Osteoporosis
pathophysiology

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- Dynamic tissue

  osteoblasts

  osteoclasts

Extracellular matrix :

sold mineral phase + organic matrix(90-95% type 1 collagen)

Non collagenous : organic matrix (serum proteins + local proteins)

Local proteins ➔attachment / signaling proteins :

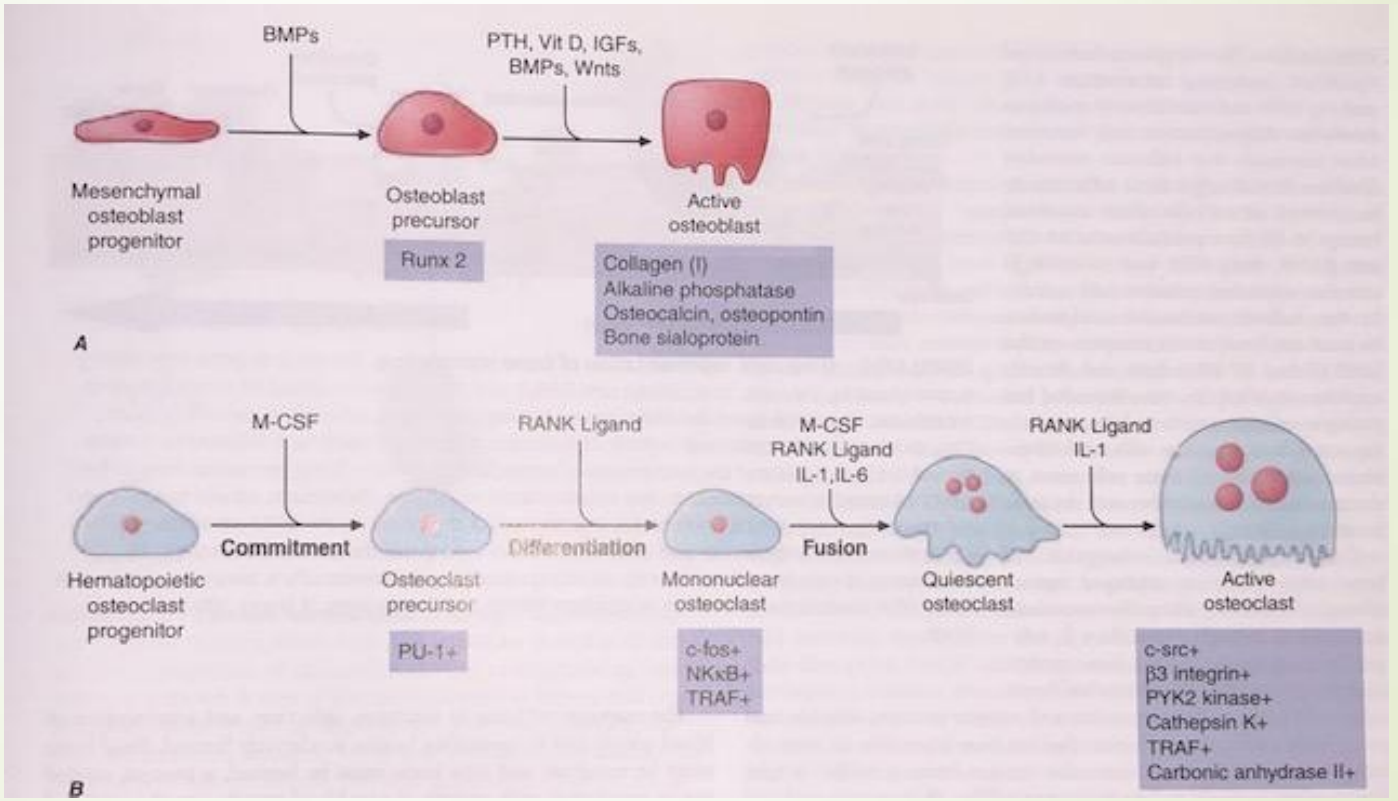
thrombospondin-osteopontin-fibronectin-calcium binding proteins(gla Pr-osteocalcin)

