



Osteoporosis and bone metabolism

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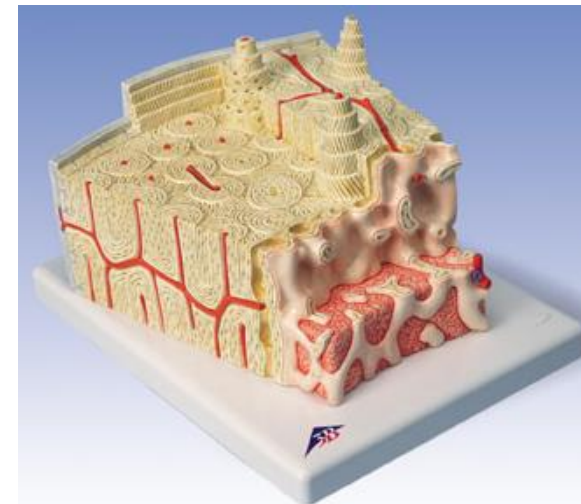
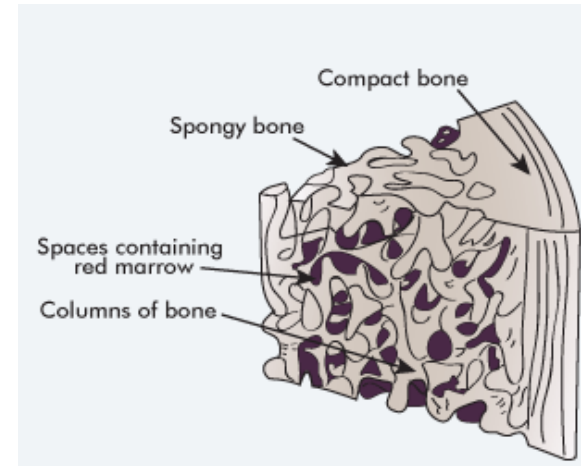
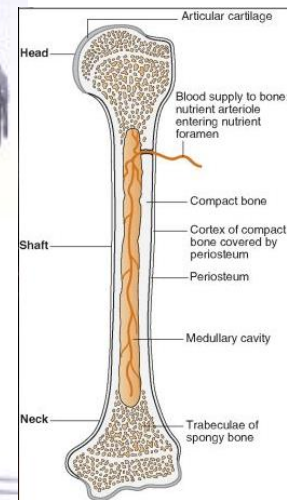
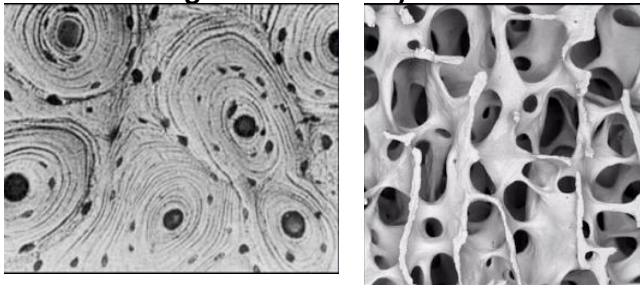
ESIM Riga 26.01.2015



Form and function of skeleton

Skeleton: cortical and trabecular bone

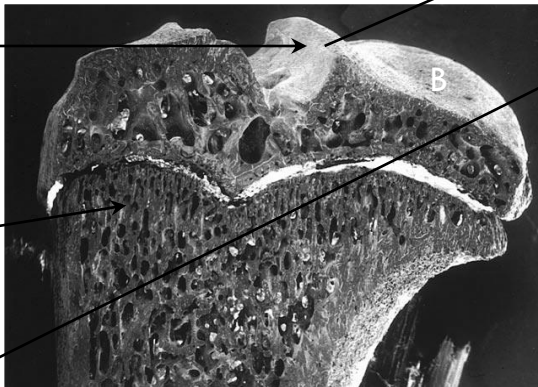
- Skeleton is a dynamic organ. It consists of more than 200 bones with mechanical, protective and metabolic function
- There is:
 - **Cortical bone** – outer layer of the bone (approx. 80% of the total mass of skeleton, regeneration rate 2-3% per year, attachment point for tendon and muscle, protects organs, solid, hard)
 - **Trabecular bone** – connects with cortical bone from within (approx. 20% of the total mass of skeleton, solid, elastic, mineral storage, regenerates faster)



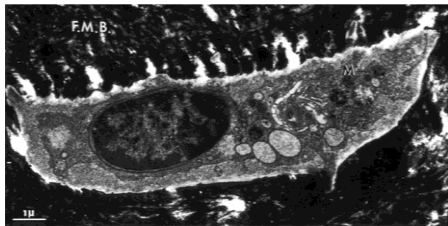
Bone anatomy:

- **Cortical bone (80%)** – outer layer of bone. Responsible for compact features and mechanical strength of skeleton
- **Trabecular bone (20%)** – in vertebrae and epiphysis of long bones. It has wide exposure to bone marrow, huge impact on bone metabolism and Ca body reserves. Higher content in vertebrae, more often affected in osteoporosis

