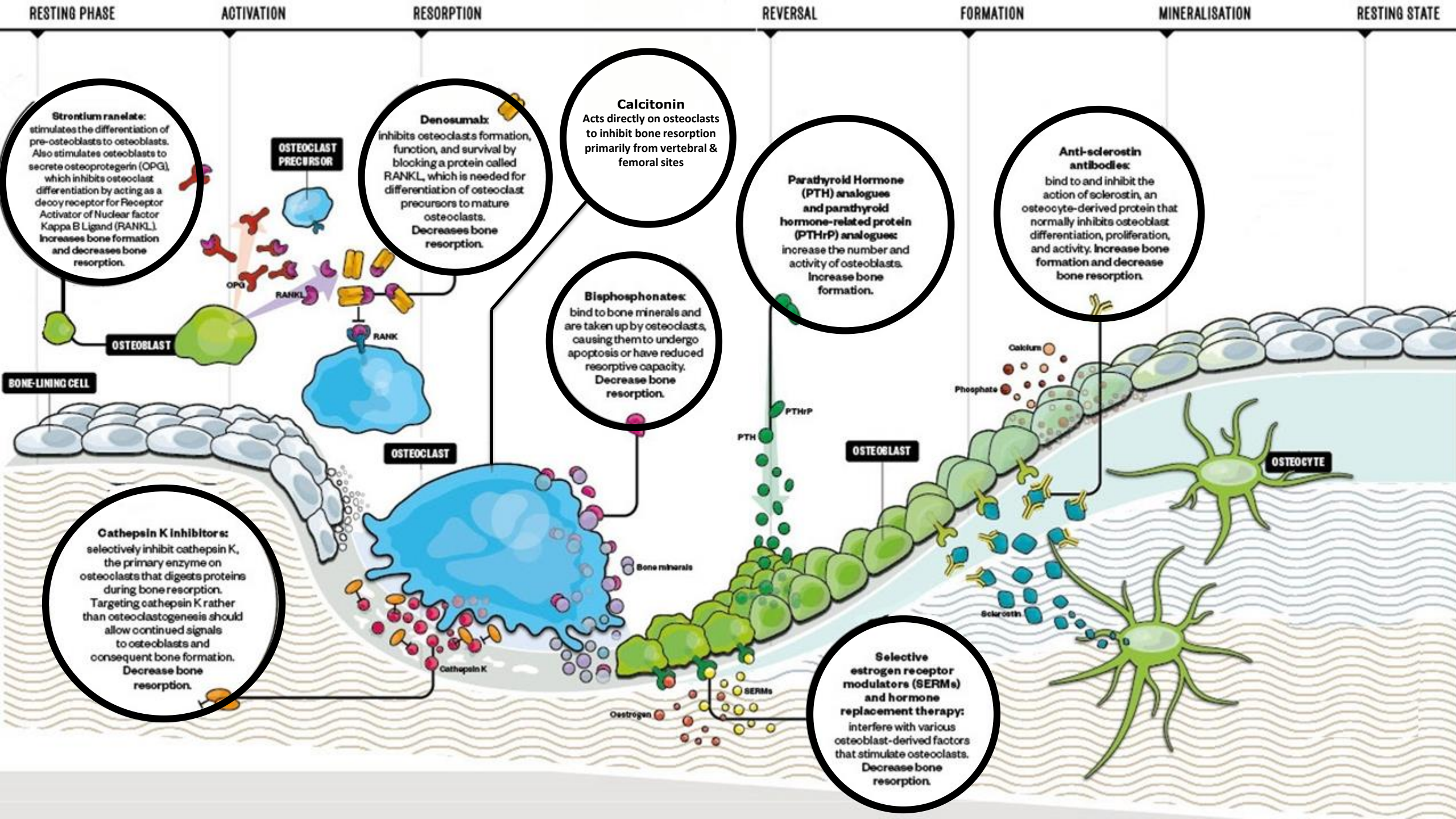


Exercise & Fall Prevention

Pharmacologic treatment

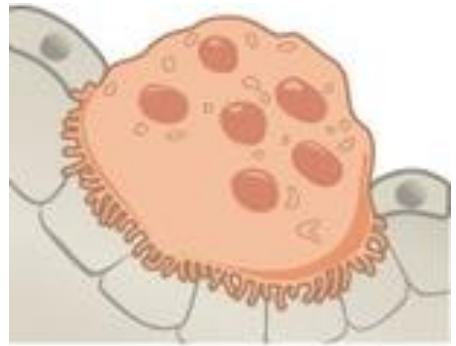
- The principle goal of pharmacological therapy is to **reduce the risk of osteoporotic fractures**.
  - **Anti-resorptive agents**
  - **Anabolic agents**


The resting bone surface is covered with lining cells, including pre-osteoblasts and osteomacs.
RESTING PHASE
The lining cells are activated by factors such as microfracture or hormones and trigger formation of large cells called osteoclasts.
ACTIVATION
Osteoclasts stick to and digest the bone, leaving holes or cavities and releasing calcium into the bloodstream.
RESORPTION
CLOSELY COUPLED
Bone resorption and formation are closely coupled, so inhibiting formation of osteoclasts (as some bone-resorption inhibiting drugs do) will interrupt signals to osteoblasts and consequent bone formation.
Debris produced during resorption is removed and osteoblasts appear on the bone surface, depositing the cement line.
REVERSAL
Osteoblasts lay down new layers of protein matrix that fill up the cavity.
FORMATION
Calcium and phosphate are embedded within the bone matrix.
MINERALISATION
Return to the resting phase completes the cycle.
RESTING STATE
Osteocytes are derived from osteoblasts and direct bone remodelling in response to mechanical strain and other stimuli.
Osteoclast Precursor
RANKL
OPG
Pre-Osteoblast
Osteoblast
Bone-Lining Cell
RANK
Osteoclast
Bone-Lining Cell
PTHrP
PTH
Osteoblast
Calcium
Phosphate
Osteocyte
Bone Minerals
(Hydroxyapatite)
Sclerostin
Cathepsin K
Estrogen
NEW BONE
CEMENT LINE
OLD BONE


RESTING PHASE
ACTIVATION
RESORPTION
REVERSAL
FORMATION
MINERALISATION
RESTING STATE
Strontium ranelate: stimulates the differentiation of pre-osteoblasts to osteoblasts. Also stimulates osteoblasts to secrete osteoprotegerin (OPG), which inhibits osteoclast differentiation by acting as a decoy receptor for Receptor Activator of Nuclear factor Kappa B Ligand (RANKL). Increases bone formation and decreases bone resorption.
OSTEOCLAST PRECURSOR
Denosumab: inhibits osteoclasts formation, function, and survival by blocking a protein called RANKL, which is needed for differentiation of osteoclast precursors to mature osteoclasts. Decreases bone resorption.
Calcitonin
Acts directly on osteoclasts to inhibit bone resorption primarily from vertebral & femoral sites
Parathyroid Hormone (PTH) analogues and parathyroid hormone-related protein (PTHrP) analogues: increase the number and activity of osteoblasts. Increase bone formation.
Anti-sclerostin antibodies: bind to and inhibit the action of sclerostin, an osteocyte-derived protein that normally inhibits osteoblast differentiation, proliferation, and activity. Increase bone formation and decrease bone resorption.
OPG
RANKL
RANK
OSTEOBLAST
BONE-LINING CELL
Bisphosphonates: bind to bone minerals and are taken up by osteoclasts, causing them to undergo apoptosis or have reduced resorptive capacity. Decrease bone resorption.
OSTEOCLAST
PTHrP
PTH
OSTEOBLAST
Calcium
Phosphate
OSTEOCYTE
Bone minerals
Sclerostin
Cathepsin K
Cathepsin K Inhibitors: selectively inhibit cathepsin K, the primary enzyme on osteoclasts that digests proteins during bone resorption. Targeting cathepsin K rather than osteoclastogenesis should allow continued signals to osteoblasts and consequent bone formation. Decrease bone resorption.
SERMs
Oestrogen
Selective estrogen receptor modulators (SERMs) and hormone replacement therapy: interfere with various osteoblast-derived factors that stimulate osteoclasts. Decrease bone resorption.

Anti-Resorptive Agents

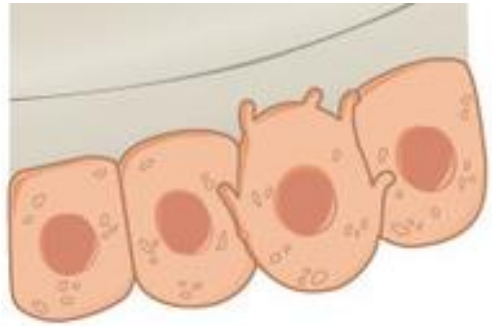
- Bisphosphonates
- Denosumab
- Selective Estrogen Receptor Modulators (SERMs)
- Calcitonin
- Cathepsin K Inhibitors
- Strontium Ranelate
- Anti-Sclerostin Antibodies



Osteoclast

Anabolic Agents

- PTH & PTH-related Protein (PTHrP) Analogues
- Strontium Ranelate
- Anti-Sclerostin Antibodies

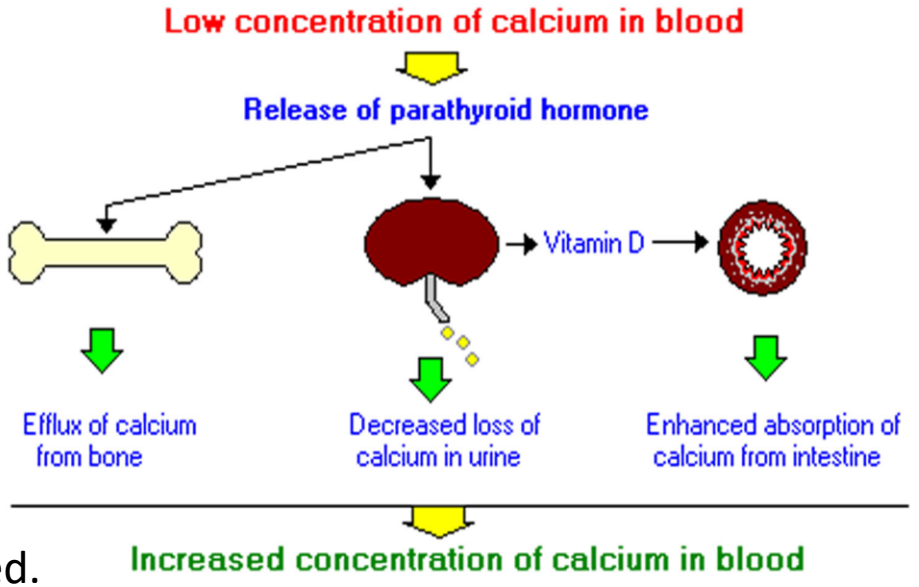


Osteoblast

Calcium

Calcium

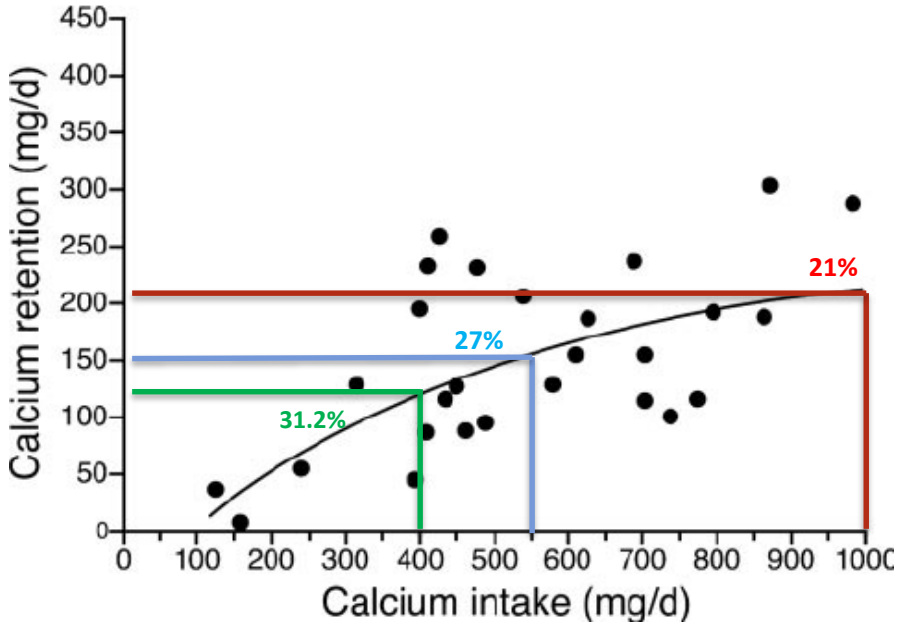
- **Low serum calcium** level will **raise PTH secretion**, which eventually causes a high bone turnover. Conversely, administration of calcium will reduce PTH release & eventually suppress bone resorption.



- However, calcium is a **threshold mineral,** that is, surplus ions are excreted.
  - Excessive intake of calcium, therefore, has no benefit for bone health.
- Therefore, calcium administration is best used only in patients whose pathology of osteoporosis is directly associated **with calcium shortage, or patients with secondary hyperparathyroidism.**
  - Hence, clinical application of calcium for osteoporosis is **supplementary to bisphosphonates or anti-RANKL drugs.**

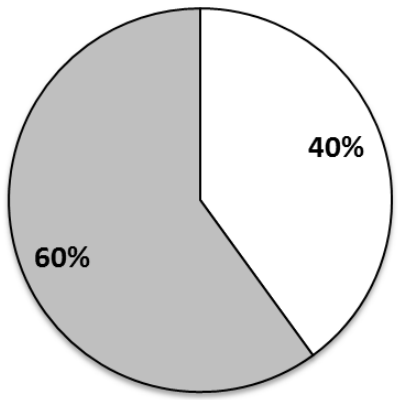
- ⬆ **BMD** (0.6%-1.8%) **; but minimal fracture prevention**
  - **Fracture prevention is only documented with concomitant vitamin D.**
- **Other benefits:** ⬇ **BP,** ⬇ **Cholesterol,** ⬇ **Colorectal cancer risk**

- **Calcium absorption**
  - Under normal conditions; 30-40%
  - With low vitamin D concentrations; 10-15%
  - **Fractional calcium absorption is dose limited;**
    Maximum single doses of **500-600 mg** or less of elemental calcium are recommended.