Mineral : ca / phosphate

- Osteoblast ➔ organic matrix
- Osteocyte ➔ FGF-23

- mineralization (primary-secondary)

  osteoblast derived alkaline phosphatase


BMPs
PTH, Vit D, IGFs,
BMPs, Wnts
Mesenchymal
osteoblast
progenitor
Osteoblast
precursor
Runx 2
Active
osteoblast
Collagen (I)
Alkaline phosphatase
Osteocalcin, osteopontin
Bone sialoprotein
A
M-CSF
RANK Ligand
M-CSF
RANK Ligand
IL-1,IL-6
RANK Ligand
IL-1
Commitment
Differentiation
Fusion
Hematopoietic
osteoclast
progenitor
Osteoclast
precursor
PU-1+
Mononuclear
osteoclast
c-fos+
NKκB+
TRAF+
Quiescent
osteoclast
Active
osteoclast
c-src+
β3 integrin+
PYK2 kinase+
Cathepsin K+
TRAF+
Carbonic anhydrase II+
B

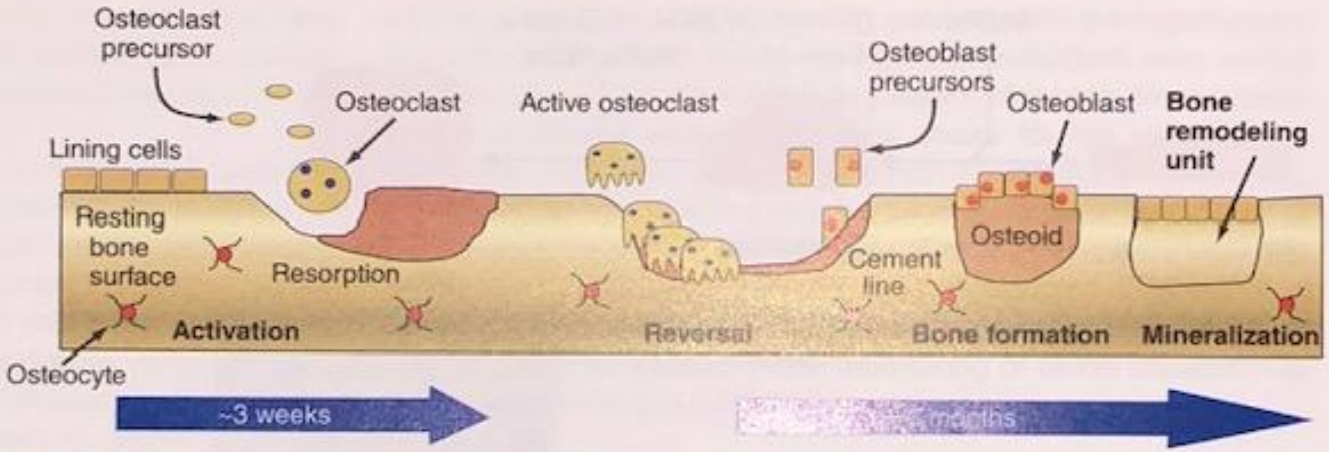


FIGURE 423-2 Schematic representation of bone remodeling. The cycle of bone remodeling is carried out by the basic multicellular unit (BMU), which consists of a group of osteoclasts and osteoblasts. In cortical bone, the BMUs tunnel through the tissue, whereas in cancellous bone, they move across the trabecular surface. The process of bone remodeling is initiated by contraction of the lining cells and the recruitment of osteoclast precursors. These precursors fuse to form multinucleated, active osteoclasts that mediate bone resorption. Osteoclasts adhere to bone and subsequently remove it by acidification and proteolytic digestion. As the BMU advances, osteoclasts leave the resorption site and osteoblasts move in to cover the excavated area and begin the process of new bone formation by secreting osteoid, which eventually is mineralized into new bone. After osteoid mineralization, osteoblasts flatten and form a layer of lining cells over new bone.