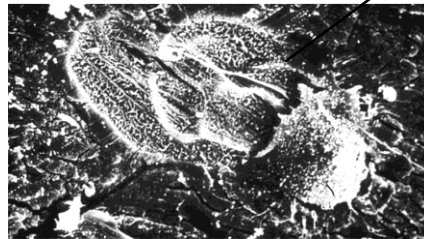
Cortical bone



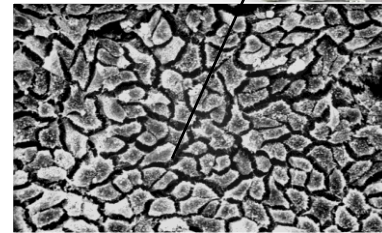
Trabecular bone



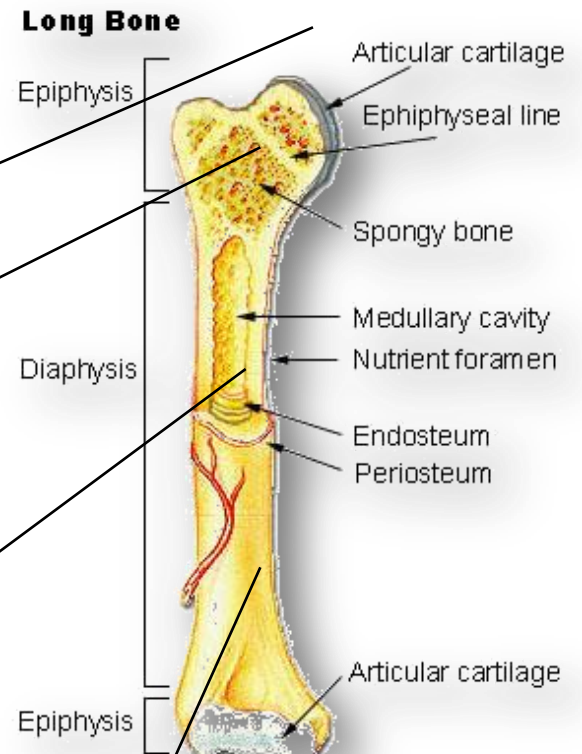
Osteocyte



Osteoclast

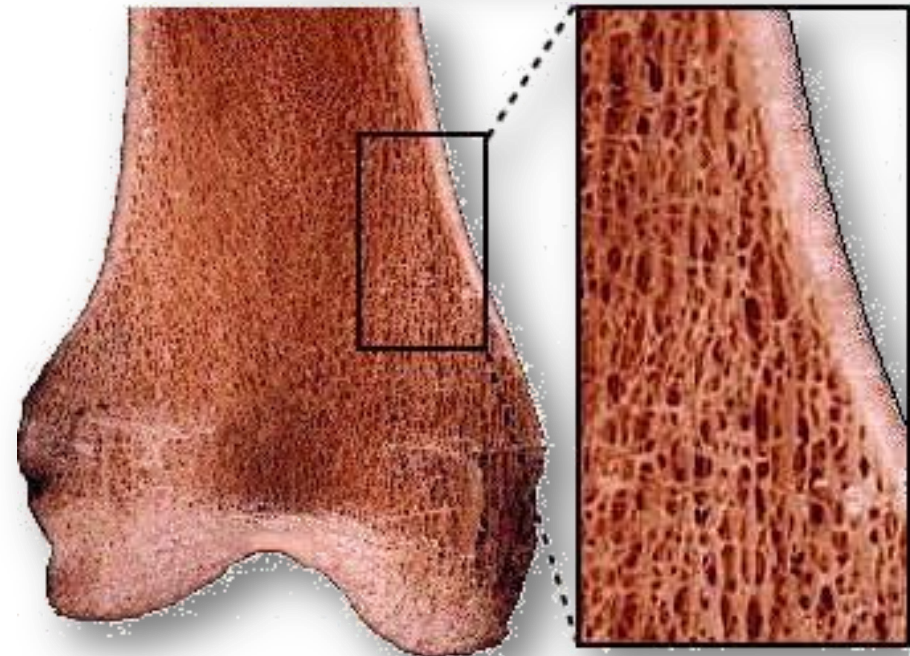
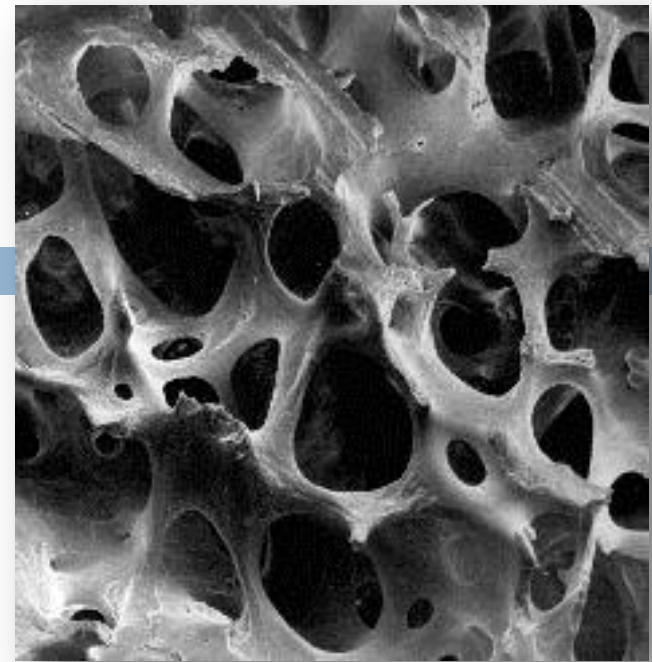


Osteoblast

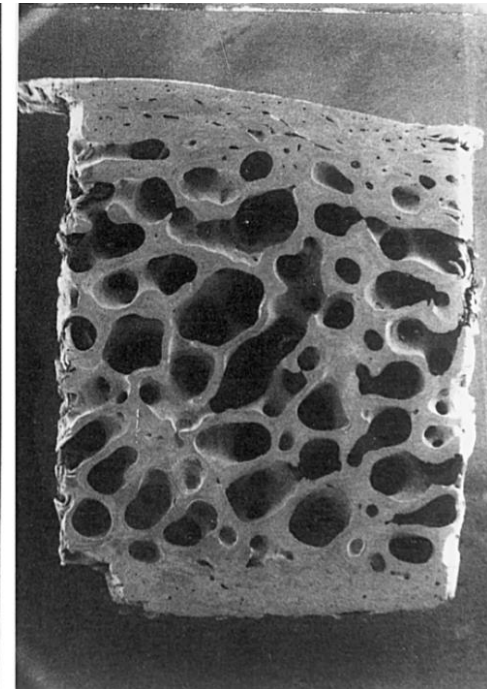
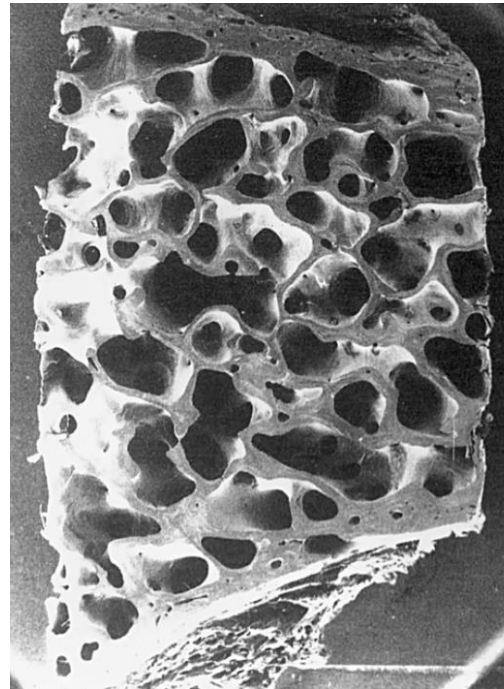
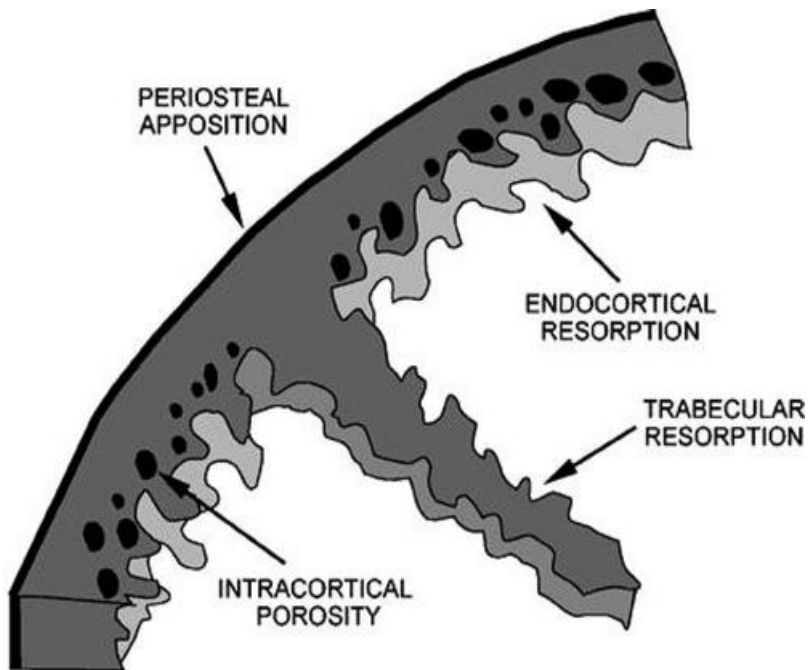


Bone function:

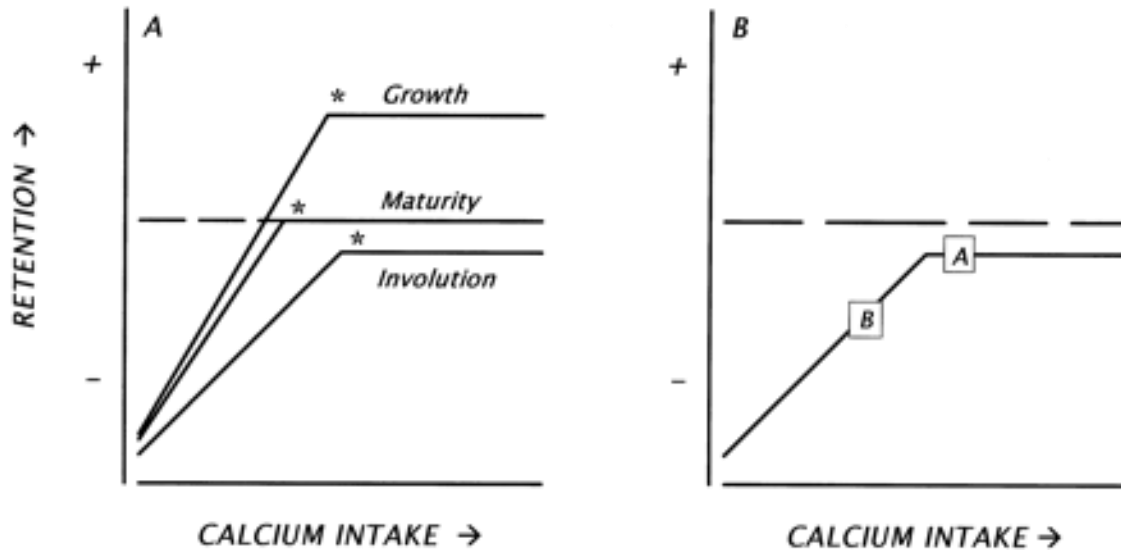
- Skeleton formation, maintenance and resorption (bone micro- and macroarchitectonics).
- Supplies body and skeleton with Ca (bone contains 1-2 kg Ca compared to 1-2 g of extracellular Ca) and P.
- ~50% total Ca is protein-bound (mostly albumin and globulin). Ionized Ca ~1.2 mmol/L, its concentration is tightly regulated by hormones.