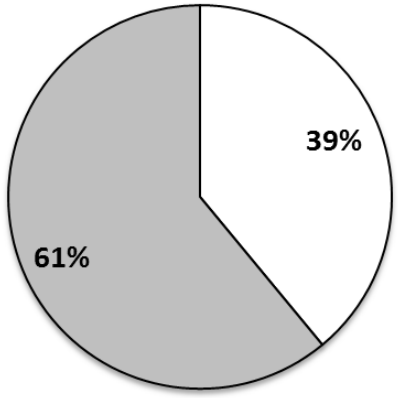


Percentage of elemental calcium in various calcium salts

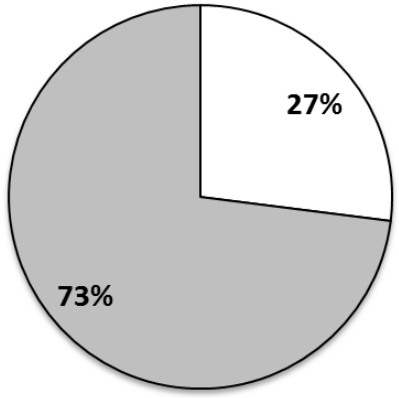
(mg elemental/1000mg salt)*100



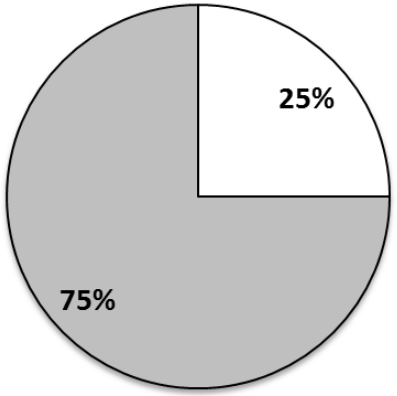
Carbonate



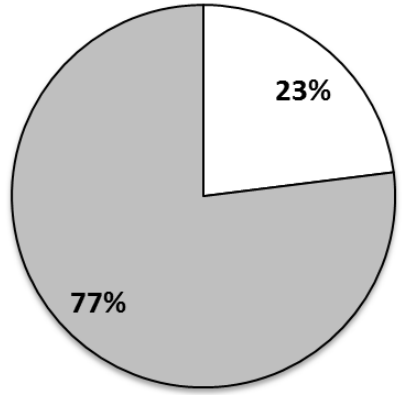
Phosphate (tribasic)



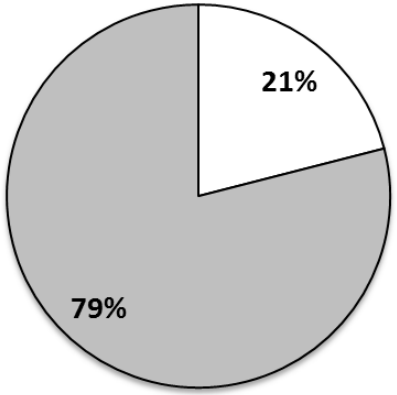
Chloride



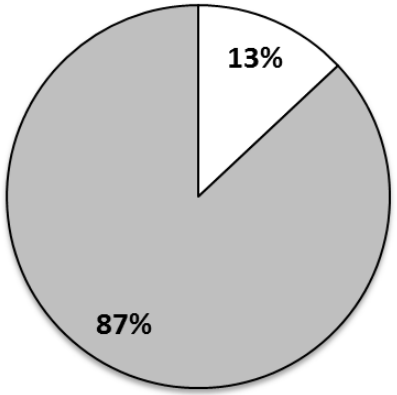
Acetate



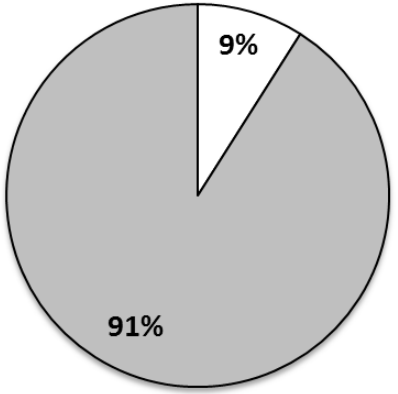
Phosphate (dibasic)



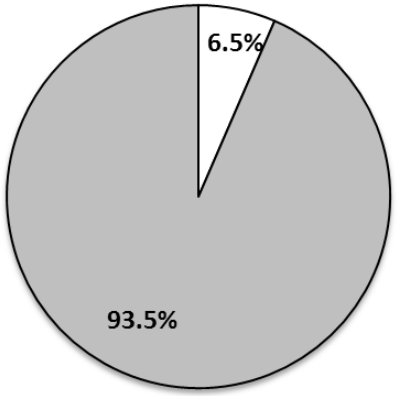
Citrate



Lactate



Gluconate



Glubionate

Calcium carbonate

- **The salt of choice:** 40% elemental calcium, the least expensive.
- **Should be taken <u>with meals</u>,** which increases gastric acidity resulting in product dissolution & disintegration.

Calcium citrate

- **<u>Absorption is acid-independent</u>** & need **<u>not</u>** be administered with meals.
- Should be used over calcium carbonate in patients with **achlorhydria**, a condition common in the elderly, & in those patients who complain of **constipation**.

- Calcium can ⬇ oral absorption of **Iron, Tetracyclines, Quinolones, Bisphosphonates, Thyroid supplements**.

Adverse effects of calcium:

Constipation

- Increased water intake, dietary fiber, exercise
- Smaller & more frequent dose or lower total daily dose of Calcium
- Use Calcium citrate instead of Calcium carbonate

GI irritation

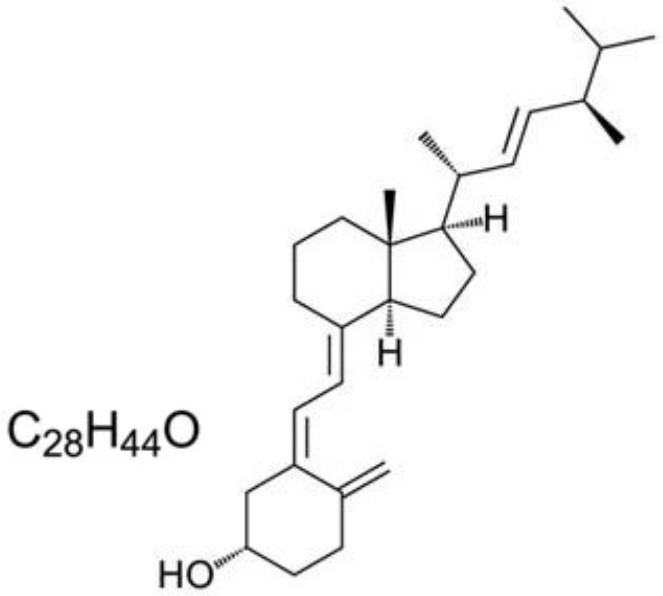
Flatulence

- Calcium carbonate can create gas & cause stomach upset
- Use Calcium citrate instead of Calcium carbonate

Kidney stone formation

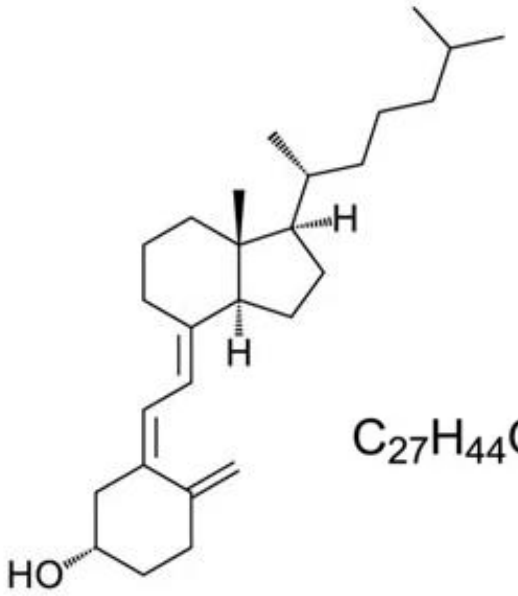
- Calcium supplementation when combined with vitamin D can increase the risk
- Increased fluid intake & decreased salt intake might be warranted to prevent kidney stones

Vitamin D



$C_{28}H_{44}O$

Vitamin D_2
Ergocalciferol



$C_{27}H_{44}O$

Vitamin D_3
Cholecalciferol

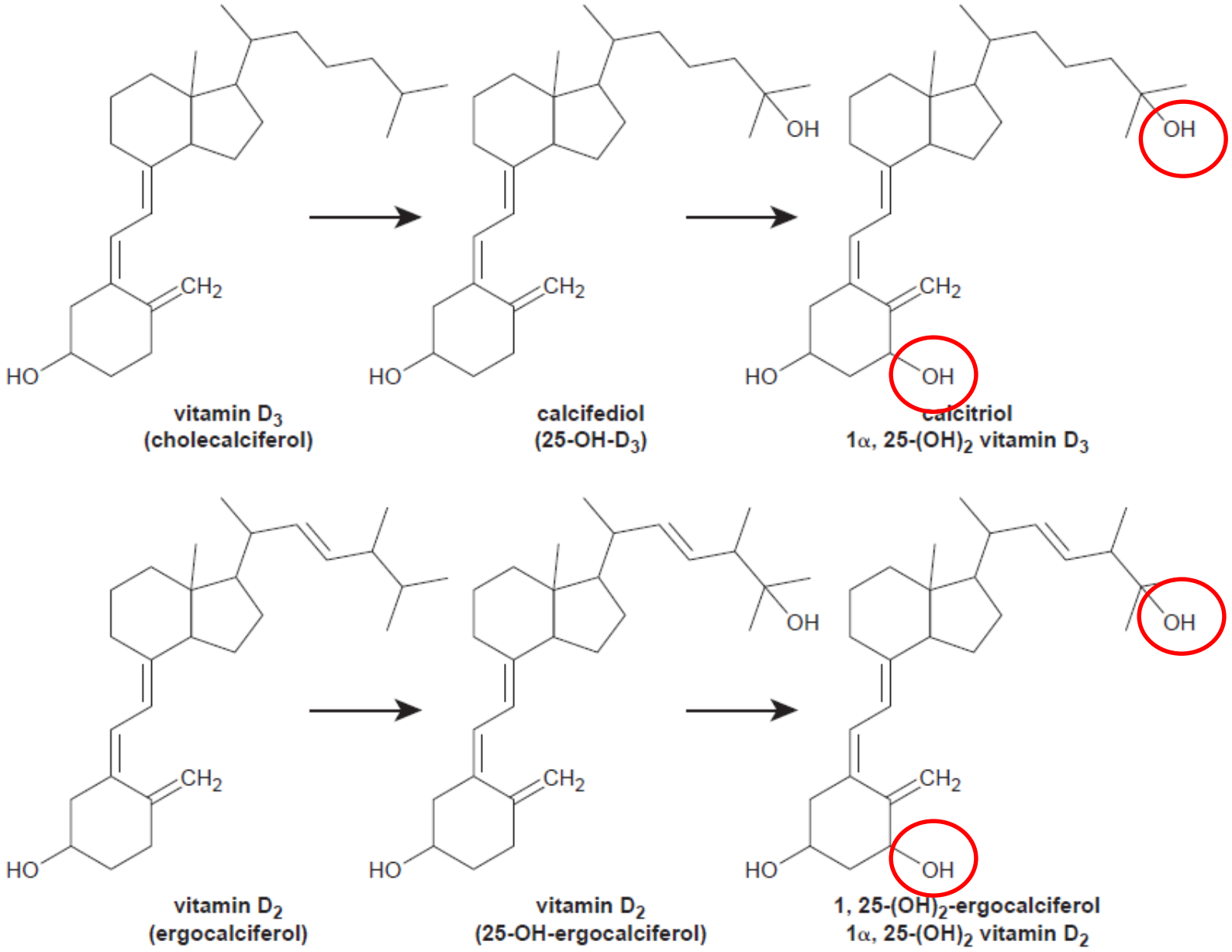
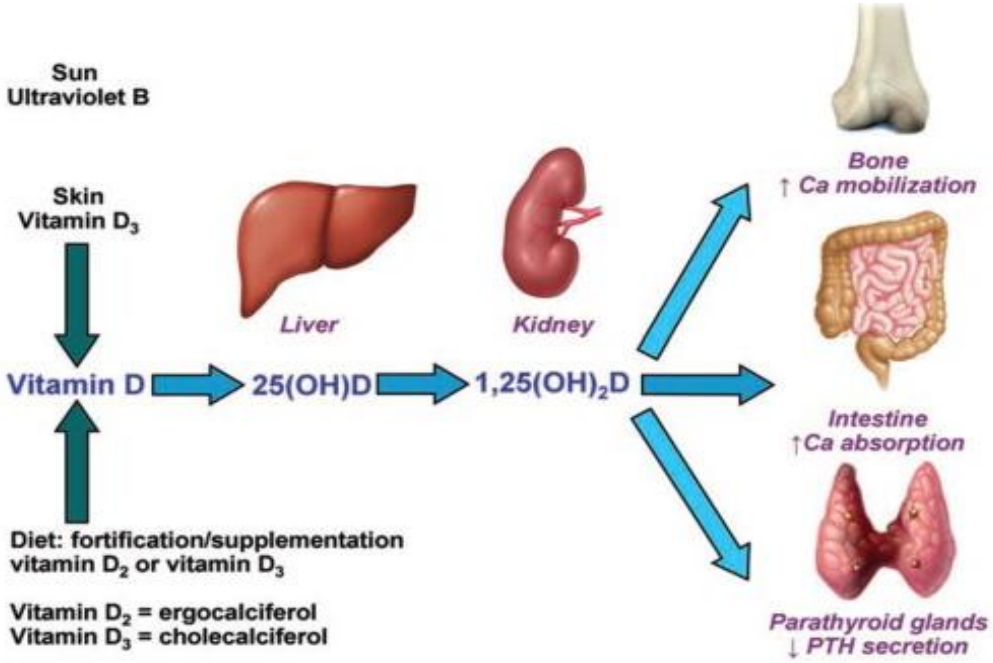


Figure 12-20. Activation of vitamin D_2 and D_3 to the 25-hydroxylated vitamin D in the liver and the 1,25-dihydroxy (1α,25-$[OH]_2$) vitamin D in the kidney.

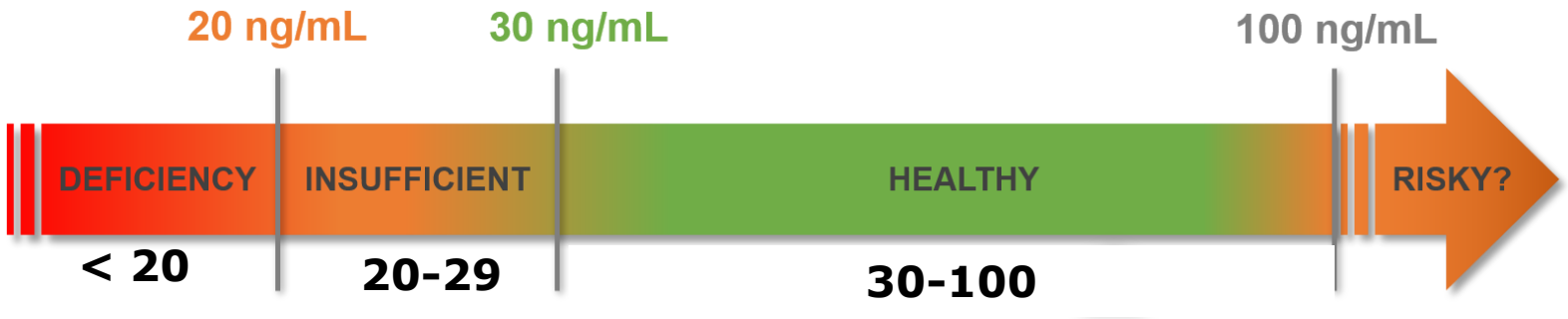
Vitamin D

- **Skeletal benefits:**
  - Regulate Calcium
  - Improvement in muscle strength & balance
  - Reduced risk of falls
    - Vitamin D shortage causes **atrophy of type II muscle fibers**, which increases propensity to fall & risk of fractures.
- **Nonskeletal benefits:**
  - Improvement in cardiovascular function
  - Decreased cancer risk (e.g., breast, colon, prostate)
  - Positive immunomodulatory effects (e.g., MS, type 1 DM, RA)



Vitamin D in conjunction with Calcium: ⬇ bone loss
Vitamin D alone: effectiveness for fracture prevention is unclear