- Genetic factors:

  sex hormones (during puberty)

  nutrition and life style

  Heritability : 50-80% for bone density and size(basis of twin studies)

  growth hormone , glococorticoids , Estrogen

Vit D receptor,type1 collagen,estrogen receptor(ER), IL-6 , IGF-1

Locus on chromosome11 ➔ high bone mass

Point mutation in LRP5(low density receptor protein) ➔ osteoporosispseudoglioma syndrome

- Runx2 :

  osterix,osteopontin,bone sialoprotein,collagen 1,osteocalcin, RANK

  Ihh (indian hegdehoge)

1,25[OH]2D / PTH/ IGFs I-II / TGF-a2 / FGFs 2,18 / PDGF

Bone resorption :

- Osteoclasts

  M-CSF : fusion of osteoclast progenitors

  TNF / RANK / osteoprotegrin (OPG) / IL-1-6-11 / Inf λ

Calcitonin ➔ osteoclast activity inhibitor (direct)

PTH / 1,25 [OH]2 vitD ➔ ↑ numbers and activity (indirect)

Estradiol ➔ ↓ bone resorption

- Osteoblast bone dependent bone resorption :

Hawship lacunae

solubilize mineral phase

proton , chloride , proteinase (extracellular lysosome)

- Enchondral bone formation

  chondrocyte proliferation➔ secrete and mineralize bone matrix ➔ hypertrophy ➔ cell death ➔ bone enlargement ➔ more bone formation