Periosteum, cortical and trabecular bone



Calcium absorption rate in different age

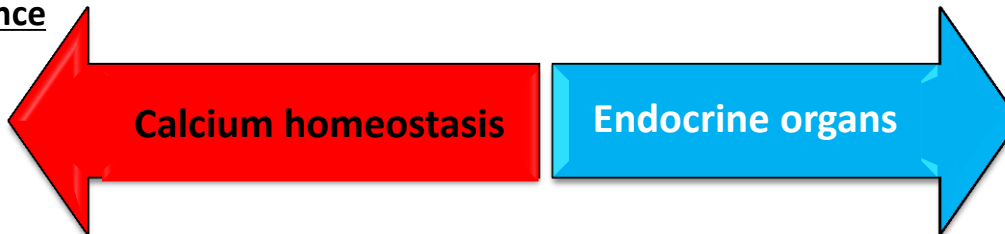


	Menarche	Menopause
Ca intake ^a	793mg/24h	474 mg/24h
Ca absorption rate ^b	35,2%	30,5%
Ca in faeces ^c	67 mg/24h	102 mg/24h
Ca absorption net	212 mg/24h	42 mg/24h

Robert P Haeney, 1998

Serious importance

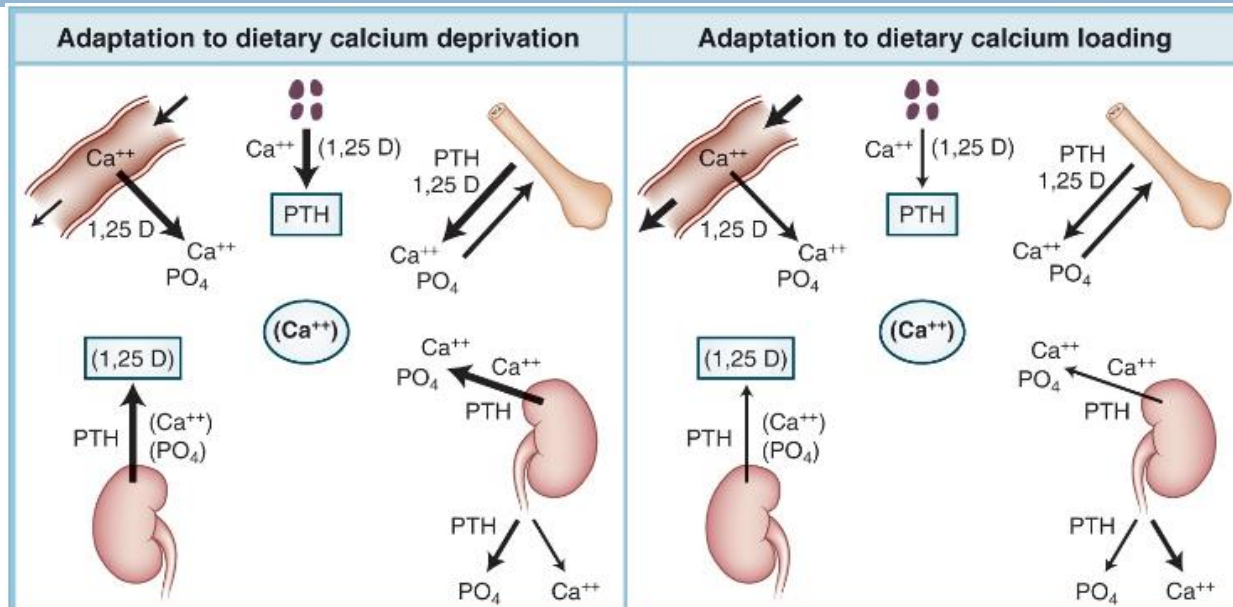
- PTH
- Calcitonin
- Vit. D



Certain importance

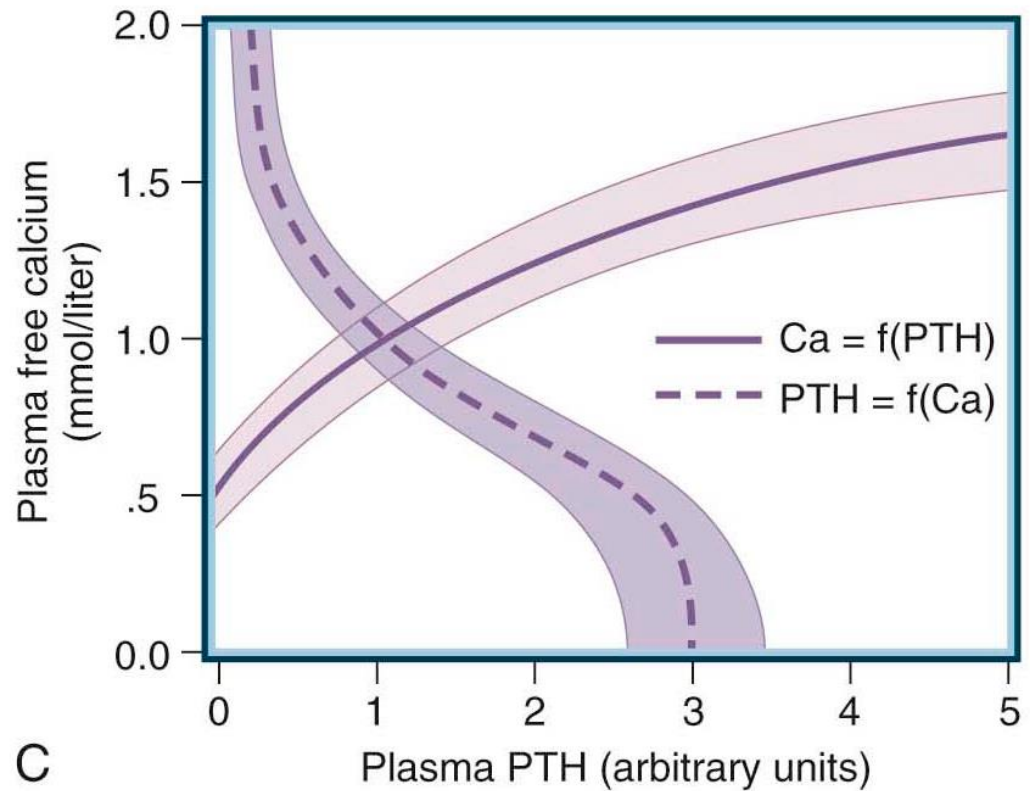
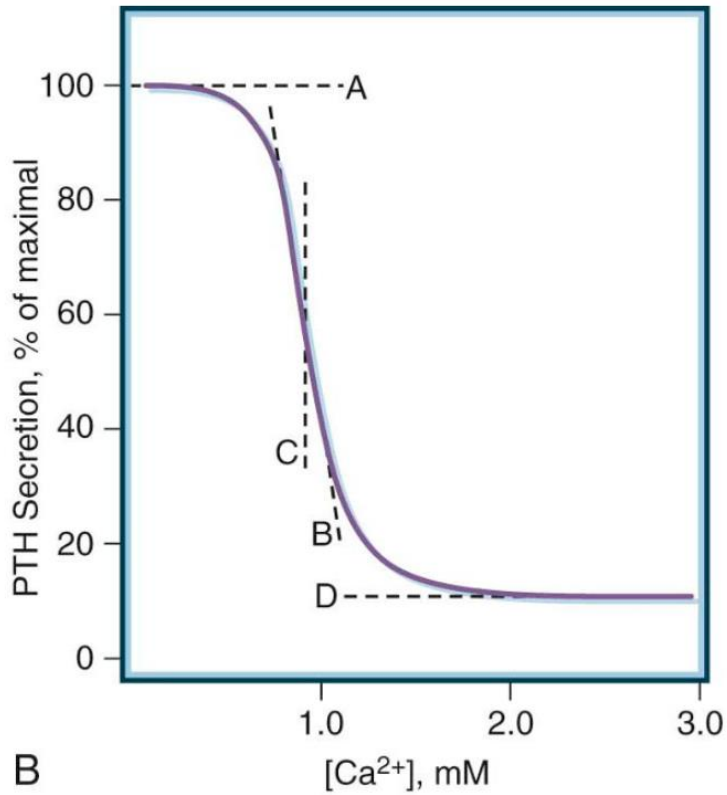
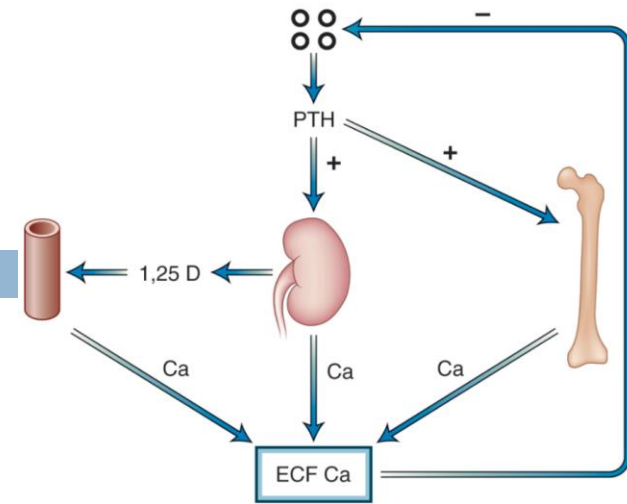
- Corticosteroids
- Estrogens and testosterone
- Thyroxine
- Growth hormone
- Glucagon