❖ Serum 25(OH) vitamin D



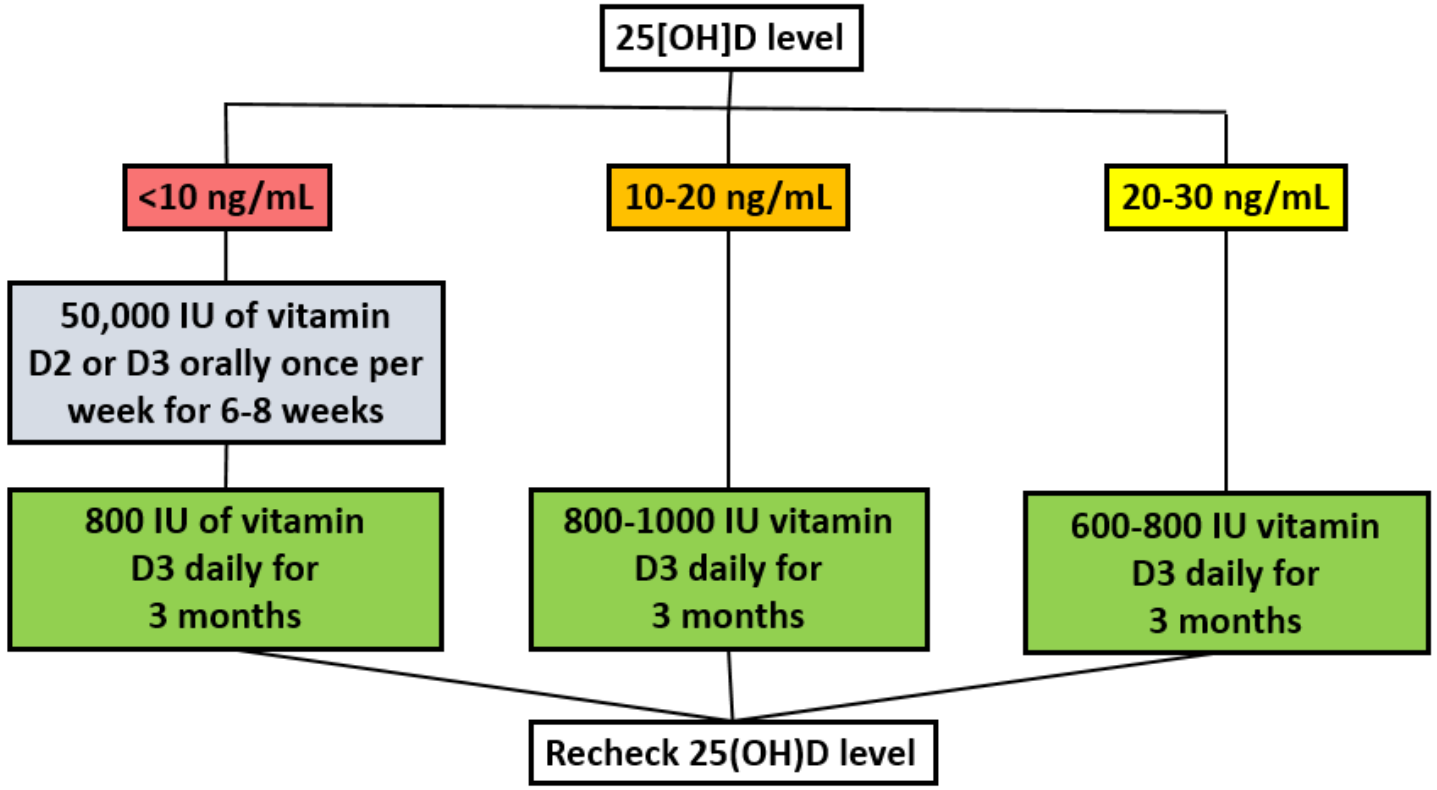
- Osteomalacia or severe vitamin D deficiency can occur at levels <10 ng/mL. **(1 ng/mL = 2.5 nmol/L)**

❖ 100 IU vitamin D_3 daily; ⬆ 25(OH) vitamin D level by 1 ng/mL.

- Half-life of vitamin D is **1 month;** 3 months of therapy are required before a new Css is achieved.

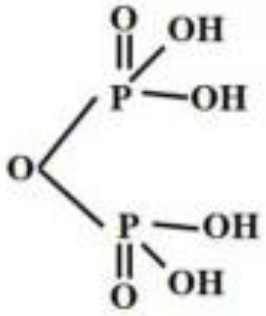
Vitamin D conversions: 1 mcg = 40 IU

Vitamin D Repletion (Adult)

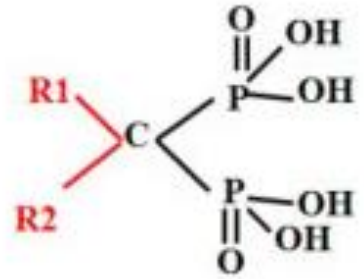


- Intermittent high doses of vitamin D (60 000 IU monthly or 500 000 IU annually) have been associated with increased risk of falls & fractures & the recommended daily dose should not exceed 4000 IU, unless the patient has documented malabsorption.

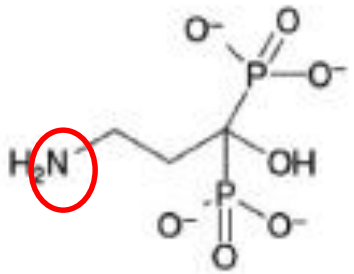
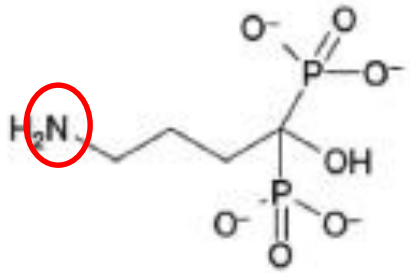
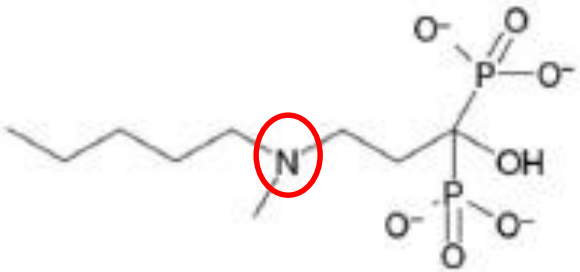
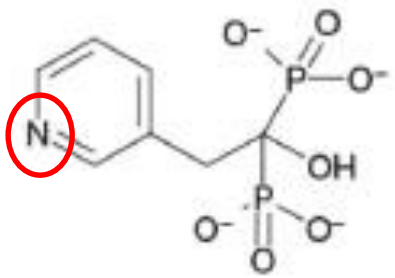
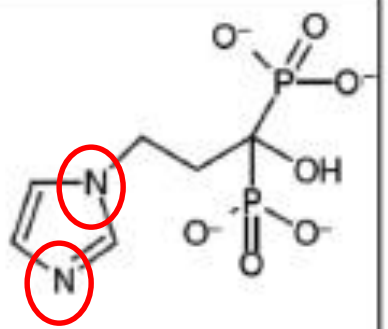
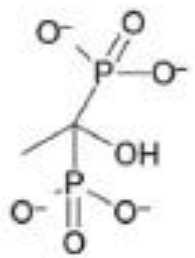
Bisphosphonates

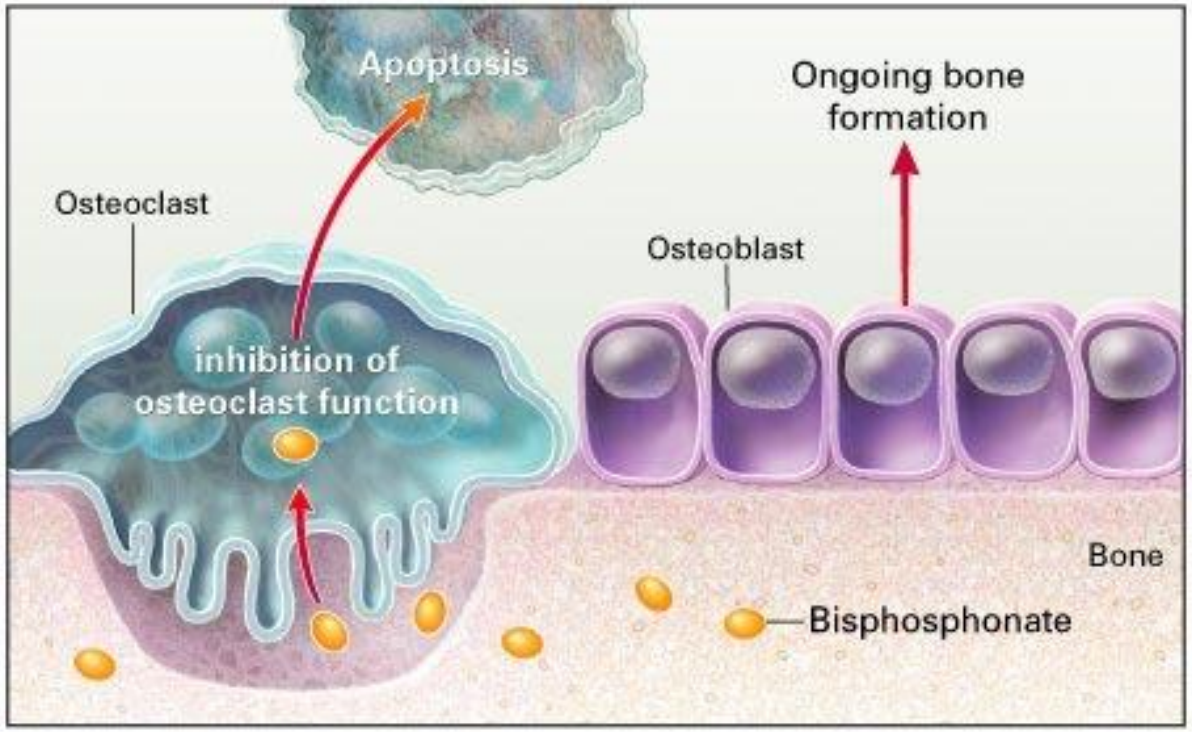


Pyrophosphonate



Bisphosphonate

 Pamidronate	 Alendronate	 Ibandronate
 Risedronate	 Zolendronate	 Etidronate



BPs have high affinities for bone hydroxyapatite & can be incorporated into bone; **Cause osteoclast apoptosis**, **⬇ Bone turnover; ⬇ Fracture rates**

- **Zoledronic acid, Alendronate, Risedronate: ⬇ Vertebral, ⬇ Nonvertebral, ⬇ Hip fracture**
- **Ibandronate; Do not show to ⬇ Nonvertebral or Hip fracture**

Strength of binding to bone:

- Zoledronic Acid> Alendronate> Ibandronate> Risedronate

- Bisphosphonates have long half-lives (**1-10 years);** Incorporation into bone.
- Bioavailability is very poor for bisphosphonates **(< 1-5%).**

FDA-indication:

- **Alendronate, Risedronate, Zoledronic acid:** Postmenopausal, Male, GIO
- **Ibandronate:** only for postmenopausal osteoporosis

Medication	Prevention	Treatment
Alendronate	5 mg PO daily 35 mg PO weekly	10 mg PO daily 70 mg PO weekly
Alendronate/ cholecalciferol		70 mg/2,800 IU PO weekly 70 mg/5,600 IU PO weekly
Ibandronate	2.5 mg PO daily 150 mg PO monthly	2.5 mg PO daily 150 mg PO monthly
Risedronate	5 mg PO daily 35 mg PO weekly 75 mg PO 2 consecutive days each month 150 mg PO monthly	5 mg PO daily 35 mg PO weekly 35 mg DR*-PO weekly 75 mg PO 2 consecutive days each month
Zoledronic acid	5 mg IV every other year	5 mg IV yearly

❖ Administration of Oral products:

- ➢ Take it early in morning on arising & **at least 30 min (60 min for ibandronate)** before ingesting food, beverage, or other medications **with 6- 8 ounces of water** (**not coffee, juice, mineral water, or milk**)
- ➢ Not lie down for **at least 30 min (60 min for ibandronate)** after ingesting.
- ➢ **Misses a weekly dose;** can take it **next day**. If **> 1 day has lapsed**, that dose is skipped until next scheduled ingestion.
- ➢ **Misses a monthly dose;** it **can be taken up to 7 days before next administration.**

❖ Administration of Zoledronic acid

- ➢ Patients should be appropriately **hydrated**
- ➢ Infusion given **over ≥15 min**, then followed by a 10 mL of normal saline flush.
- ➢ To ⬇acute-phase reaction symptoms, **acetaminophen given postinfusion**.

Adverse Effects

- **GI symptoms:** acid regurgitation, abdominal distention, nausea, dyspepsia
- **Esophageal adverse effects;** esophagitis, esophageal ulcers/erosions
  - **Zoledronic acid:⬇ incidence of GI adverse events**
- **Musculoskeletal pain, headaches, rash**
- **Acute phase reactions** (fevers, flu-like symptoms, headache, arthralgias) within first 3 days after infusion of Zoledronic acid.
- **Osteonecrosis of the jaw (ONJ)**
- **Atypical fractures of the femoral shaft**

❖ Osteonecrosis of the jaw (ONJ)

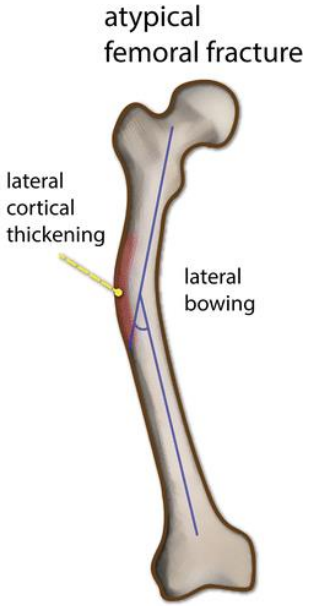
- Associated with Both IV & oral bisphosphonates
- **Risk factors:** diagnosis or previous history of cancer; invasive dental procedures; concurrent use of chemotherapy, corticosteroids, or angiogenesis inhibitors; poor oral hygiene; preexisting dental disease or infection; anemia & coagulopathy. The risk of ONJ increases at higher doses & with duration of exposure.

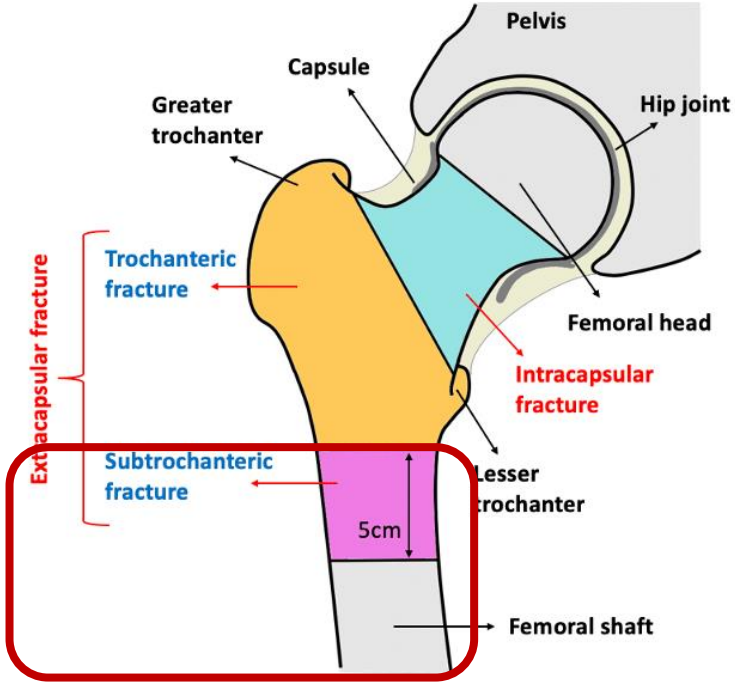
➢ **American Association of Oral & Maxillofacial Surgeons suggest:**

- **Patients treated with oral bisphosphonates for <3 years:** performing dentoalveolar surgery, such as extractions & implants, **as usual**
- **Patient has been treated for > 3 years:** discontinuing oral bisphosphonates **for 3 months** prior to performing dental surgery & **restarting when bone has healed**.