- Intramembranous bone formation

Osteoporosis

- Definition

T-score <-2.5

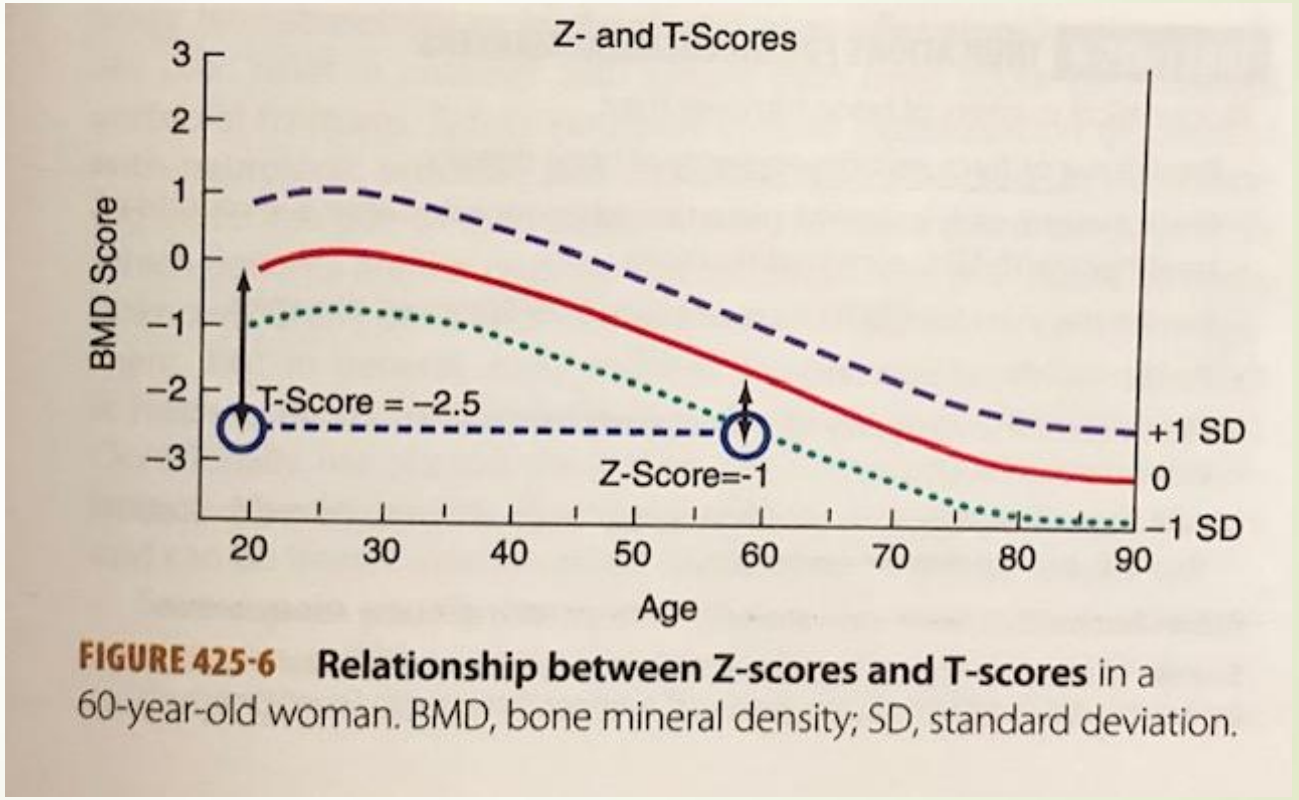


FIGURE 425-6 Relationship between Z-scores and T-scores in a 60-year-old woman. BMD, bone mineral density; SD, standard deviation.

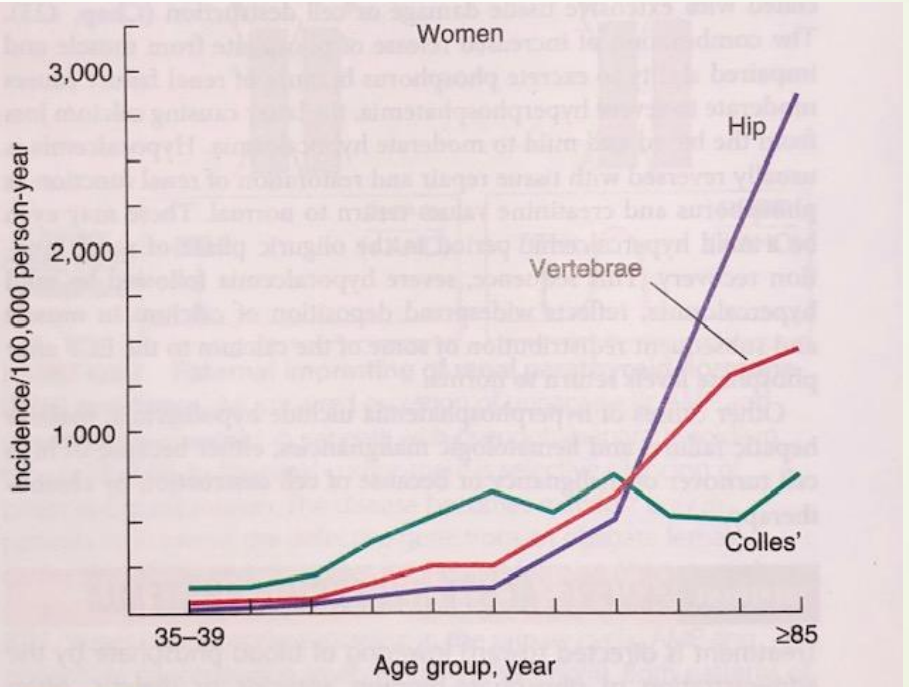


FIGURE 425-1 Epidemiology of vertebral, hip, and Colles' fractures with age. *(Adapted from C Cooper, LJ Melton III: Trends Endocrinol Metab 3:224, 1992; with permission.)*