Calcium metabolism – homeostasis, Ca and P distribution and function

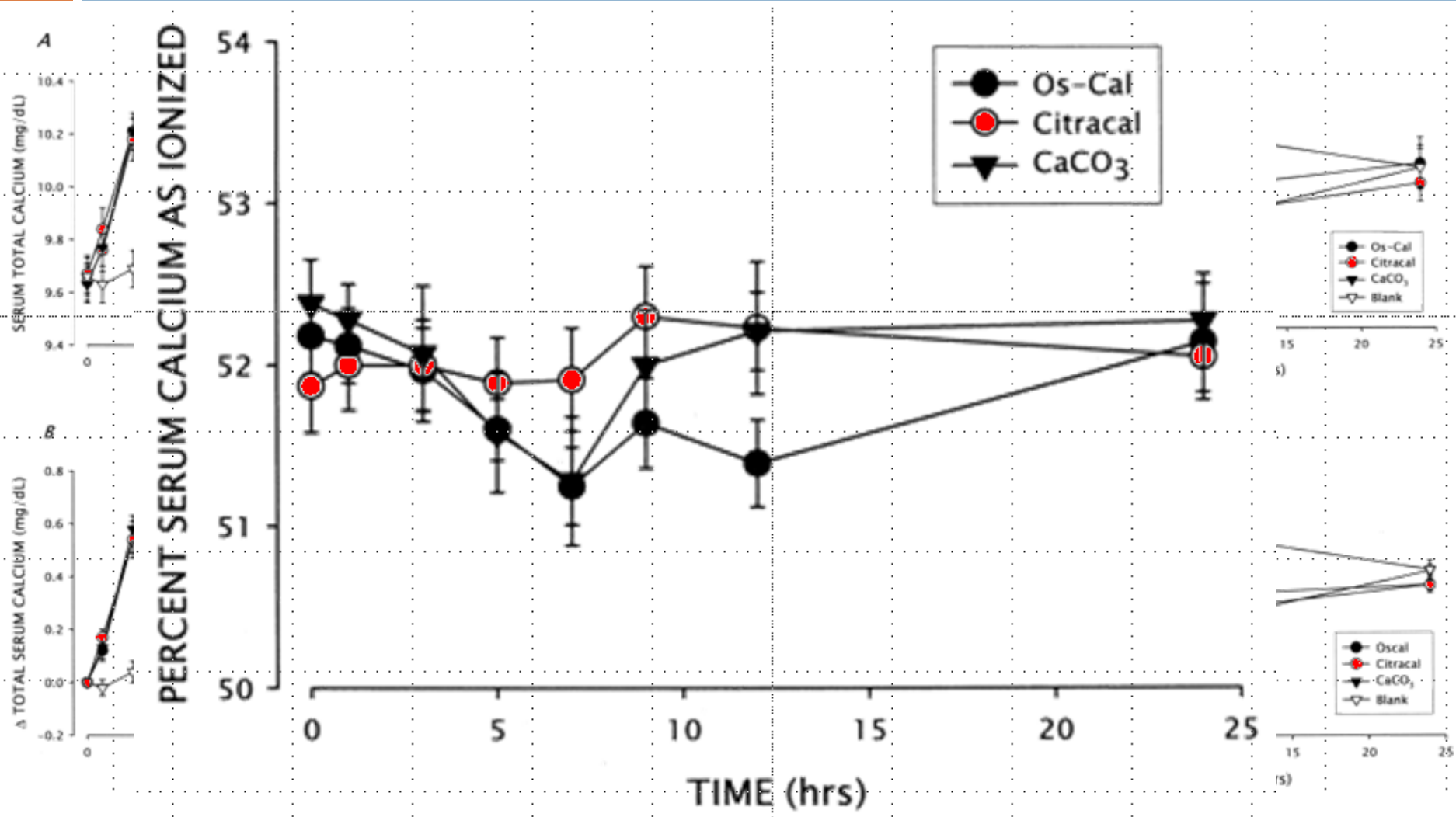


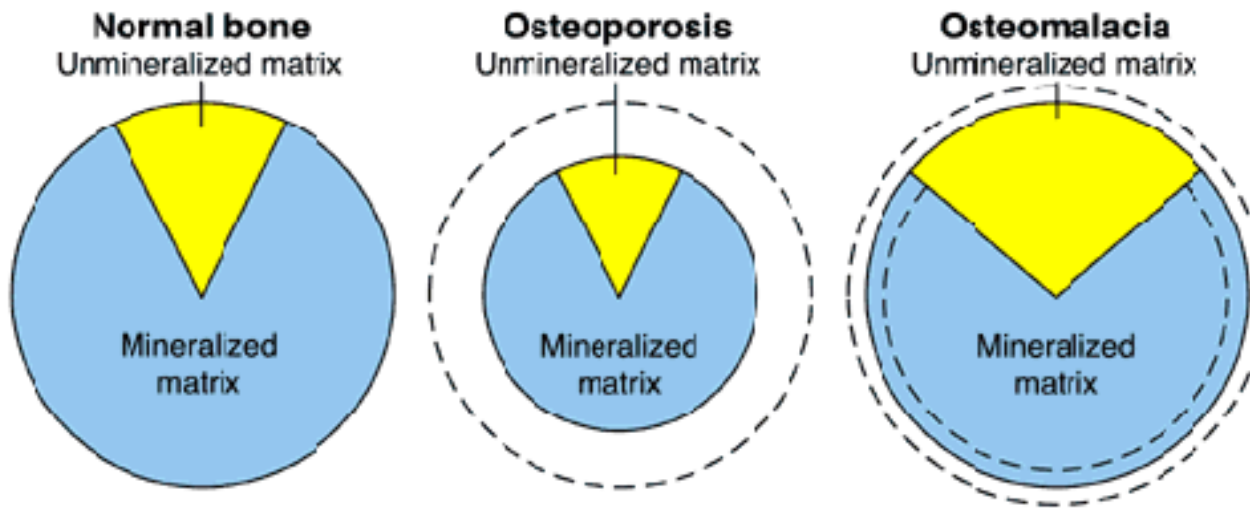
	Ca ions	P ions
Concentration e/c	$2,5 \times 10^{-3}M$ (serum)	$1,00 \times 10^{-3}M$
Free Ca	$1,2 \times 10^{-3}M$ (free)	$0,85 \times 10^{-3}M$
Function	<ul style="list-style-type: none"> Mineralisation Coagulation Membrane excitability 	<ul style="list-style-type: none"> Mineralisation
Concentration i/c	$10^{-7}M$	$1-2 \times 10^{-3}M$
Function	<ul style="list-style-type: none"> Neurone activation Hormone secretion Muscle contraction 	<ul style="list-style-type: none"> Structural importance High energy bounds Protein regulation by phosphorylation