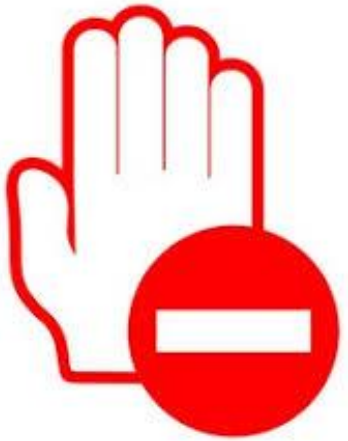
❖ Atypical fractures of the femoral shaft

- A warning is included in the manufacturers' information for all bisphosphonate drugs. A clear connection has not been found.
- The mechanism of action is not clear; however, bone is normally subject to microdamage with every day stresses & this initiates bone remodeling. **Antiresorptive agents may oversuppress bone turnover** causing **microdamage to accumulate** which may lead to brittle bone & an increased risk of fracture.
- If a patient has prodromal pain in the thigh or leg or has suffered an atypical fracture while on bisphosphonate therapy, it would be reasonable to discontinue therapy & evaluate.





❖ Contraindications & Precautions



- ClCr<35 mL/min : alendronate & zoledronic acid not recommended
- ClCr<30 mL/min : risedronate & ibandronate not recommended
- **Hypocalcemia**, if it exists, should be corrected before beginning therapy.
- **Patients with GERD, esophageal disease: Caution is warranted**
- **A patient who cannot sit upright for at least 30 min (60 min for ibandronate) after ingesting the drug should not use oral bisphosphonates.**

Length Of Treatment

- Incorporation of bisphosphonates into bone results in a reservoir of available drug that is slowly released over time. Peak effect of reducing bone turnover markers occurs in 3-6 months & **continues for months to years with discontinuation.**

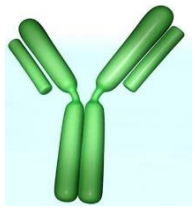
Guide to bisphosphonate drug holidays according to fracture risk:

- **Mild risk—treat for 3-5 years then consider a 1 year drug holiday**
- **Moderate risk—treat for 5 -10 years then consider a 3-5 year drug holiday**
- **High risk—treat for 10 years then consider a drug holiday for 1-2 years;** treat with a nonbisphosphonate such as raloxifene or teriparatide.

Denosumab


prolia®
(denosumab) injection


XGEVA®
(denosumab) injection
120 mg/1.7 mL vial

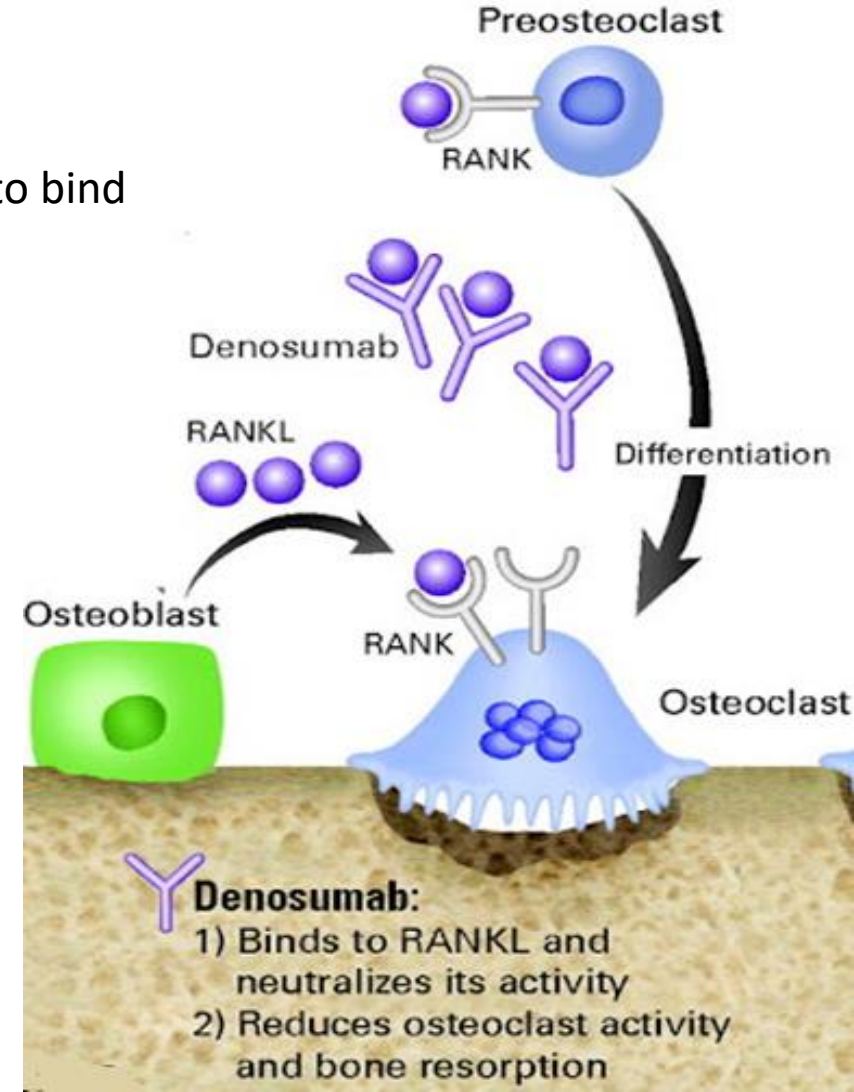


Denosumab

- **Fully human** monoclonal antibody that binds to **RANKL**, blocking its ability to bind to RANK on the surface of osteoclast precursor cells & mature osteoclasts; **Inhibits osteoclastogenesis & ⬆ osteoclast apoptosis**.

- **⬇ Vertebral, ⬇ Nonvertebral, ⬇ Hip fractures**

- **Treatment of postmenopausal women** with osteoporosis who are at high to very high risk for fracture.
  - **60 mg SC every 6 months**



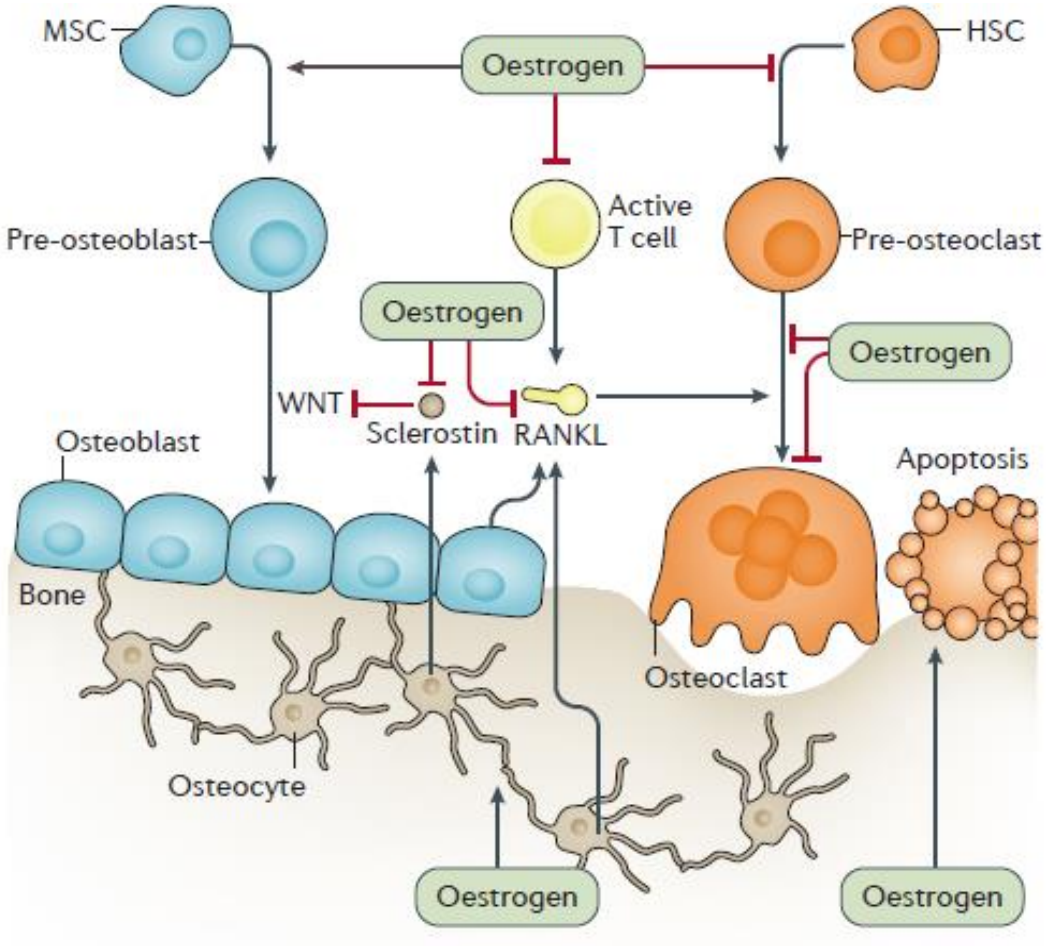
Adverse effects:

- Musculoskeletal pain, hypercholesterolemia, cystitis, ⬇serum calcium, & **skin problems (eczema, cellulitis)**.
- **Rare, serious ADRs:** serious infections (diverticulitis, pneumonia, appendicitis, labyrinthitis), **ONJ, bone turnover suppression.**

- **Denosumab is no restriction of use in ClCr <35 mL/min.**
  - These patients are at higher risk for hypocalcemia; **Calcium should be measured 10 days after administration**.
  - Monitoring of serum calcium is not required in patients with normal renal function.

- Denosumab has a **more rapid on-off effect** on bone than bisphosphonates. Discontinuation results in bone loss **within 12 months.**

Estrogen Therapy



Estrogen Therapy

- **Estrogen: Antiresorptive activity; ⬇ Bone loss, ⬇ Fracture rates**
  - **10-15% of a woman's bone mass is estrogen dependent**

- **Prevention of osteoporosis**
  - **EPT:** for postmenopausal women **with uterus.**
  - **ET**: for postmenopausal women **without uterus.**

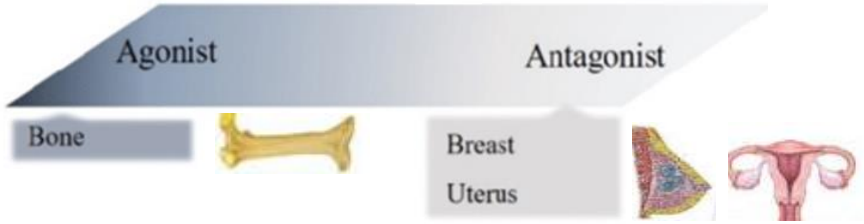
- ET & EPT should be used at the lowest effective doses & the shortest duration indicated. Longer therapy should only be prescribed in women who have failed or contraindicated to other osteoporosis therapies.

Selective Estrogen Receptor Modulators (SERMs)

Raloxifene

Selective Estrogen Receptor Modulators (SERMs):

- Have estrogen agonist, antagonist, or both activities in various tissues
- **Raloxifene:**
  - Agonistic effects on bone & serum lipid
  - Antagonistic effects on endometrial & breast tissues



- **Prevention & Treatment of postmenopausal osteoporosis**:
  - **60 mg/day**
- **Has an FDA-approved indication for invasive breast cancer risk reduction.** Thus in a subset of women, this additional benefit might warrant raloxifene use for dual osteoporosis & breast cancer prevention.

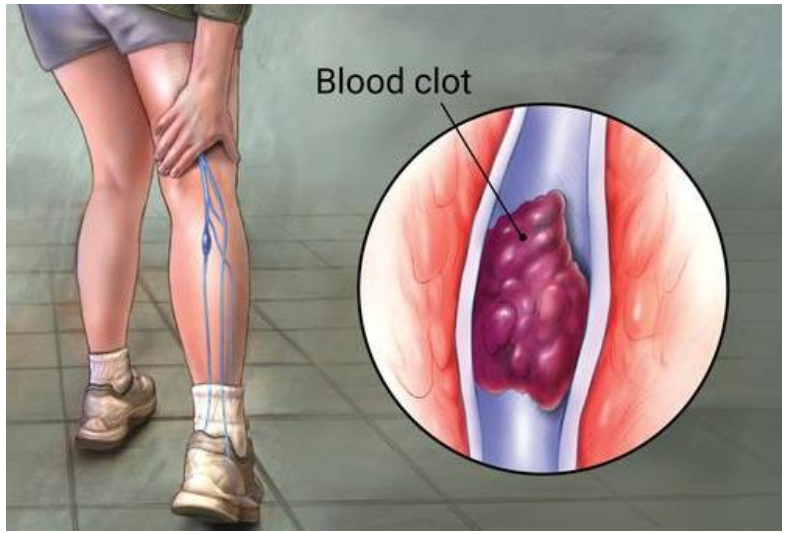
❖ ⬇ **Bone resorption, ⬇ Rate of bone turnover; ⬆ BMD**

- ➢ Can ⬇ **Vertebral fractures** by up to 41% while ⬆ BMD by only 2-3%
- ➢ **Not have a significant effect on hip fractures**

  - **Estrogen receptors**
    - **Cancellous bone: β-receptor sites are predominant ;** raloxifene bind to it
    - **Cortical bone: α-receptor is predominant**
  - **Threshold for preventing osteoclastic activity**
    - **In cancellous bone may be lower than in cortical bone**; It may require a more potent antiresorptive agent to ⬆ BMD in the hips.

❖ Adverse Effects

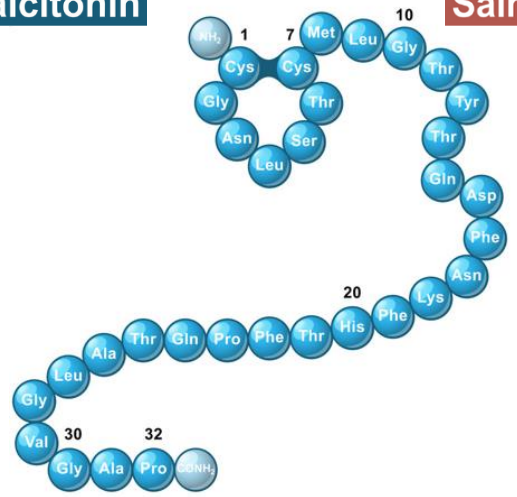
- ⬆ **Risk for venous thromboembolic disease;** raloxifene should be discontinued **for at least 72 h** before immobilization such as that associated with surgery.
- Flu syndrome, headache, hot flashes
- Nausea, diarrhea, flatulence, gastroenteritis
- Leg cramps, peripheral edema, arthralgia, neuralgia
- Sinusitis, bronchitis, rash, sweating, conjunctivitis
- **Slight increase in stroke; black box warning**



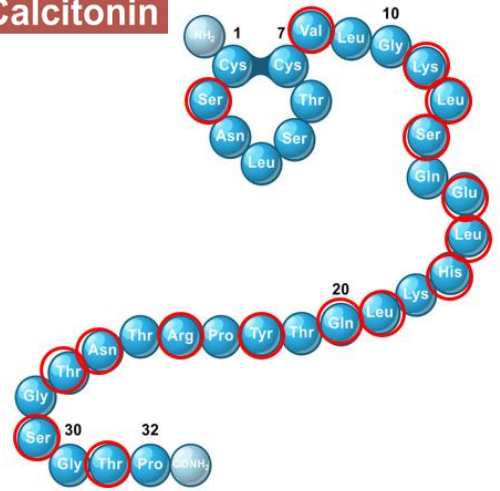
Calcitonin

Miacalcin®
(calcitonin-salmon)