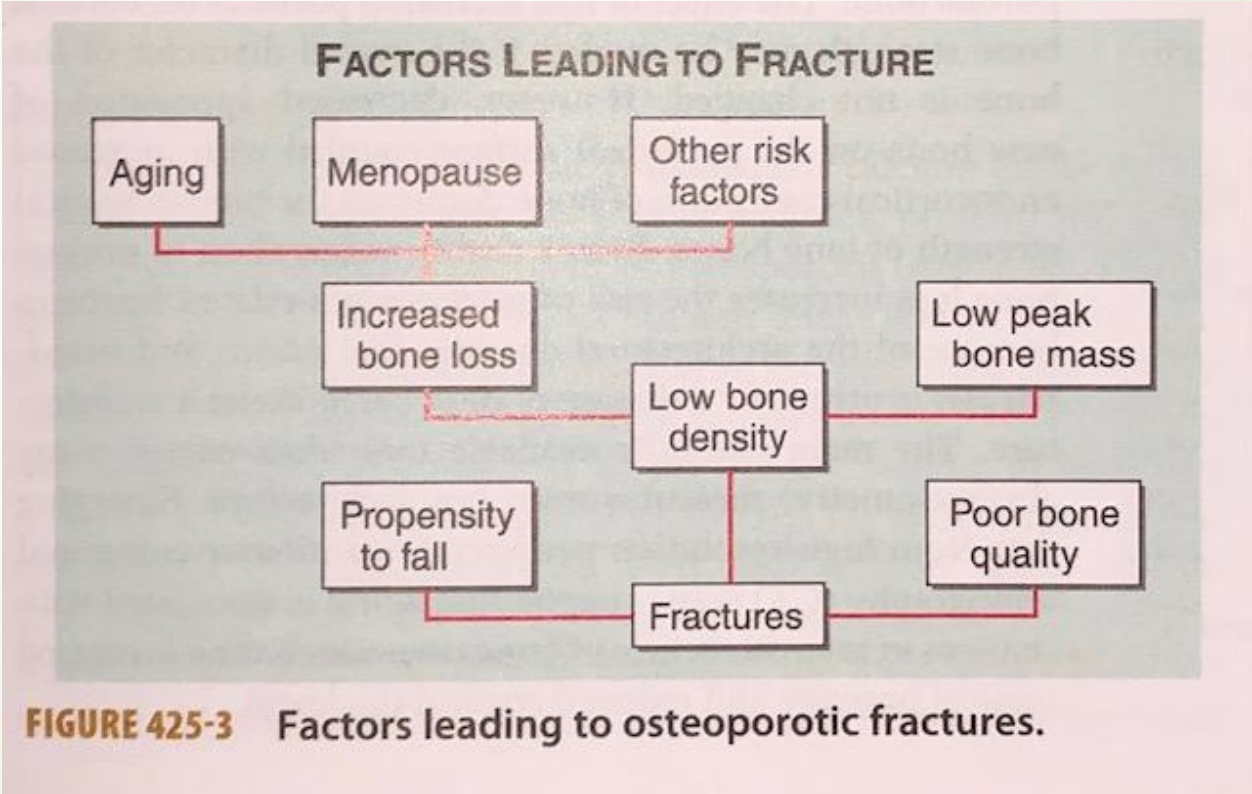


FIGURE 425-3 Factors leading to osteoporotic fractures.

- Bone remodeling :