PTH and Ca^{2+} homeostasis determines vitamin D normal range



Differences in absorption rate of various Ca salts and ionized Ca and PTH





Normal bone Unmineralized matrix	Osteoporosis Unmineralized matrix	Osteomalacia Unmineralized matrix
Normal bone mass fully mineralized	Reduced bone mass fully mineralized	Variable bone mass undermineralized
Usual age at onset:	Postmenopausal women, elderly of both sexes	Adults of any age, plus children with rickets
Mechanism:	Bone loss	Incomplete mineralization
Common causes:	Lack of sex hormones, old age, inactivity, corticosteroid therapy	Vitamin D and / or calcium deficiency
Main symptoms:	None, until fracture or deformity occurs (late)	Generalized bone pain and deformity (early)

Biochemical changes due to bone metabolism diseases

	Ca	P	AP	PTH
Osteomalacia	N or ↓	↓	↑	↑
Osteoporosis	N	N	N	N
Hyperparathyroidism	↑	↓	↑	↑
Malignant hypercalcemia	↑	N or ↓	N or ↑	↓
Hypoparathyroidism	↓	↑	N	↓

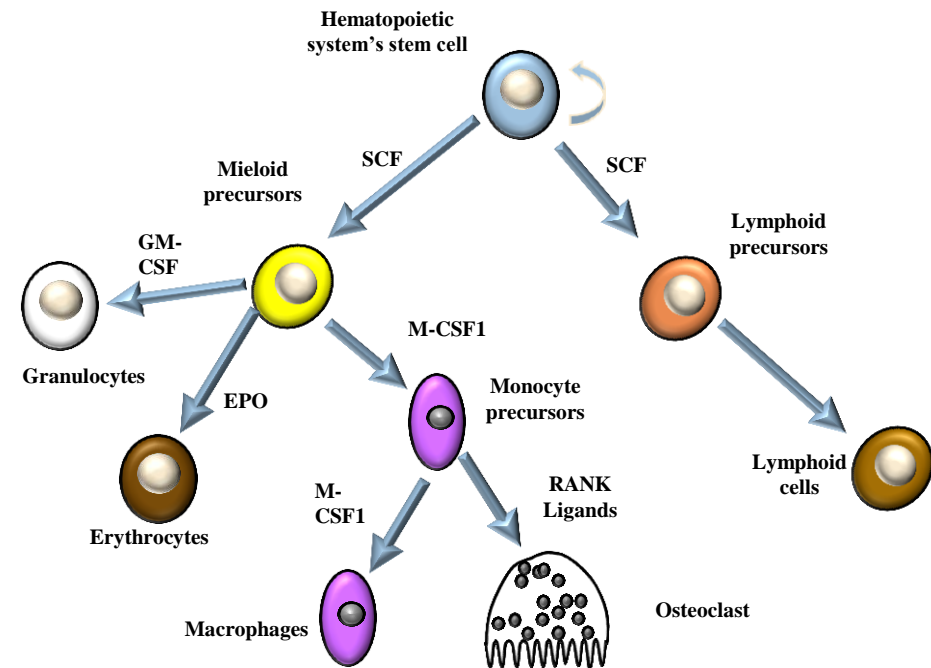
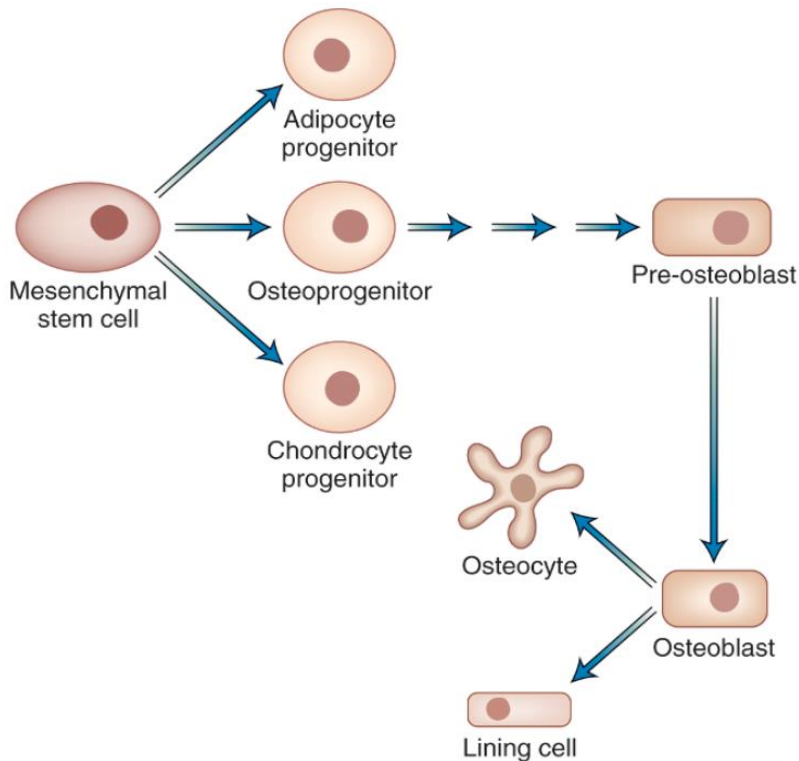


Bone biology



My understanding of osteoporosis in 1997

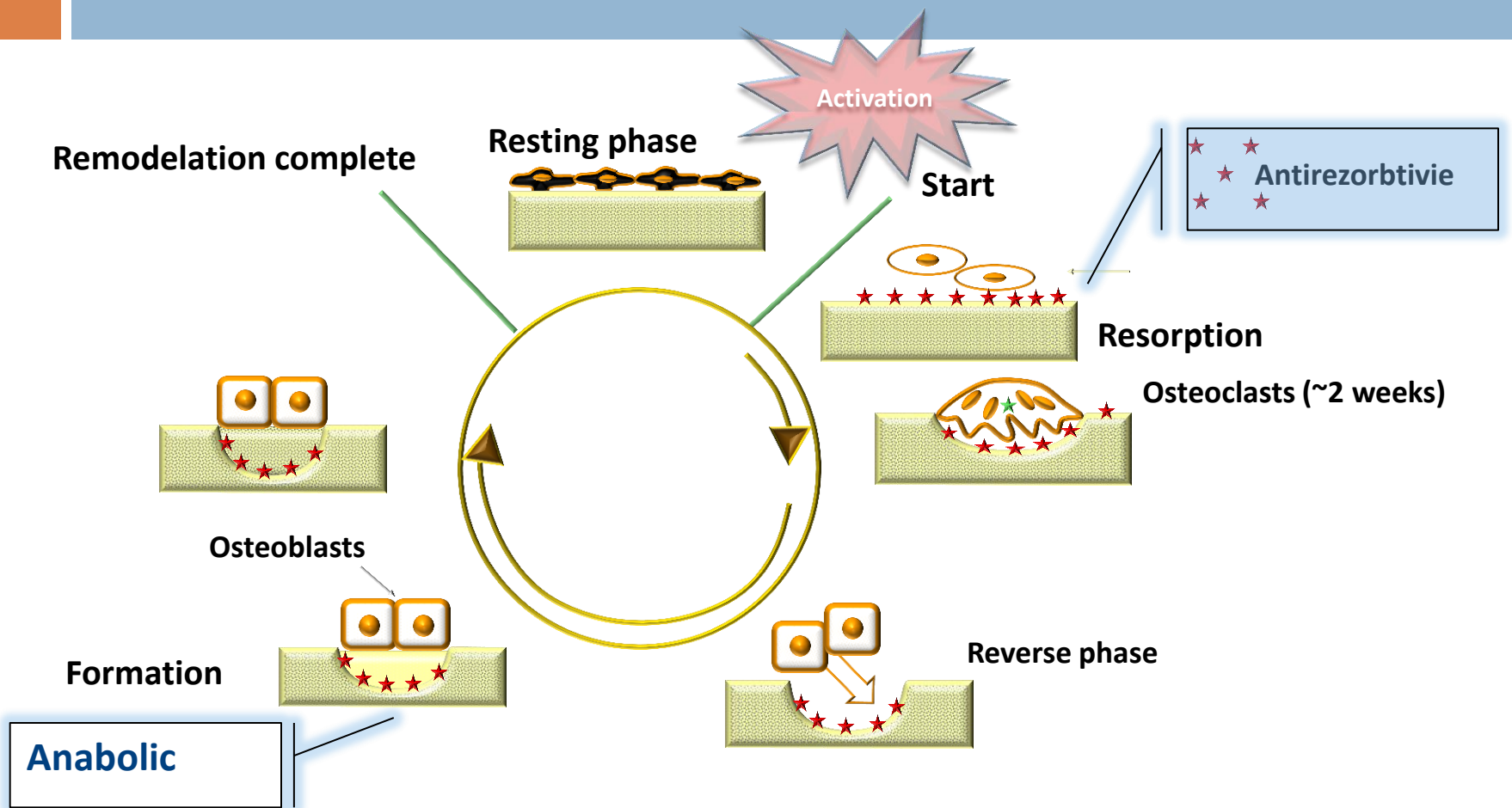
Bone cells and relation to hematopoietic system (stem cell)