Human Calcitonin

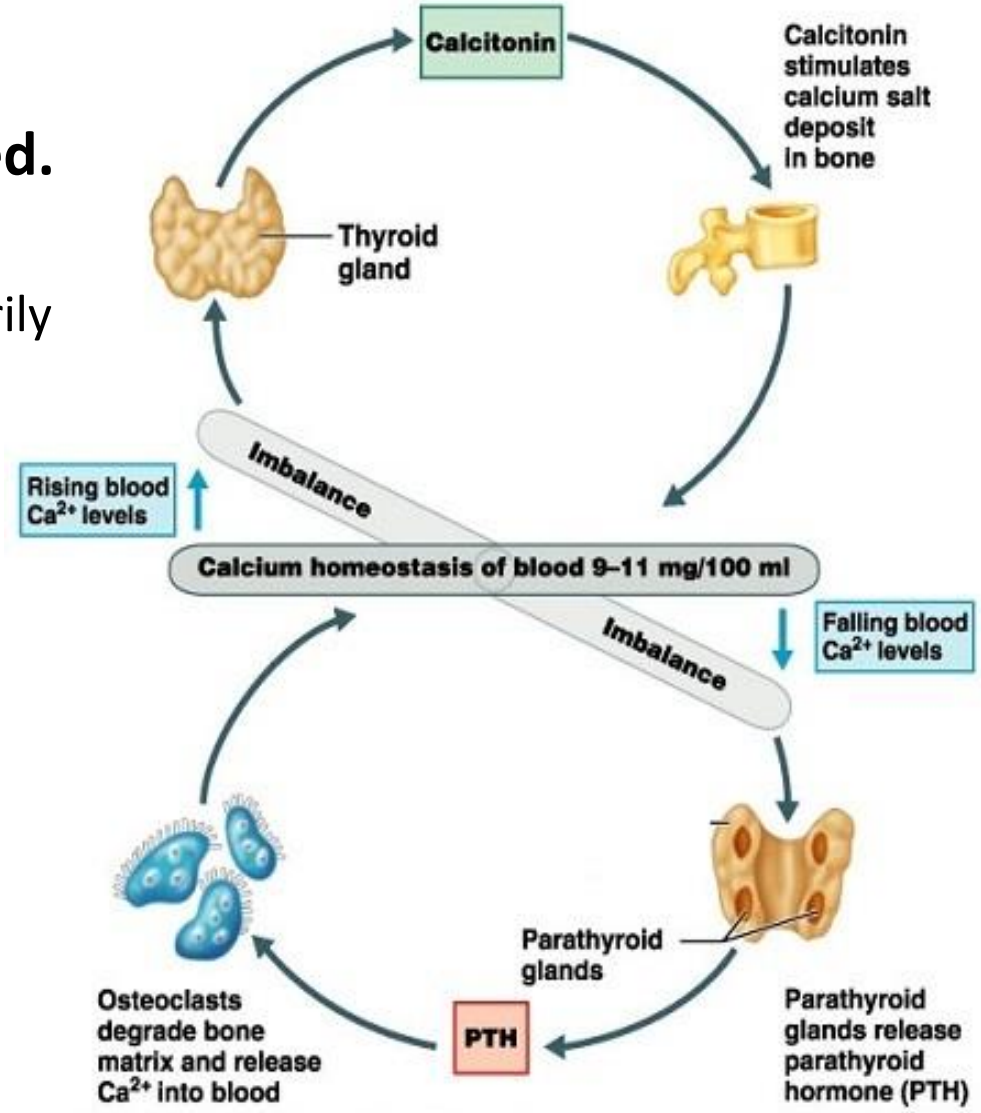


Salmon Calcitonin



Calcitonin

- Released from **thyroid** **when serum calcium is elevated.**
  - Acts **directly on osteoclasts** to inhibit bone resorption primarily from vertebral & femoral sites.
  - In addition, calcitonin possesses a pain relief effect.
  - **Salmon calcitonin is more potent & longer lasting than mammalian form.**



FDA indication

- **Both injection & intranasal spray:**
  - **Osteoporosis treatment for women who are at least 5 years past menopause.**
- **Injectable calcitonin:**
  - Treatment of hypercalcemia & paget disease.

Efficacy

- ⬆ BMD in the lumbar spine by 1-3%; **Only ⬇ Vertebral fractures**
- **Does not affect hip BMD & does not ⬇ hip fracture risk.**

- Because efficacy is less robust, calcitonin is reserved as **third-line treatment.**
- **Calcitonin might provide pain relief** in patients with acute vertebral fractures; It should be prescribed for **short-term (4 weeks)** treatment.

Administration

- Intranasal (Miacalcin): 200 IU in One nostril daily
- SC or IM (Calcimar): 100 IU/day
- Injectable calcitonin should be refrigerated. Intranasal preparation should be refrigerated until it is opened for use; **it is stable for 30 days at room temperature.**

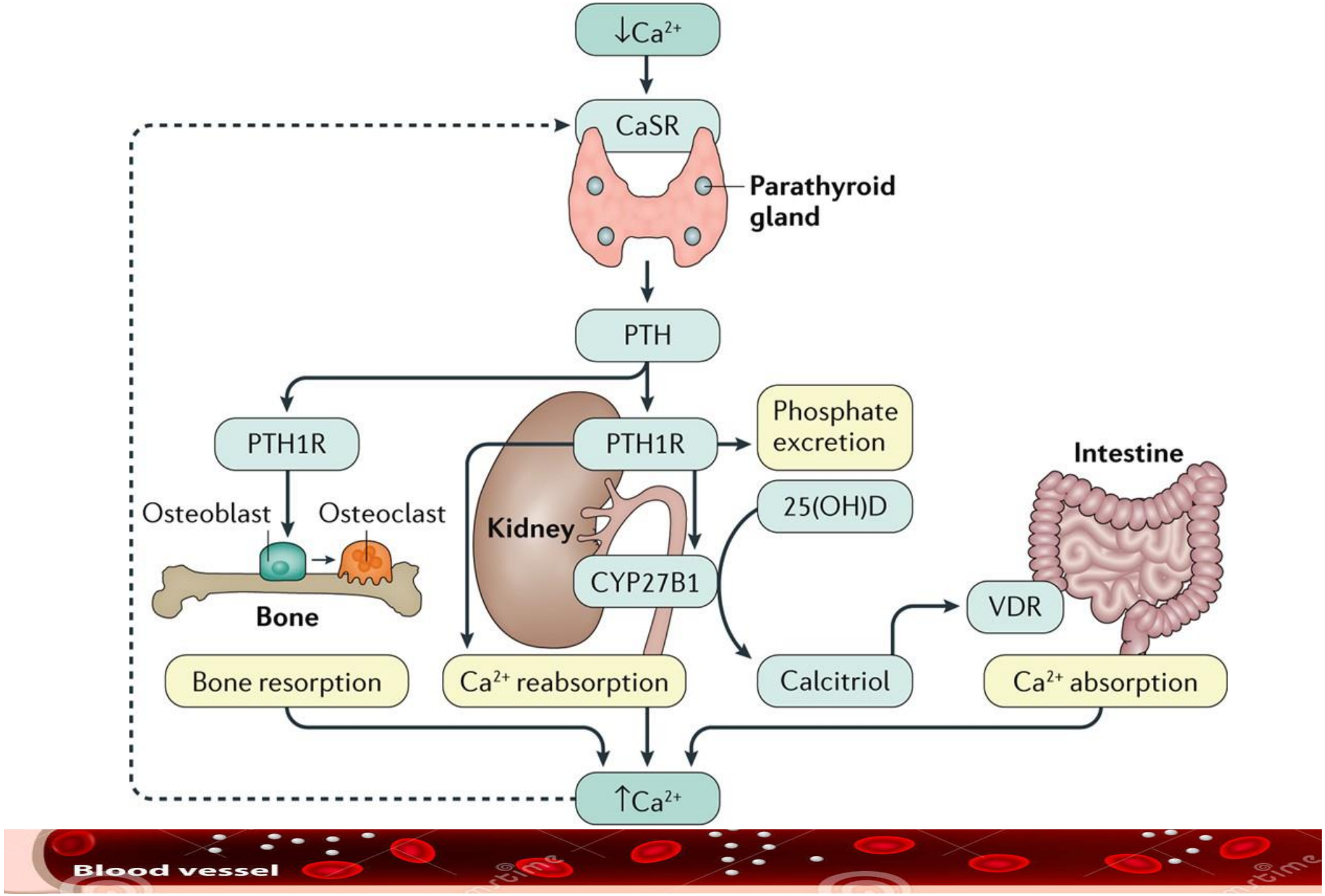
Adverse effects

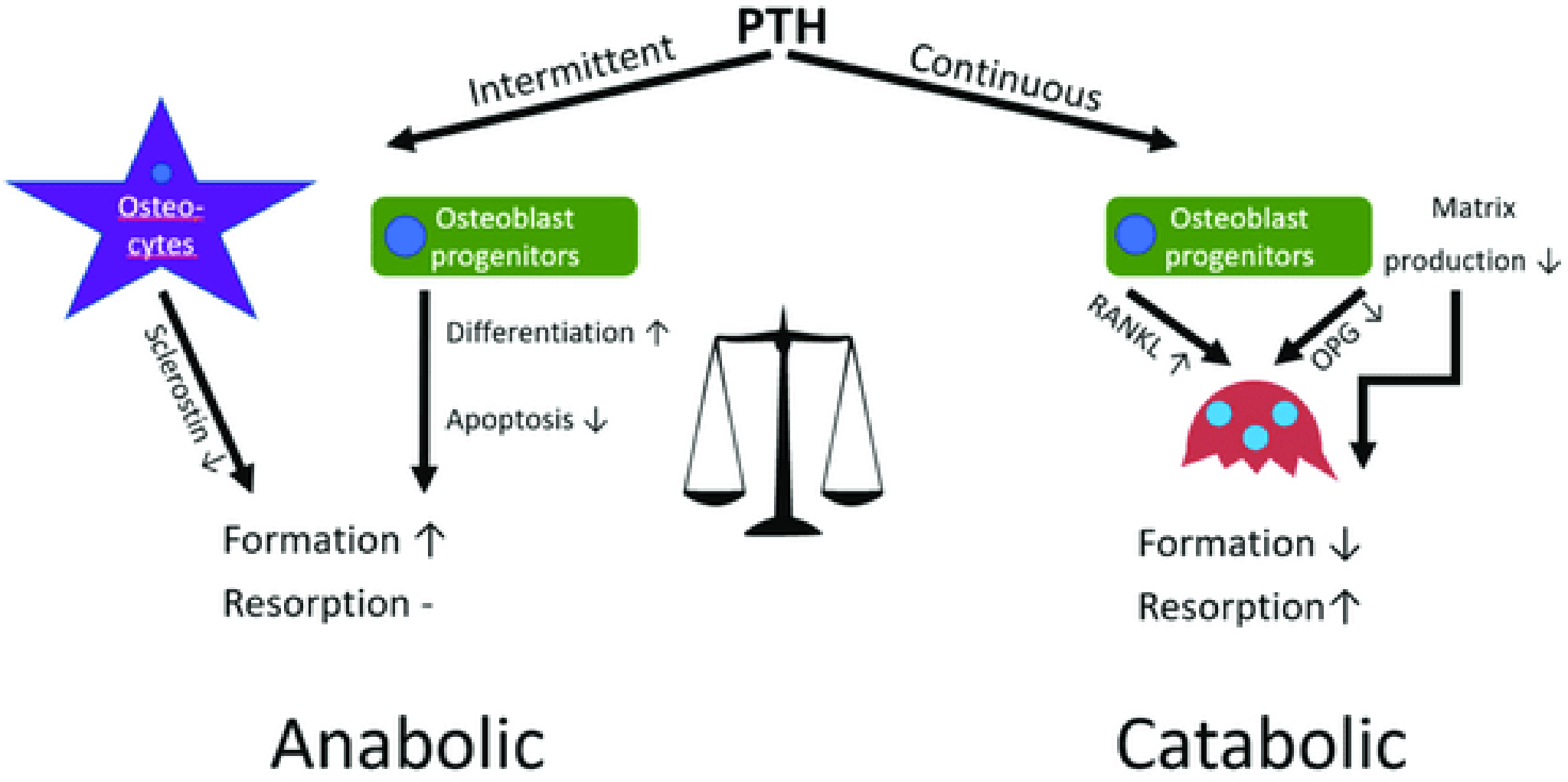
- **Intranasal : rhinitis, epistaxis,** arthralgia, headache, back pain.
- **Injection:** flushing (2-5%), nausea & vomiting (10%), local irritation.
  - Flushing typically occurs on the hands & face.
  - Nausea & vomiting usually subside with time.

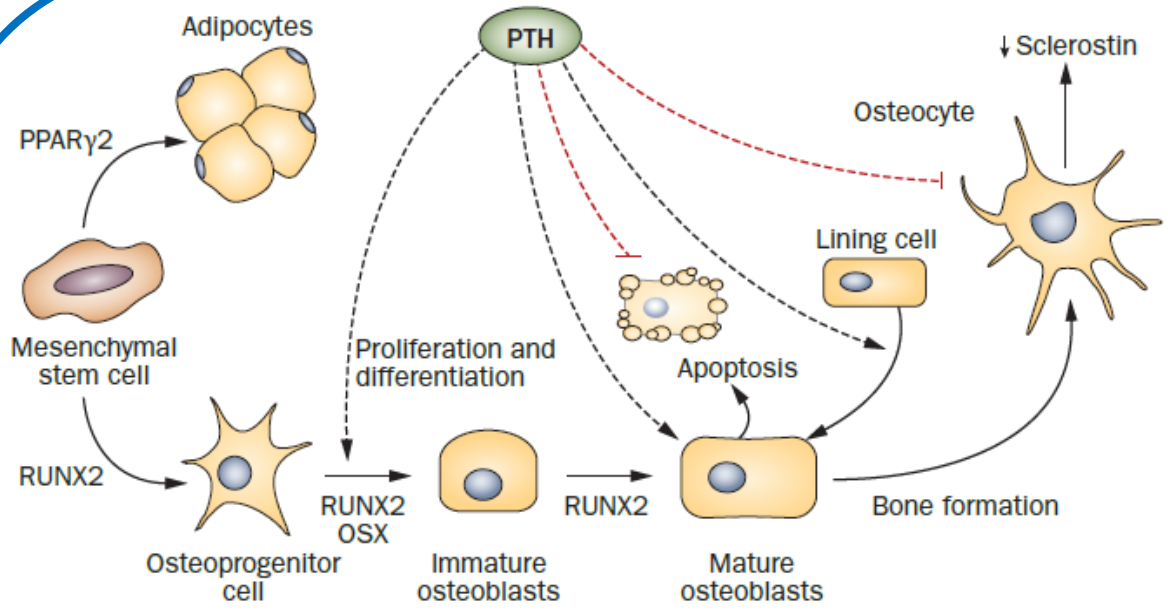
PTH analogs

Teriparatide FORTEO®

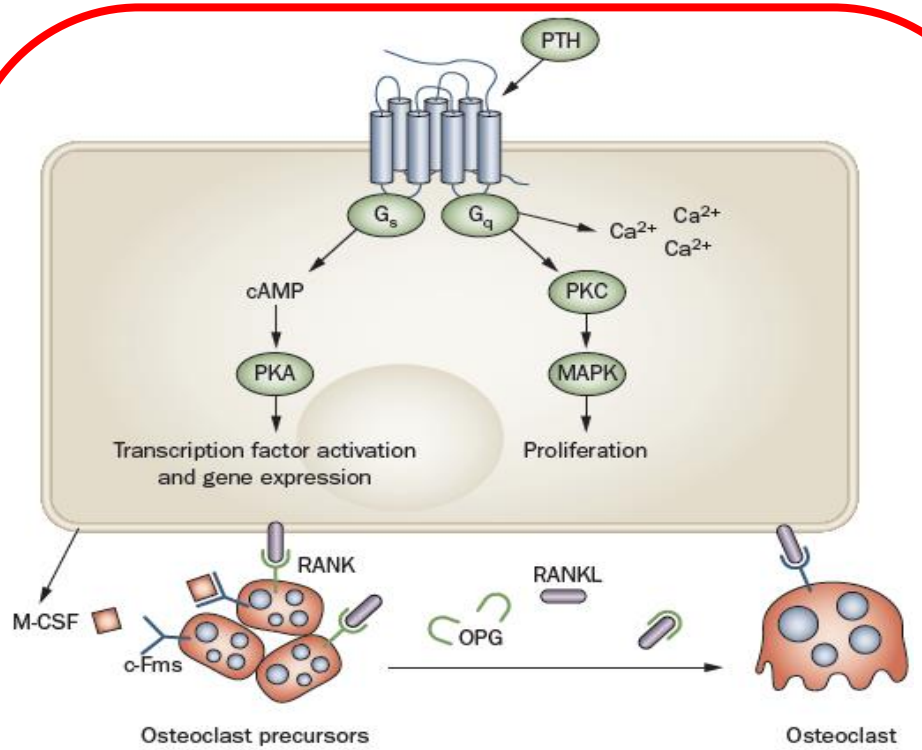
Abaloparatide TYMLOS®


↓Ca2+
CaSR
Parathyroid gland
PTH
PTH1R
Osteoblast
Osteoclast
Bone
Kidney
PTH1R
Phosphate excretion
25(OH)D
CYP27B1
Intestine
VDR
Bone resorption
Ca2+ reabsorption
Calcitriol
Ca2+ absorption
↑Ca2+
Blood vessel