1- repair of microdamage

2- supply calcium

- Acute demand of calcium
- Chronic demand of calcium

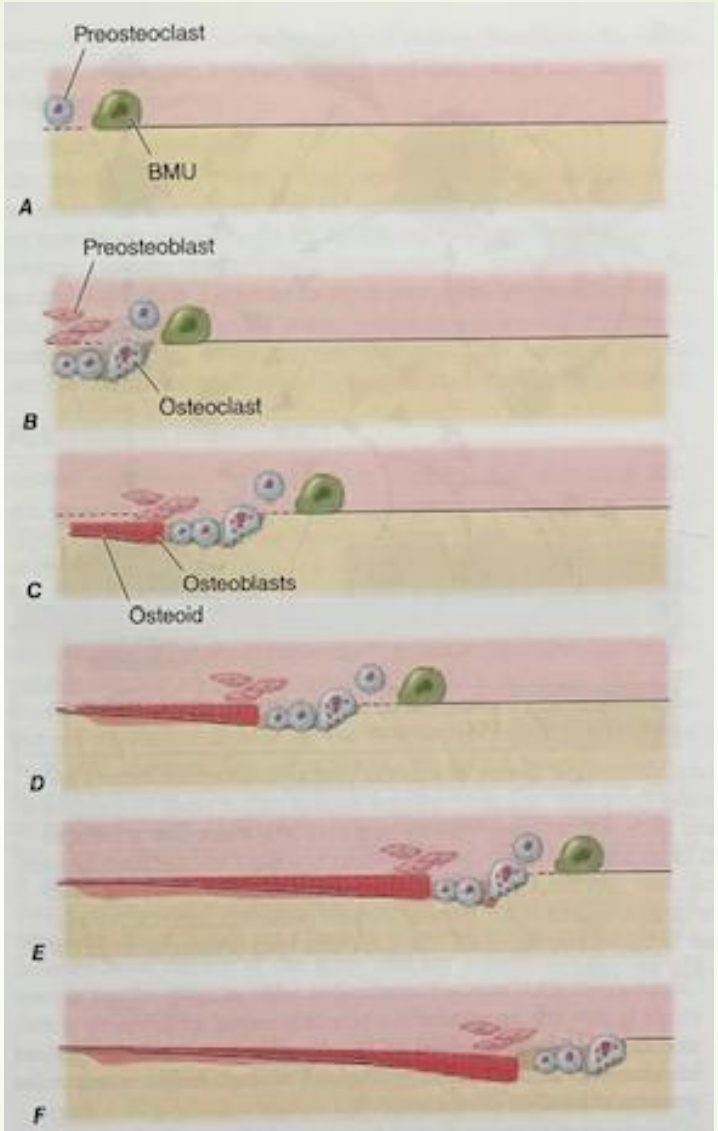


FIGURE 425-4 Mechanism of bone remodeling. The basic molecular unit (BMU) moves along the trabecular surface at a rate of about 10 μm/d. The figure depicts remodeling over ~120 days. ***A.*** Origination of BMU-lining cells contracts to expose collagen and attract preosteoclasts. ***B.*** Osteoclasts fuse into multinucleated cells that resorb a cavity. Mononuclear cells continue resorption, and preosteoblasts are stimulated to proliferate. ***C.*** Osteoblasts align at bottom of cavity and start forming osteoid (*black*). ***D.*** Osteoblasts continue formation and mineralization. Previous osteoid starts to mineralize (*horizontal*

- Circulating hormones :

  PTH,estrogens,androgens,vitD

  +

  local growth factors :