EPO – erythropoietin; GM-CSF – granulocyte macrophages colony stimulation factor; M-CSF1 - macrophages colony stimulation factor; SCF - stem cell factor

- ✓ **Osteoblasts (derivatives of mesenchymal stem cells) contain: osteoblasts, osteocytes and bone lining cells. Osteoblasts synthesize organic matrices and create new bone tissue**
- ✓ **Osteoclasts (hematopoietic system precursors) resorb bone tissue releasing enzymes of hydrolase.**

Bone remodelling process (approx. 200 days)



Baron R. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 5th ed. 2003:1-8.

Bringhurst FR, et al. Harrison's Principles of Internal Medicine 16th ed. 2005: 2238-2249.

Lindsay R, et al. Treatment of the Postmenopausal Woman: Basic and Clinical Aspects. 2nd ed. 1999:305-314

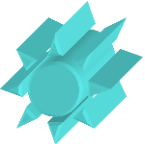
Concept of RANK/RANK ligands and OPG

Receptor



RANK - Receptor Activator of Nuclear factor-KappaB

Ligand



RANK Ligand is a protein binding to a receptor on the surface of osteoclast creating intramolecular signal

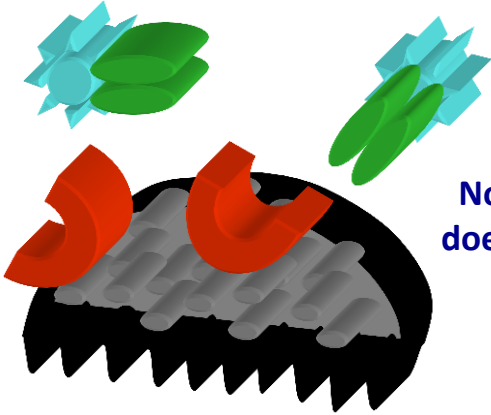
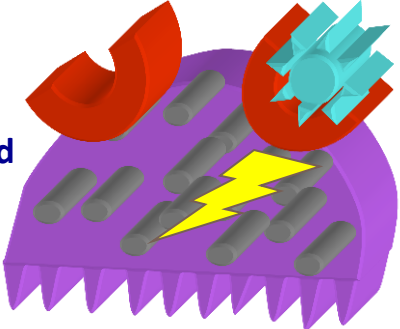
Specific receptor



OPG – osteoprotegerin is a protein specific against RANK ligand, it cannot bind to the receptor



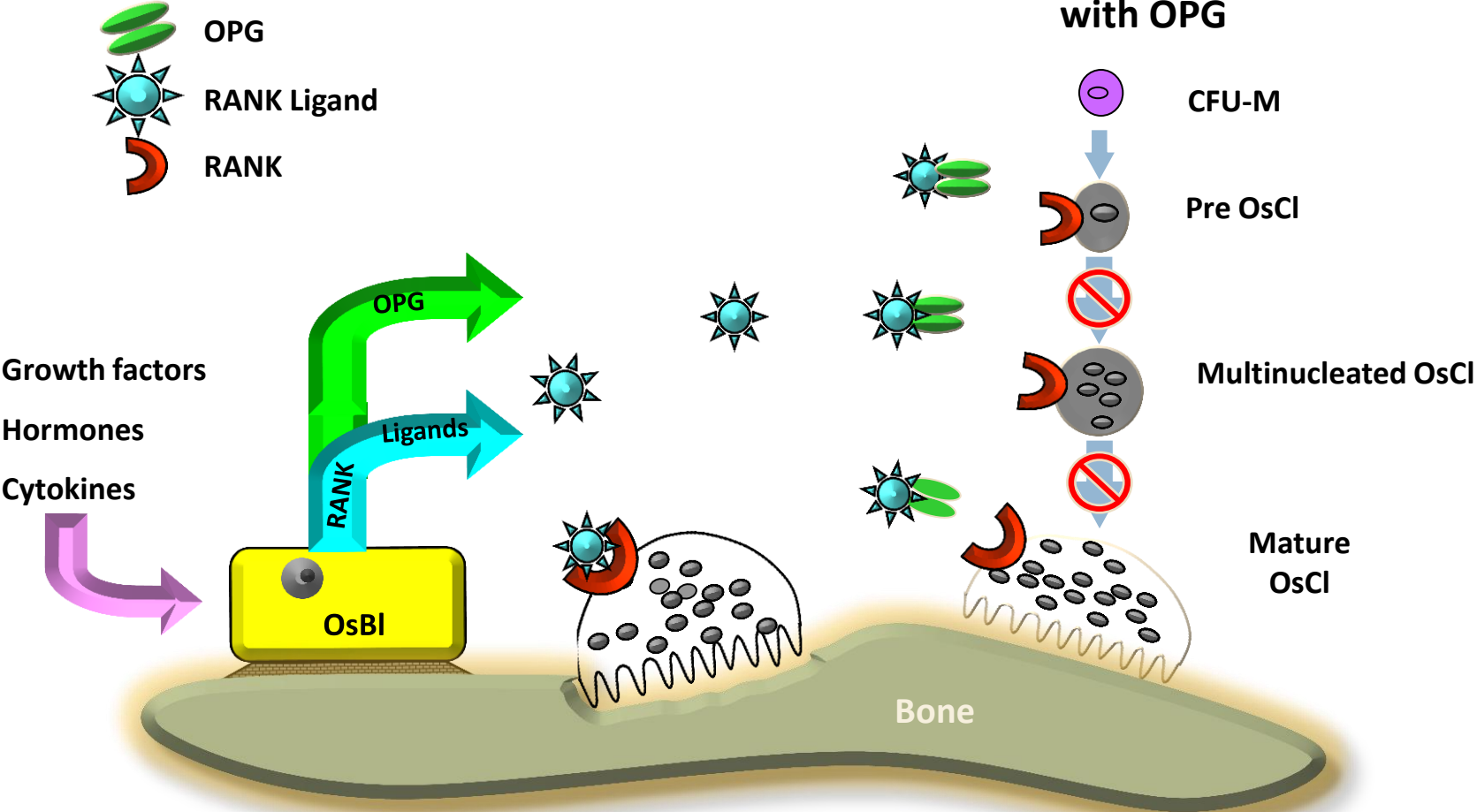
A cell signal is activated when ligand binds to receptor