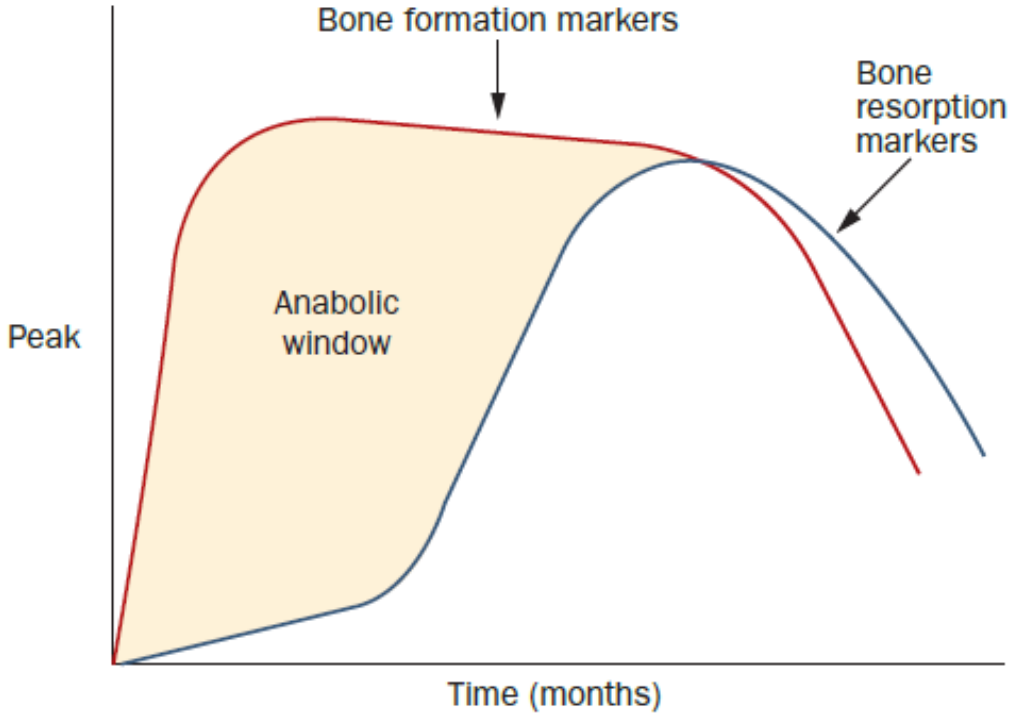

PTH
Intermittent
Continuous
Osteo-
cytes
Sclerostin ↓
Osteoblast
progenitors
Differentiation ↑
Apoptosis ↓
Formation ↑
Resorption -
Anabolic
Osteoblast
progenitors
Matrix
production ↓
RANKL ↑
OPG ↓
Formation ↓
Resorption ↑
Catabolic



❖ Schematic representation of the action of **intermittent PTH** on cells of the osteoblast lineage & on bone formation. PTH induces RUNX2 expression in osteoblasts, increases osteoblast numbers, induces differentiation of committed osteoblast precursors, prolongs osteoblast survival, stimulates transformation of lining cells into active osteoblast & reduces production of sclerostin (a bone-formation inhibitor). Abbreviations: OSX, osterix; PPARγ2, peroxisome proliferator-activated receptor γ2; PTH, parathyroid hormone; RUNX2, Runt-related transcription factor 2.

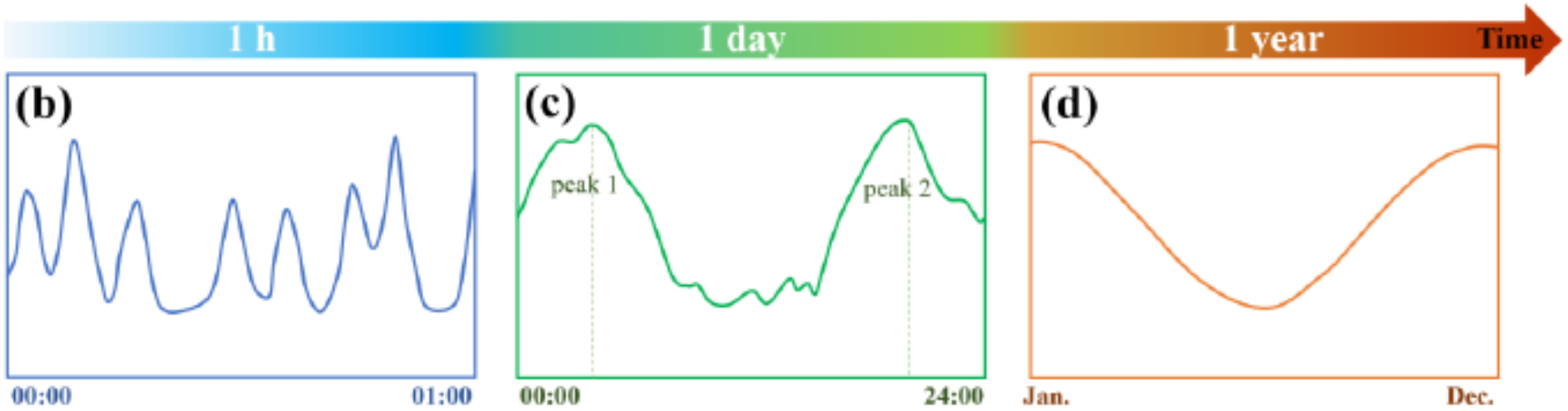


❖ The catabolic effect of **continuous exposure** of osteoblasts to PTH is mediated through increases of the expression of macrophage colony-stimulating factor 1 (M-CSF) & RANKL & a concerted decrease in osteoprotegerin expression, which increase osteoclastogenesis. The RANKL–osteoprotegerin system is the common central pathway that regulates differentiation & activation of osteoclasts by osteoblasts.

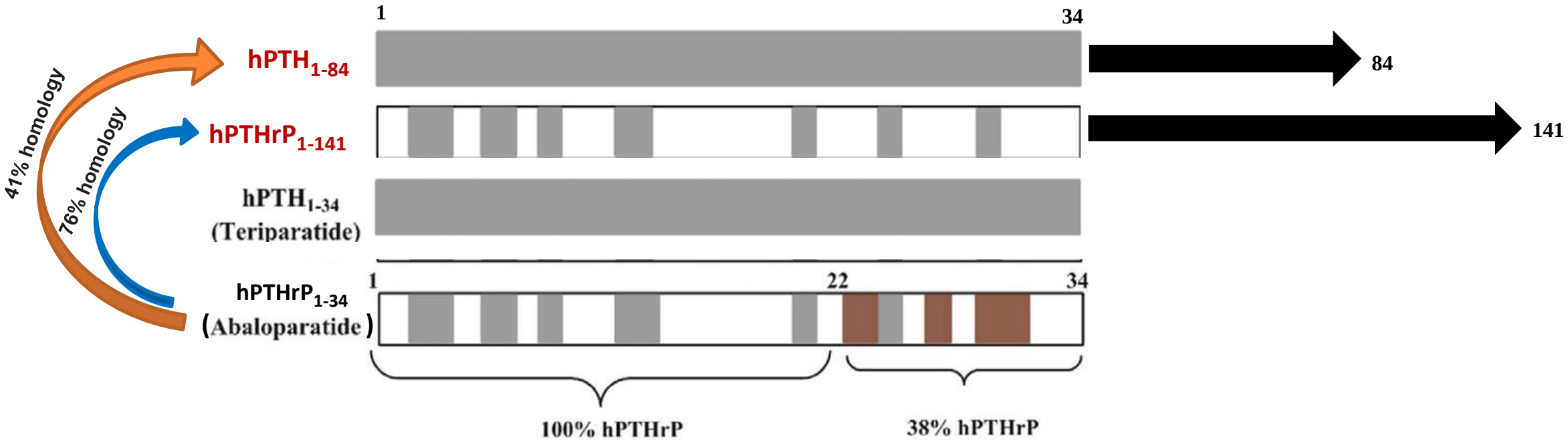


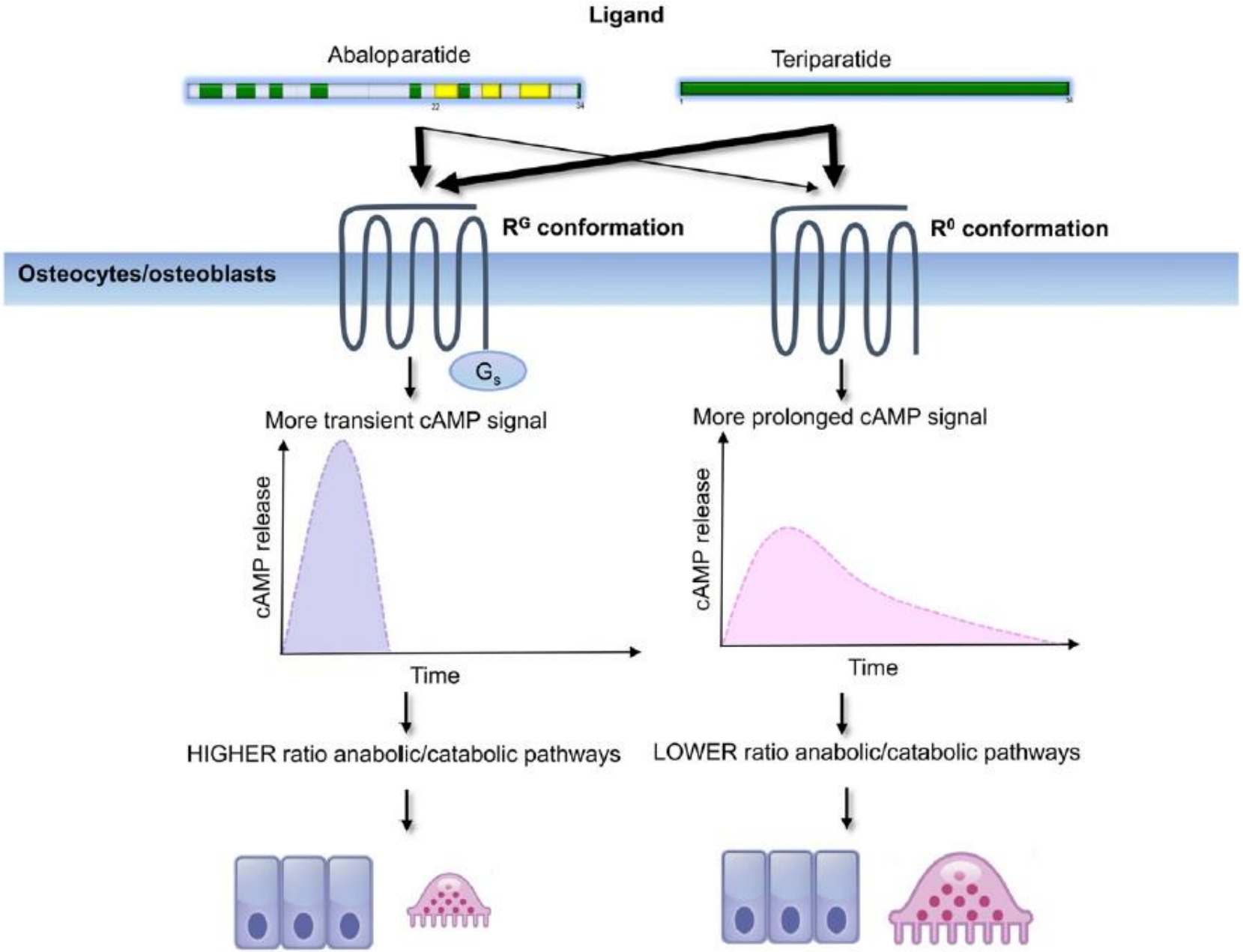
The anabolic window

- Histomorphometric studies & the rapid increase in bone formation markers after initiation of intermittent rhPTH treatment suggest that, **in the early phase of treatment, PTH action is mainly, if not exclusively, anabolic**. Later on, the anabolic effects of PTH seem dependent on bone remodeling—resorption lacunae are refilled & partially 'overfilled'. The sequence of stimulation of bone formation before bone resorption is referred to as an 'anabolic window', a period of time when the anabolic action of PTH prevails.



- (B) schematic diagram of dual fashion characteristic of PTH with 30% tonic secretion & 70% pulsatile secretion. Pulses happen 6 or 7 times per hour.
- (C) schematic diagram of circadian rhythm of PTH with significant rises in the early morning & late afternoon, & a trough in the late morning.
- (D) schematic diagram of circannual rhythm of PTH with a lower level in summer & a higher level in winter.


41% homology
76% homology
hPTH1-84
hPTHrP1-141
hPTH1-34
(Teriparatide)
hPTHrP1-34
(Abaloparatide)
1
34
84
141
1
22
34
100% hPTHrP
38% hPTHrP



A more potent anabolic activation has been proposed with R_G-selective ligands compared to R_0- selective ligands.

Teriparatide

- Recombinant product representing **first 34 amino acids in human PTH**.
- **⬆ Bone formation, ⬆ Bone remodeling rate, ⬆ Osteoblast number & activity;**
  - **Both bone mass & architecture are improved.**
  - Stimulates the interaction of preosteoblasts to osteoblasts within the first month of treatment, peaking 6-9 months after daily administration.
- **Treatment of postmenopausal women** with osteoporosis who are at high to very high risk for fracture.
  - **20 mcg SC once daily**

Efficacy

- ⬇ **Vertebral & Nonvertebral fracture risk.**
- ⬆ **Lumbar spine BMD greater than other medications.**
- **Safety & efficacy have not been studied beyond 2 years & therapy is not recommended after 2 years.**
  - Using a second course of teriparatide is controversial; One study found that a second course ⬆ BMD but not to the extent with the first course.
- **Slight benefit in combination with bisphosphonates;** Concurrent therapy with BPs **should be avoided**, but sequential therapy with antiresorptive agents may consolidate the beneficial effects on the skeleton.
- **More significant effects when combined with denosumab**
- Used to treat & promote healing of bisphosphonate- or denosumab-induced ONJ.
- Discontinuation results in a ⬇ in BMD.