  IGF-1, IGH-II , TGF-β , PTHrP , Ils , prostaglandins , TNFs

- RANKL

  receptor activator of nuclear factor k ligand

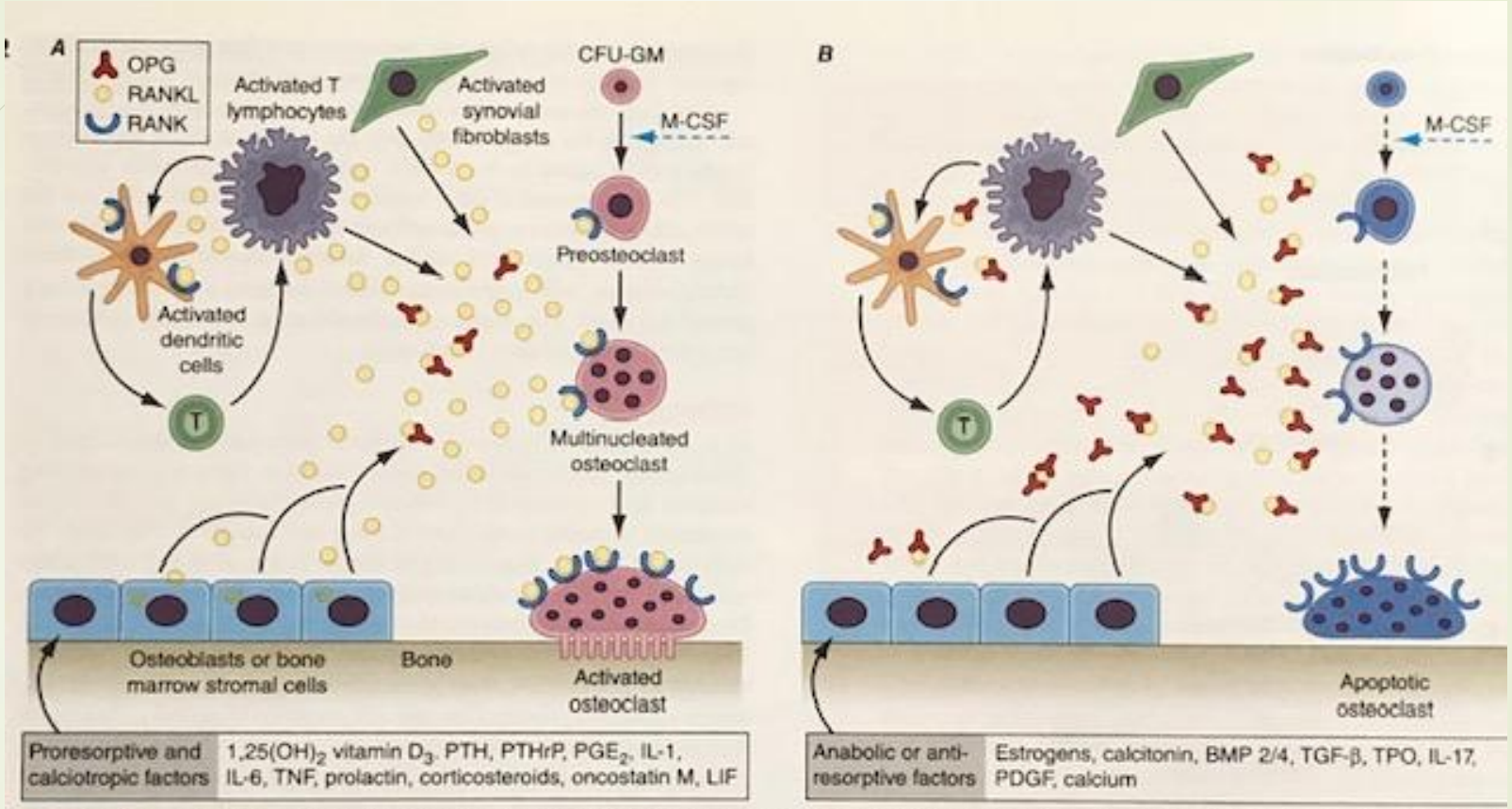


FIGURE 425-5 Hormonal control of bone resorption. ***A.*** Proresorptive and calciotropic factors. ***B.*** Anabolic and antiosteoclastic factors. RANK ligand (RANKL) expression is induced in osteoblasts, activated T cells, synovial fibroblasts, and bone marrow stromal cells. It binds to membrane bound receptor RANK to promote osteoclast differentiation, activation, and survival. Conversely, osteoprotegerin (OPG) expression is induced by factors that block bone catabolism and promote anabolic effects. OPG binds and neutralizes RANKL, leading to a block in osteoclastogenesis and decreased survival of preexisting osteoclasts. CFU-GM, colony-forming units, granulocyte macrophage; IL, interleukin; LIF, leukemia inhibitory factor; M-CSF, macrophage colony-stimulating factor; OPG-L, osteoprotegerin-ligand; PDGF, platelet-derived growth factor; PGE_2, prostaglandin E_2; PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor nuclear factor-κB; TGF-β, transforming growth factor β; TNF, tumor necrosis factor; TPO, thrombospondin. *(From WJ Boyle et al: Nature 423: 337, 2003.)*

- In young adults , resorbed bone is replaced by an equal amount of new bone tissue
- After age 30-45 the resorption and formation processes become imbalanced
- Resorption exceeds formation

- Excessive bone loss
  - increase in osteoclastic activity
  - decrease in osteoblastic activity

- Increased recruitment of bone remodeling :

  trabecular bone : impaired cancellous connectivity

  cortical bone : increased porosity of bone

- Calcium nutrition : 1200 mg/day
- Vit D : optimum level : 30ng/mL
  colorectal/prostate/breast CA
  autoimmune disease
  diabetes

- Estrogen status :