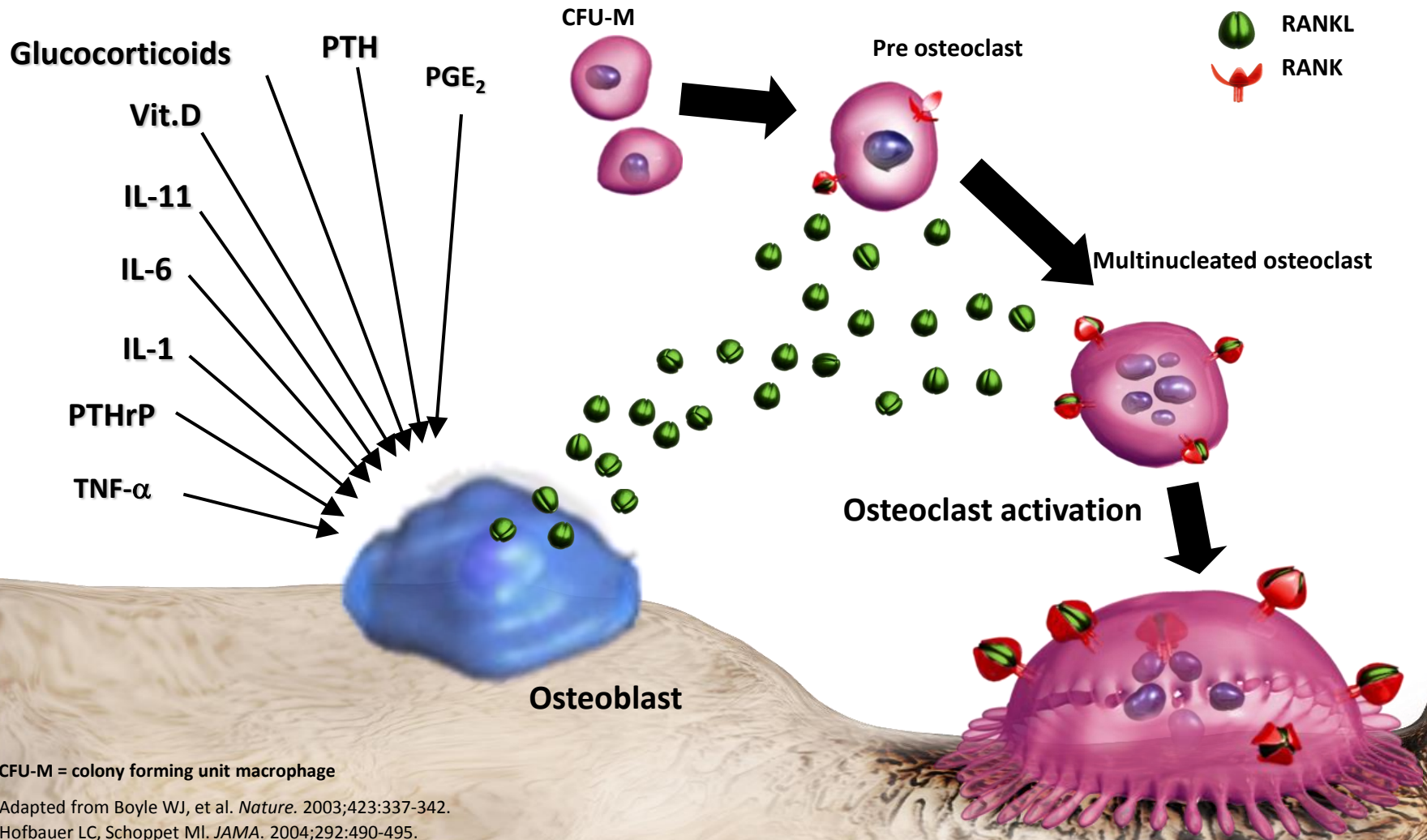
No cell activity if ligand does not bind to receptor

Osteoprotegerin (OPG) blocks RANK ligand

OsCl formation, function and survival blocked with OPG



Multiple factors contribute to RANK ligand excretion from osteoblast

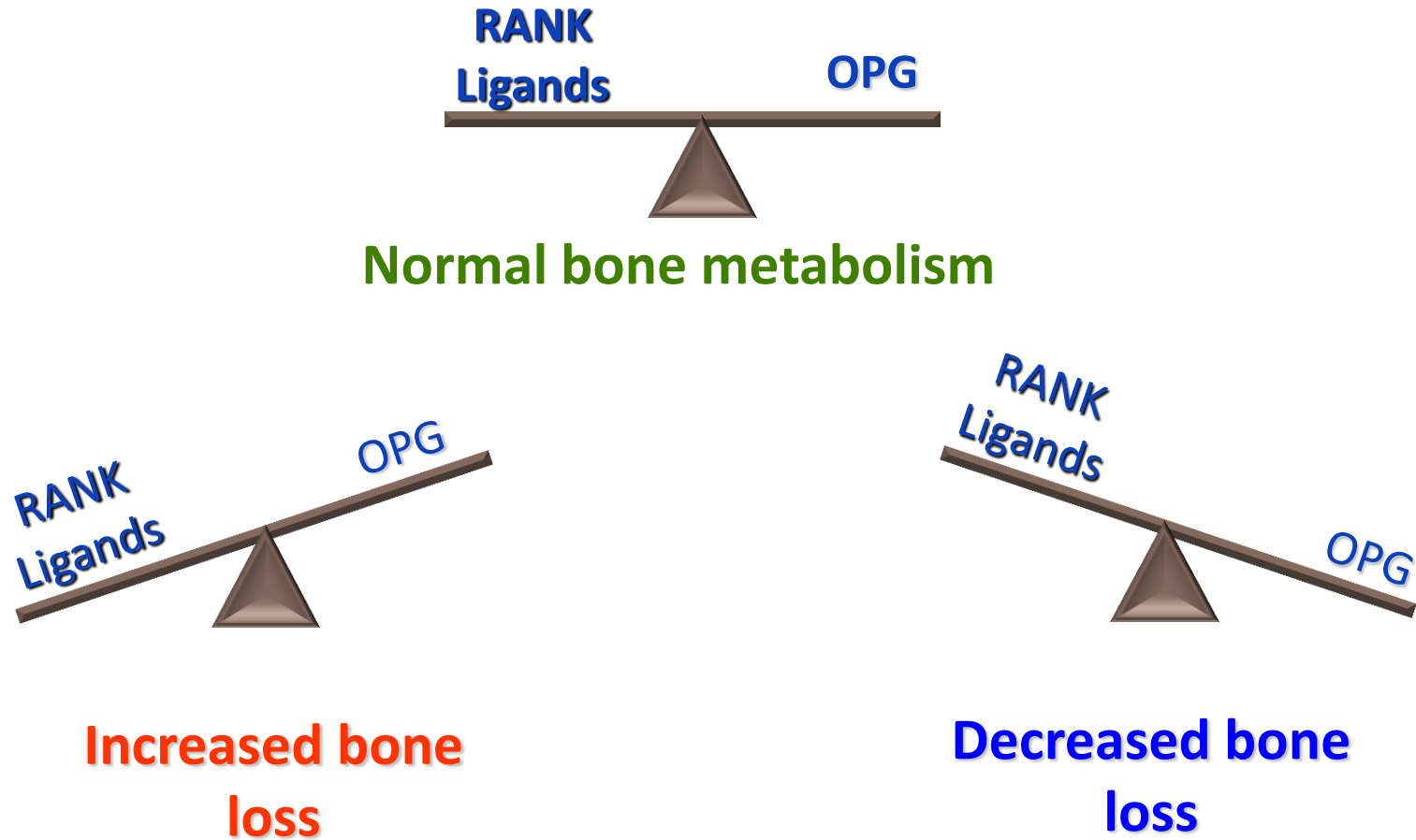


CFU-M = colony forming unit macrophage

Adapted from Boyle WJ, et al. *Nature*. 2003;423:337-342.

Hofbauer LC, Schoppet MI. *JAMA*. 2004;292:490-495.

Bone health depends on relationship of RANK ligand and OPG



RANK ligand is significant to development of osteoporosis and other conditions related to bone loss or destruction