Adverse Events

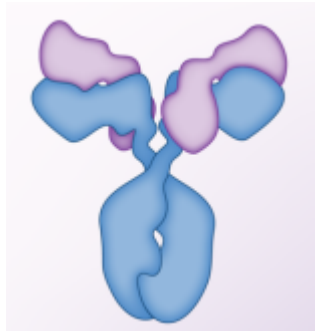
- **<u>Hypercalcemia</u>, leg cramps, nausea, dizziness**
  - Serum calcium after 1 month: If >10.6 mg/mL; ↓ calcium intake
  - Hypercalcemia is generally corrected by reducing calcium or vitamin D supplementation. If these measures fail, a dosage adjustment of teriparatide from daily to every other day administration is usually effective.
- **Orthostatic hypotension**
  - **May occur within 4 h** & spontaneously resolves after a few minutes to hours for the first several doses; patient either sitting or lying down (**at night**)

Administration

- Pen must be kept 2-8°C; can be used immediately after removing from refrigerator
- Pens are stable **for up to 28 days**, including the first injection.
- **After use, the pen should be recapped & protected from light.**

Abaloparatide

- Binds with a much higher affinity to the transient R_G conformation of the PTH type 1 receptor, compared with teriparatide;
  - This mechanism may increase bone formation & decrease bone resorption more than teriparatide.
- **Treatment of postmenopausal women at high fracture risk (year 2017)**
  - **80 mcg SQ daily**
- **Adverse Events**
  - Dizziness, hypercalcemia, hyperuricemia, & injection-site reactions (> 10% of the patients).
  - It be administered in a setting where the patient can sit or lie down if an episode of hypotension occurs.
  - **Incidence of hypercalcemia was significantly lower with abaloparatide compared with teriparatide.**



Romosozumab

EVENITY®

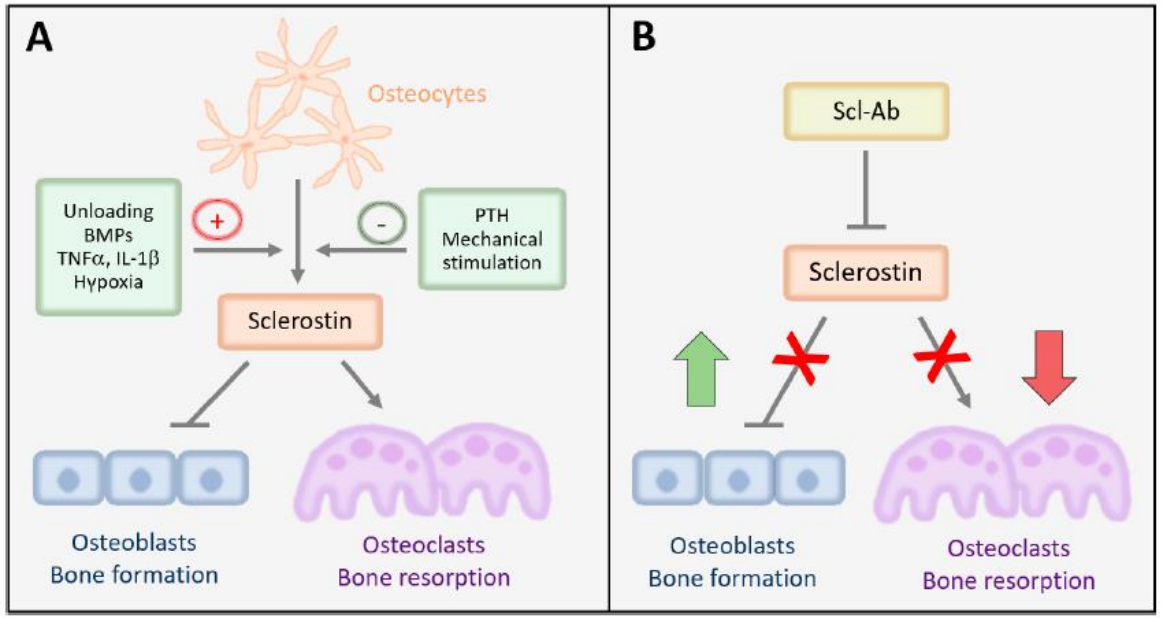
(romosozumab-aqqg)

injection 105 mg/1.17 mL

Romosozumab

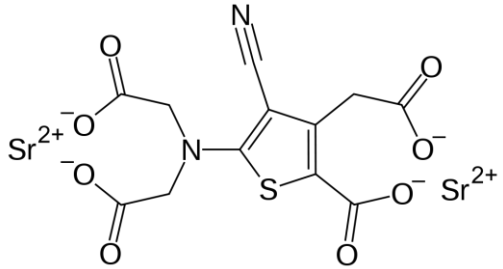
- A humanized monoclonal antibody & **sclerostin inhibitor**, promoting the Wnt pathway that increases bone formation & decreases bone resorption.
- **Sclerostin is responsible for inhibiting the Wnt pathway & decreasing overall bone formation.**

- **Treatment of postmenopausal women at high fracture risk (year 2019)**
  - **210 mg via SC injection once monthly for 12 months.**
    - Use is limited to 12 months as studies evaluating bone turnover markers demonstrated a **waning effect** after this treatment period.



Strontium ranelate

Strontium ranelate



- Consisting of two atoms of strontium & an organic moiety (ranelic acid).
- **Have a modest antiresorptive effect,** with **little** effect on bone formation.
- ⬇ **Spine & Nonspine fractures (35-49%),** ⬆spine BMD (14%), ⬆ femoral neck BMD(8%).
- A substantial proportion of ⬆ in BMD is due to the physical effect of strontium accumulation in bone tissue; therefore the magnitude of change in BMD is not indicative of greater fracture risk reduction.
- **Treatment of postmenopausal osteoporosis**
  - **2 g/day** dissolved in water, prior to bedtime
  - Clcr <30 mL/min: Not recommended
  - **Diarrhea, venous thromboembolism, pulmonary embolism, skin reactions (DRESS, SJS, TEN);**
    - Not prescribe to patients with current VTE, history of VTE, or to patients who are immobilized.
    - It should be discontinued if a skin reaction develops, & **treatment should not be restarted.**

Others

Vitamin K

- Is a cofactor for **carboxylation (activation) of proteins**, such as **osteocalcin**, which are involved in bone formation; Vitamin K deficiency can contribute to bone loss & an ⬆ risk for fractures.
- **Studies evaluating benefits of vitamin K supplementation are conflicting.**

Magnesium

- **Affects the concentration of PTH**, is involved in the formation of bone.
- Low dietary intake of magnesium has been associated with **lower BMD**, but not an increase in the incidence of hip fracture or total fractures.
- People who might need extra magnesium beyond that found in their diets most likely are **elderly women or individuals with GI disease.**

Dietary Soy

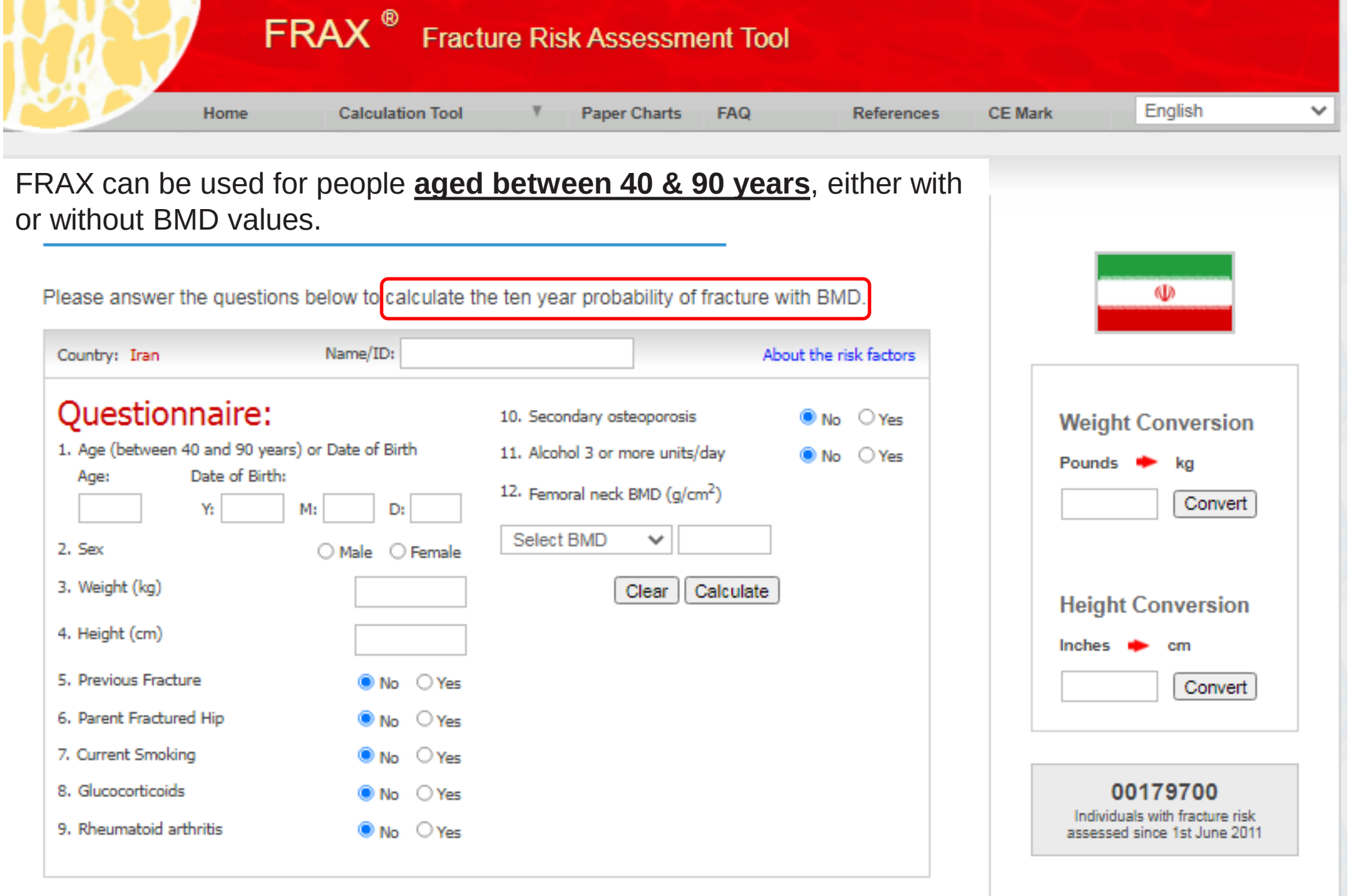
- Isoflavone phytoestrogens possess **weak estrogenic agonist & antagonist effects**.
- The evidence supporting a positive bone benefit from soy protein intake is **conflicting**, with **some studies showing improvements in BMD with larger isoflavone intakes.**

Thiazides

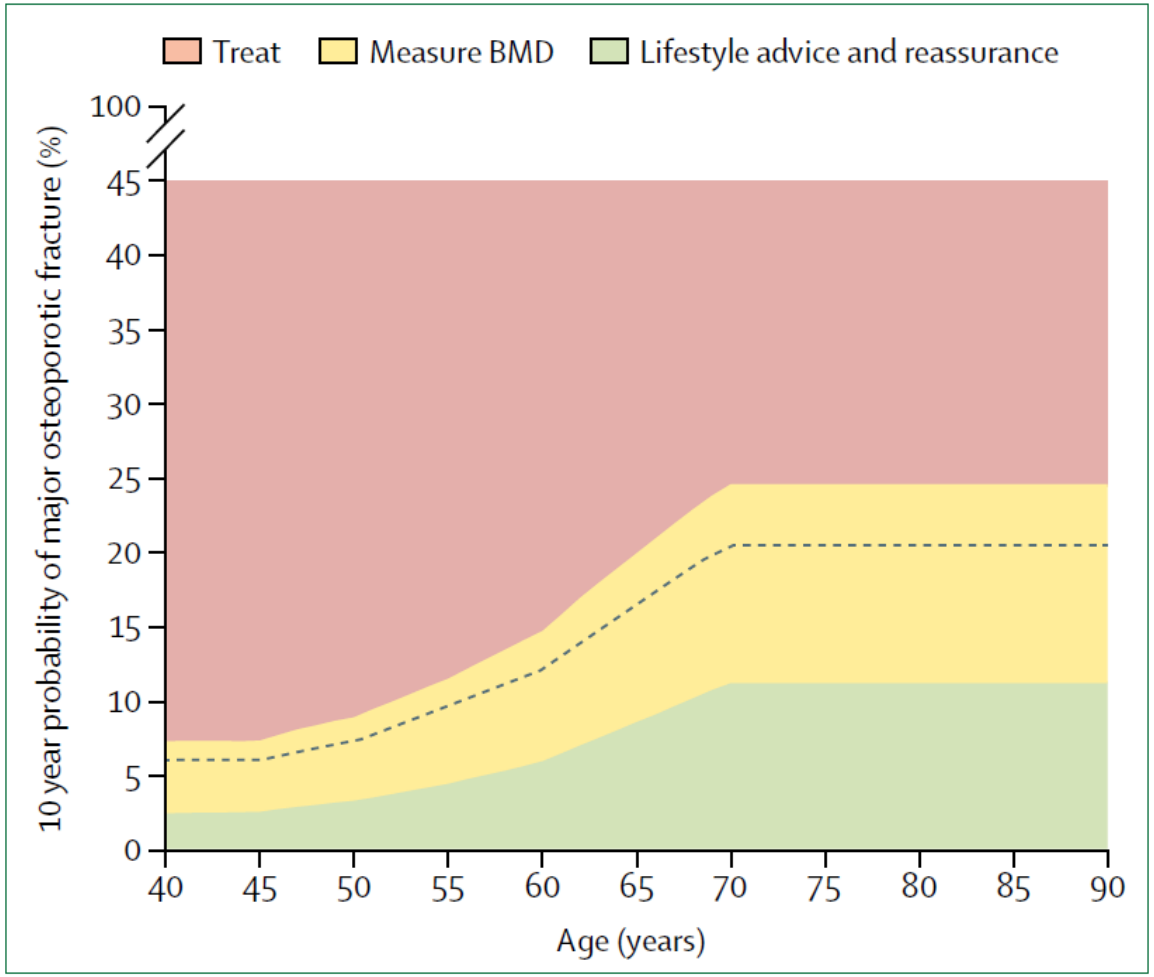
- **Thiazides may ↑ Ca retention**. Whether this effect has a long-term benefit on Ca balance is debatable.
- Thiazide therapy may have a positive effect on BMD.

Potassium, Boron

- **Minimal to no data exist**


FRAX ® Fracture Risk Assessment Tool
Home
Calculation Tool
Paper Charts
FAQ
References
CE Mark
English
FRAX can be used for people aged between 40 & 90 years, either with or without BMD values.
Please answer the questions below to calculate the ten year probability of fracture with BMD.
Country: Iran
Name/ID:
About the risk factors
Questionnaire:
1. Age (between 40 and 90 years) or Date of Birth
Age:
Date of Birth:
Y:
M:
D:
2. Sex
Male
Female
3. Weight (kg)
4. Height (cm)
5. Previous Fracture
6. Parent Fractured Hip
7. Current Smoking
8. Glucocorticoids
9. Rheumatoid arthritis
10. Secondary osteoporosis
11. Alcohol 3 or more units/day
12. Femoral neck BMD (g/cm2)
Select BMD
No
Yes
Clear
Calculate
Weight Conversion
Pounds
kg
Convert
Height Conversion
Inches
cm
Convert
00179700
Individuals with fracture risk assessed since 1st June 2011

UK National Osteoporosis Guidelines Group assessment & treatment thresholds



- **Green** denotes that an individual's risk lies below the intervention threshold—ie, pharmacological intervention is not required.
- **Red** denotes that the fracture probability is consistently above the upper assessment threshold, & pharmacological intervention is strongly recommended in most cases.
- Patients with fracture probabilities in the intermediate category (**yellow**) should be considered for **BMD assessment using DEXA**, & fracture probability should then be recomputed using the FRAX. Pharmacological intervention would be recommended if the recomputed fracture probability exceeds the intervention threshold (dashed line).