1- activating of new bone remodeling sites

2- exaggeration of the imbalance between bone formation and resorption

Post menopause :

↓ Estrogen ➔ ↑ RANKL ➔ ↓ Production of OPG

- Controlling the rate of apoptosis

Estrogen → life span of osteoblasts

→ longevity and activity of osteoclasts

The most common site of fracture : trabecular bone (vertebrae)

- Physical activity :

  during growth , before the age of puberty ➔ higher bone mass

- Chronic diseases :

  genetic or acquired

  multifactorial

- **Medications** :

  glucocorticoids
  thyroid hormone
  anticonvulsants
  immunosuppressants
  aromatase inhibitors
  SSRI
  PPI
  Thiasolidinedions

- Cigarette smoking :

  direct

  indirect

secondary effects :

intercurent respiratory

frailty

decreased exercise/poor nutrition / need of additionbal medications

TABLE 425-1 CONDITIONS, DISEASES, AND MEDICATIONS THAT CONTRIBUTE TO OSTEOPOROSIS AND FRACTURES

Lifestyle factors		
Alcohol abuse	High salt intake	Falling
Low calcium intake	Inadequate physical activity	Excessive thinness
Vitamin D insufficiency	Immobilization	Prior fractures
Excess vitamin A	Smoking (active or passive)	
Genetic factors		
Cystic fibrosis	Homocystinuria	Osteogenesis imperfecta
Ehlers-Danlos syndrome	Hypophosphatasia	Parental history of hip fracture
Gaucher's disease	Idiopathic hypercalciuria	Porphyria
Glycogen storage diseases	Marfan's syndrome	Riley-Day syndrome
Hemochromatosis	Menkes' steely hair syndrome	
Hypogonadal states		
Androgen insensitivity	Hyperprolactinemia	Athletic amenorrhea
Anorexia nervosa and bulimia	Premature menopause	Panhypopituitarism
Turner's & Klinefelter's syndromes	Premature ovarian failure	
Endocrine disorders		
Adrenal insufficiency	Cushing's syndrome	Central adiposity
Diabetes mellitus (types 1 and 2)	Hyperparathyroidism	Thyrotoxicosis
Gastrointestinal disorders		
Celiac disease	Inflammatory bowel disease	Primary biliary cirrhosis
Gastric bypass	Malabsorption	
Gastrointestinal surgery	Pancreatic disease	
Hematologic disorders		
Multiple myeloma	Monoclonal gammopathies	Sickle cell disease
Hemophilia	Leukemia and lymphomas	Systemic mastocytosis
Thalassemia		
Rheumatologic and autoimmune diseases		
Ankylosing spondylitis	Lupus	Rheumatoid arthritis
Other rheumatic and autoimmune diseases		
Central nervous system disorders		
Epilepsy	Parkinson's disease	Stroke
Multiple sclerosis	Spinal cord injury	
Miscellaneous conditions and diseases		
AIDS/HIV	Congestive heart failure	Posttransplant bone disease
Alcoholism	Depression	Sarcoidosis
Amyloidosis	End-stage renal disease	Weight loss
Chronic metabolic acidosis	Hypercalciuria	
Chronic obstructive lung disease	Idiopathic scoliosis	
	Muscular dystrophy	
Medications		
Aluminum (in antacids)	Glucocorticoids (≥5 mg/d prednisone or equivalent for ≥3 months)	Tamoxifen (premenopausal use)
Anticoagulants (heparin)	Gonadotropin-releasing hormone antagonists and agonists	Thiazolidinediones (such as pioglitazone and rosiglitazone)
Anticonvulsants	Lithium	Thyroid hormones (in excess)
Aromatase inhibitors	Methotrexate	Parenteral nutrition
Barbiturates	Proton pump inhibitors	
Cancer chemotherapeutic drugs	Selective serotonin reuptake inhibitors	
Cyclosporine A and tacrolimus		
Depo-medroxyprogesterone (premenopausal contraception)		

Source: From the 2014 National Osteoporosis Foundation Clinician's Guide to the Prevention and


با تشکر از توجه شما