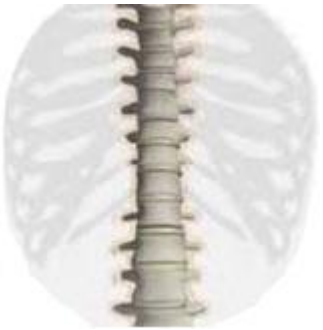
Fracture risk

High risk

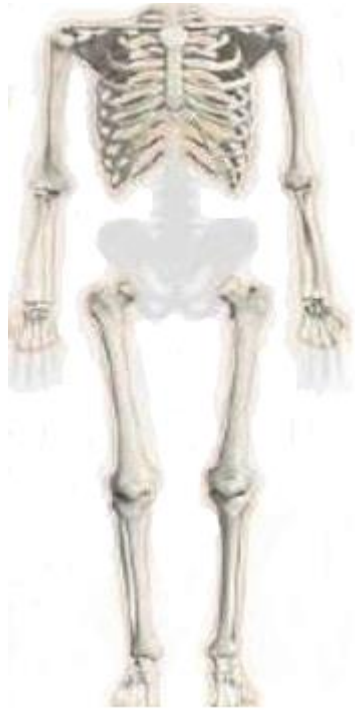
- Prior spine or hip fracture
- T-score at hip or spine of <-2.5 or below
- 10-year hip fracture risk >3%
- Risk of major osteoporotic fracture >20%

Very high risk

- History of multiple spinal fractures is present, along with a diagnostic T-score.

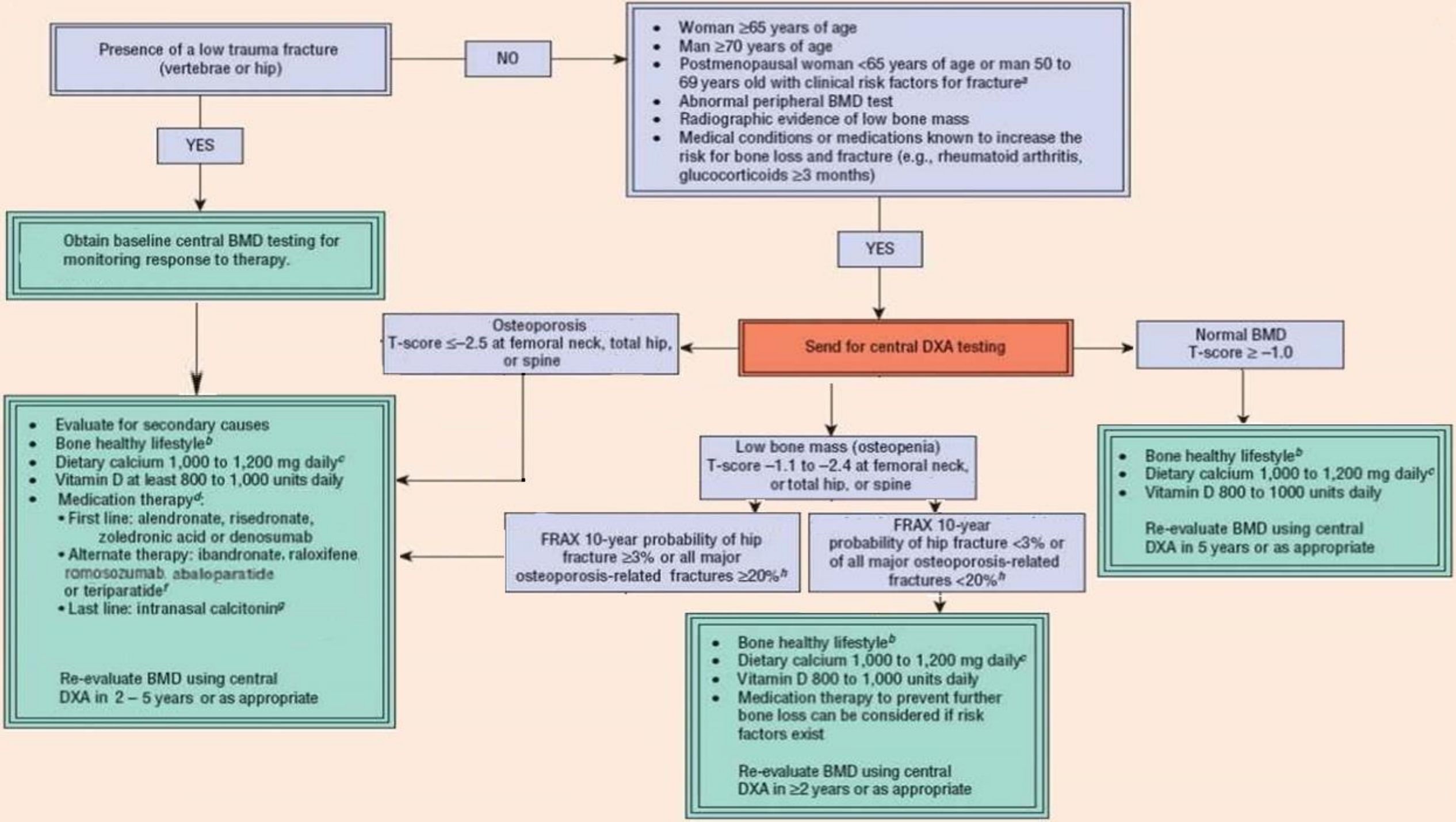


Vertebral Fracture



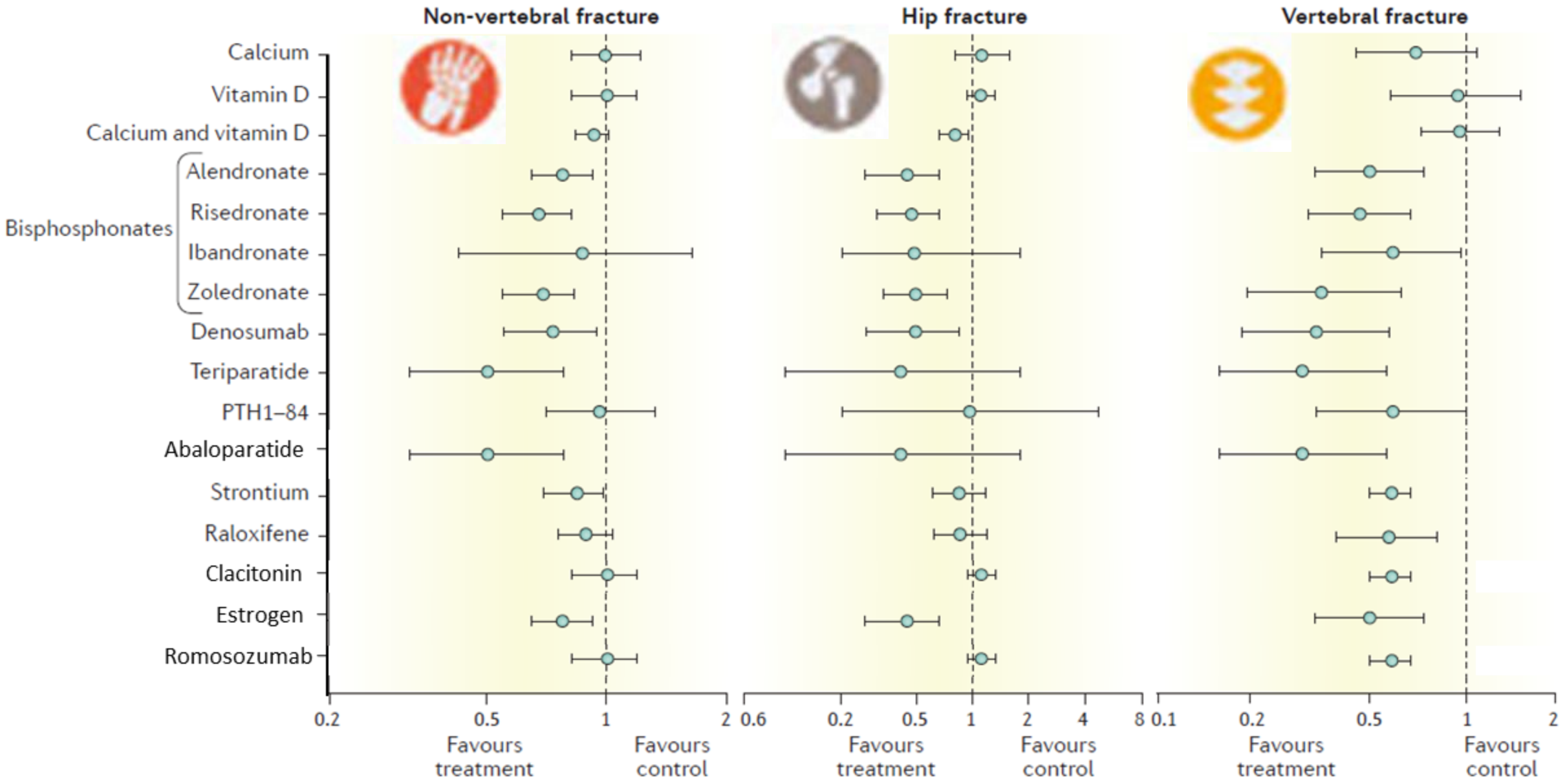
Nonvertebral Fracture

Hip Fracture


Presence of a low trauma fracture (vertebrae or hip)
NO
Woman ≥65 years of age
Man ≥70 years of age
Postmenopausal woman <65 years of age or man 50 to 69 years old with clinical risk factors for fracture[a]
Abnormal peripheral BMD test
Radiographic evidence of low bone mass
Medical conditions or medications known to increase the risk for bone loss and fracture (e.g., rheumatoid arthritis, glucocorticoids ≥3 months)
YES
YES
Obtain baseline central BMD testing for monitoring response to therapy.
Osteoporosis
T-score ≤–2.5 at femoral neck, total hip, or spine
Send for central DXA testing
Normal BMD
T-score ≥ –1.0
Evaluate for secondary causes
Bone healthy lifestyle[b]
Dietary calcium 1,000 to 1,200 mg daily[c]
Vitamin D at least 800 to 1,000 units daily
Medication therapy[d]:
First line: alendronate, risedronate, zoledronic acid or denosumab
Alternate therapy: ibandronate, raloxifene romosozumab, abaloparatide or teriparatide[f]
Last line: intranasal calcitonin[g]
Re-evaluate BMD using central DXA in 2 – 5 years or as appropriate
Low bone mass (osteopenia)
T-score –1.1 to –2.4 at femoral neck, or total hip, or spine
FRAX 10-year probability of hip fracture ≥3% or all major osteoporosis-related fractures ≥20%[h]
FRAX 10-year probability of hip fracture <3% or of all major osteoporosis-related fractures <20%[h]
Bone healthy lifestyle[b]
Dietary calcium 1,000 to 1,200 mg daily[c]
Vitamin D 800 to 1000 units daily
Re-evaluate BMD using central DXA in 5 years or as appropriate
Bone healthy lifestyle[b]
Dietary calcium 1,000 to 1,200 mg daily[c]
Vitamin D 800 to 1,000 units daily
Medication therapy to prevent further bone loss can be considered if risk factors exist
Re-evaluate BMD using central DXA in ≥2 years or as appropriate

		Dose	Route	Type of Fracture Prevention
Bisphosphonate	Alendronate	10 mg daily 70 mg weekly	Oral	
	Risedronate	5 mg daily 35 mg weekly 150 mg monthly	Oral	
	Ibandronate	2.5 mg daily 150 mg monthly 3 mg Q3 months	Oral Oral Intravenous	
	Zoledronic acid	5 mg Yearly	Intravenous	
RANK Ligand Inhibitor	Denosumab	60 mg Q6 months	Subcutaneous	
Selective Estrogen Receptor Modulators	Raloxifene	60 mg daily	Oral	
PTH Analogs	Teriparatide	20 mg daily (for 2 years)	Subcutaneous	
	Abaloparatide	80 mg daily (for 2 years)	Subcutaneous	
Sclerostin Inhibitor	Romosozumab	210 mg monthly (for 1 years)	Subcutaneous	
Calcitonin	Calcitonin	200 IU daily 100 IU daily	Intranasal Subcutaneous	

Fracture prevention by osteoporotic agents



Medication	Vertebral Fracture	Nonvertebral Fracture	Hip Fracture	% Change in Spine BMD[b]	% Change in Hip BMD[b,c]
Abaloparatide	86%↓	43%↓	↔	10.4%↑	4.3%↑
Teriparatide	65%↓	53%↓	↔	8.6%-9.7%↑	3.5%↑
Bazedoxifene	35%-40%↓	↔[d]	↔	2.2%↑	0.5%↑
Bazedoxifene with conjugated equine estrogens	ND	ND	ND	0.24%-1.6%↑	0.2%-1.5%↑
Raloxifene	30%-68%↓	↔	↔	2.6%↑	2.1%↑
Estrogen with or without a progestogen	33%- 40%↓	13%-27%↓	30%-50%↓	3.5%-7%↑[f]	1.7%-5%↑
Bisphosphonates	40%-70%↓	25%-40%↓[e]	40%-53%↓[f]	4.3%-6.7%↑	2.8%-6.0%↑
Denosumab	68%↓	20%↓	40%↓	9.2%↑	6.0%↑
Calcitonin	33%↓	↔	↔	3%↑	↔
Romosozumab	73%↓	25%↓	ND	13.3%↑	6.8%↑

[a]Fracture reductions are relative risk reductions, no head to head fracture studies except for raloxifene and bazedoxifene, data should only be used for relative between class comparisons, clinical trials have different patient samples and study designs, most pivotal fracture trials were of 3-year duration except for abaloparatide (2 year), romosozumab (1 year) and teriparatide studies (18 months).

[b]Relative to placebo; may vary based on duration of therapy and timing relative to menopause.

[c]Total hip (alendronate, ibandronate, zoledronic acid, bazedoxifene, denosumab, estrogen, abaloparatide, teriparatide, romosozumab) or femoral neck (calcitonin, estrogen, risedronate, and raloxifene).

[d]50% decreases in nonvertebral fractures in subgroup of high-risk postmenopausal women (very low BMD and or previous fractures).

[e]Risedronate and zoledronic acid only; nonvertebral fracture reductions with ibandronate were not significant.

[f]Alendronate, risedronate, and zoledronic acid only; hip fracture data not reported with ibandronate.

%, percent; BMD, bone mineral density; ↓, decrease; ↑, increase; ↔, no significant change; ND, no data.

Combination Therapies

➢ Teriparatide & Denosumab

- Did result in greater hip BMD effects, but long-term results are generally similar to sequential therapy.

➢ Teriparatide & Raloxifene

- Was associated with greater improvement in hip BMD than was teriparatide alone in a 6-month trial.

➢ Teriparatide & Oral BPs

- Does not produce any meaningful benefit over monotherapy; resulted in less BMD gains than monotherapy, & thus is not used.

➢ Two antiresorptive agents

- did not increase bone mass compared to monotherapy.

➢ Two anabolic agents

- did not increase bone mass compared to monotherapy.

Sequential Therapy

- In sequential therapy, **an anabolic agent is given first** to increase bone remodeling units & bone mass, **followed by an antiresorptive agent** to continue with bone formation.
  - **Starting with an antiresorptive first & then switching to teriparatide results in lower BMD increases.** However, this therapy will be used, especially for patients who have fractured or continue to lose bone mass while on antiresorptive therapy.

- **The anabolic agent teriparatide is used for up to 2 years** & then followed by an antiresorptive agent (eg, alendronate or denosumab).
- **Sequential therapy is reserved for patients with severe osteoporosis because of the cost of anabolic agents.**

- Small increases in BMD can be seen when **switching from an oral bisphosphonate to denosumab**. This sequential therapy can be used during a bisphosphonate drug holiday or for bisphosphonate treatment failures (no BMD changes or fracture).
- **Bisphosphonates can be initiated after estrogen discontinuation** to help negate the accelerated bone loss that occurs once estrogen is stopped.

Thanks

Dr_Taraz_Drugstore