Postmenopausal osteoporosis



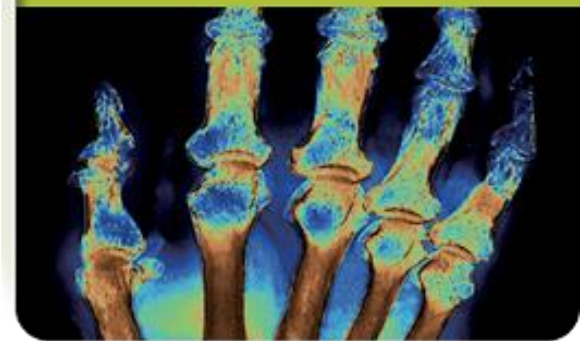
Bone loss due to therapy



Bone destruction caused by cancer

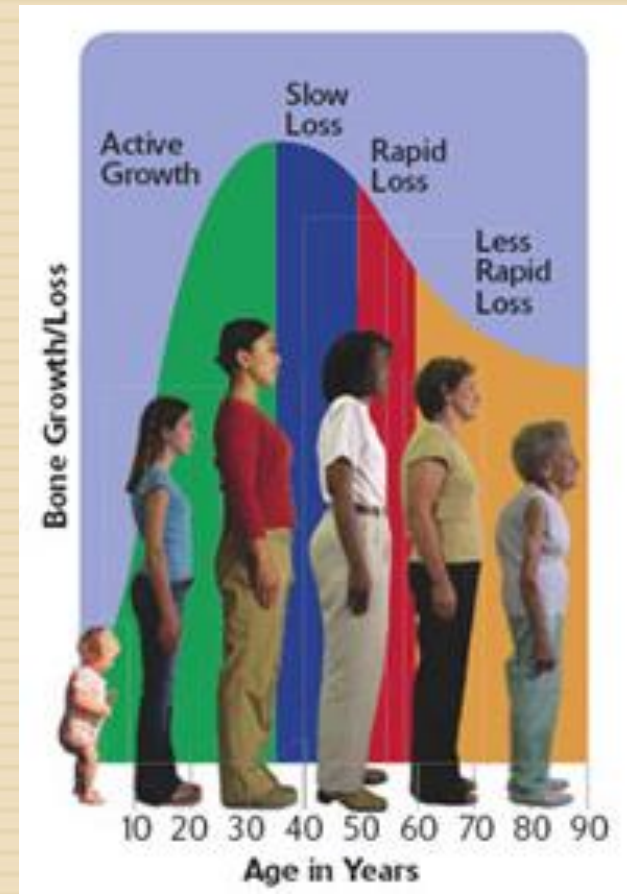
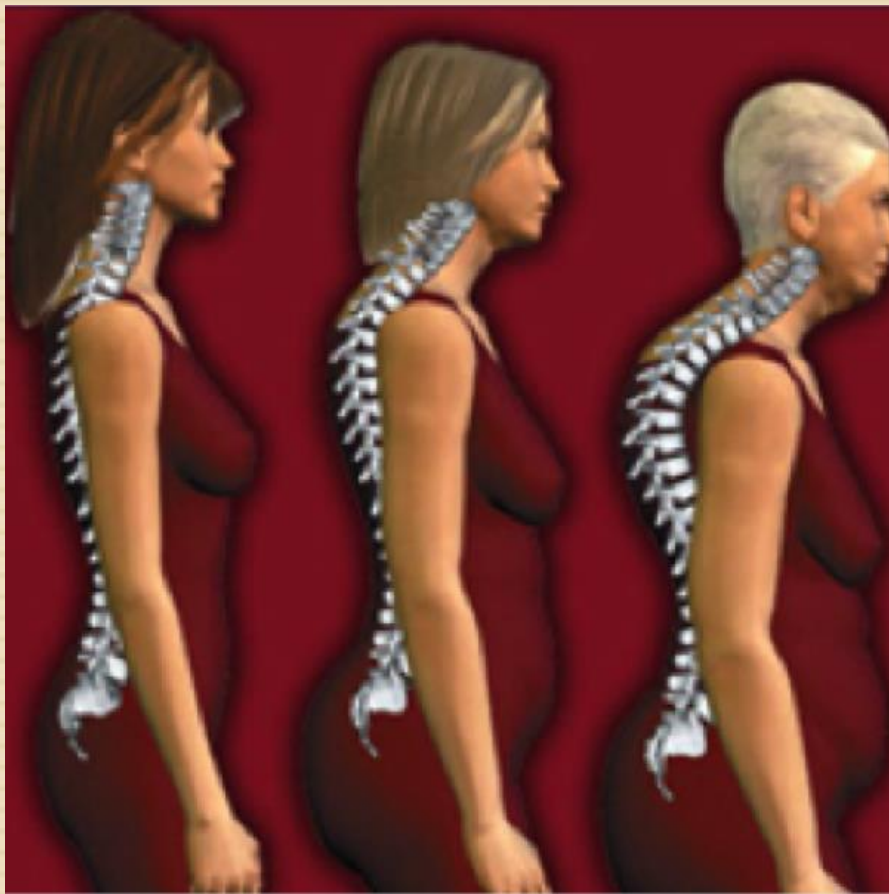


Bone erosion due to RA



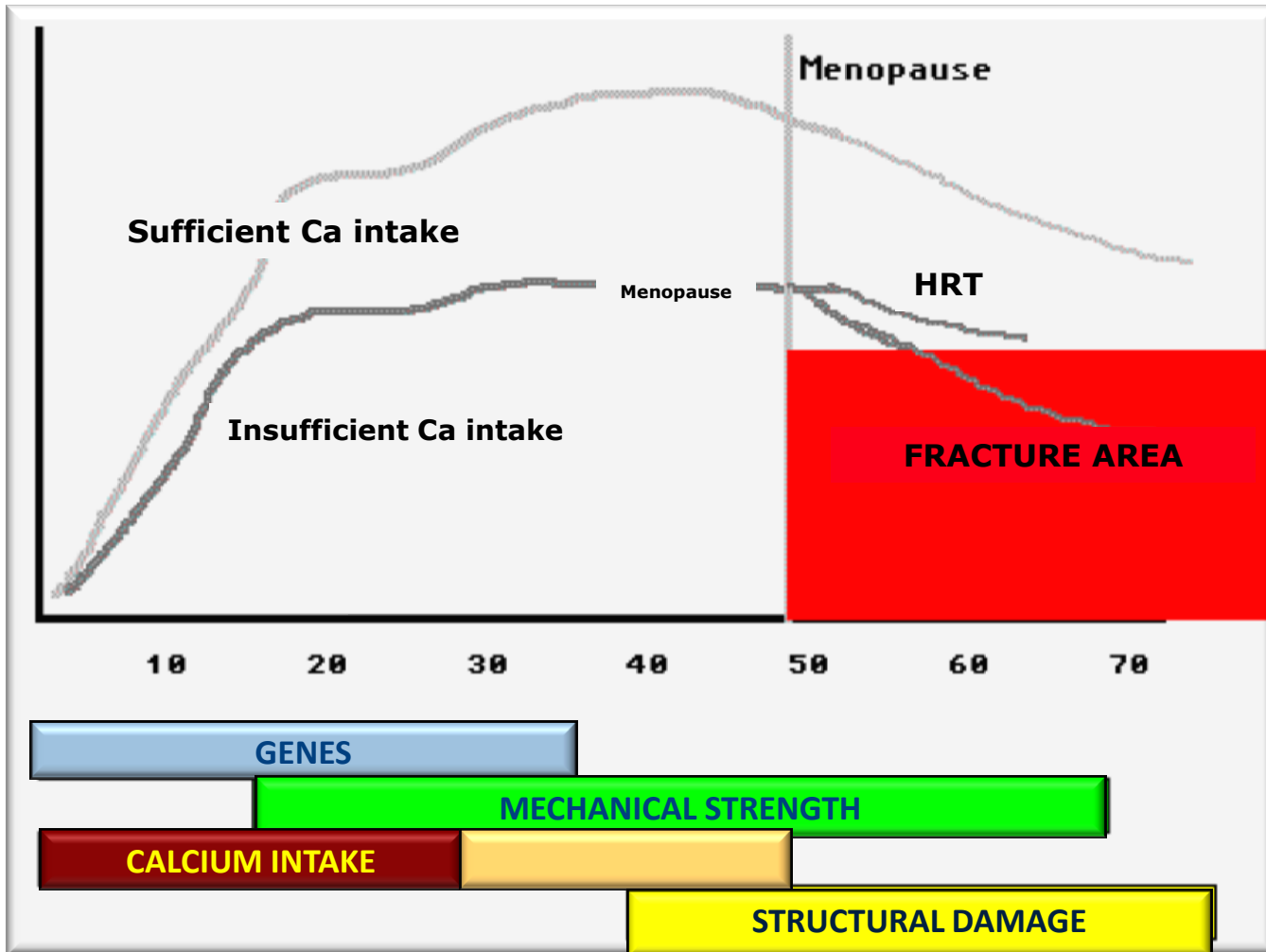
Hofbauer LC, Schoppet M. *JAMA*. 2004;292:490-495.
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Hofbauer LC, et al. *Endocrinology*. 1999;140:4382-4389.
Theriault RL. *Oncology*. 2004;18(Suppl 3):11-15.

Gravallese EM, et al. *Arthritis Rheum*. 2000;43:250-258.
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Kitazawa S, et al. *J Pathol*. 2002;198:228-236.

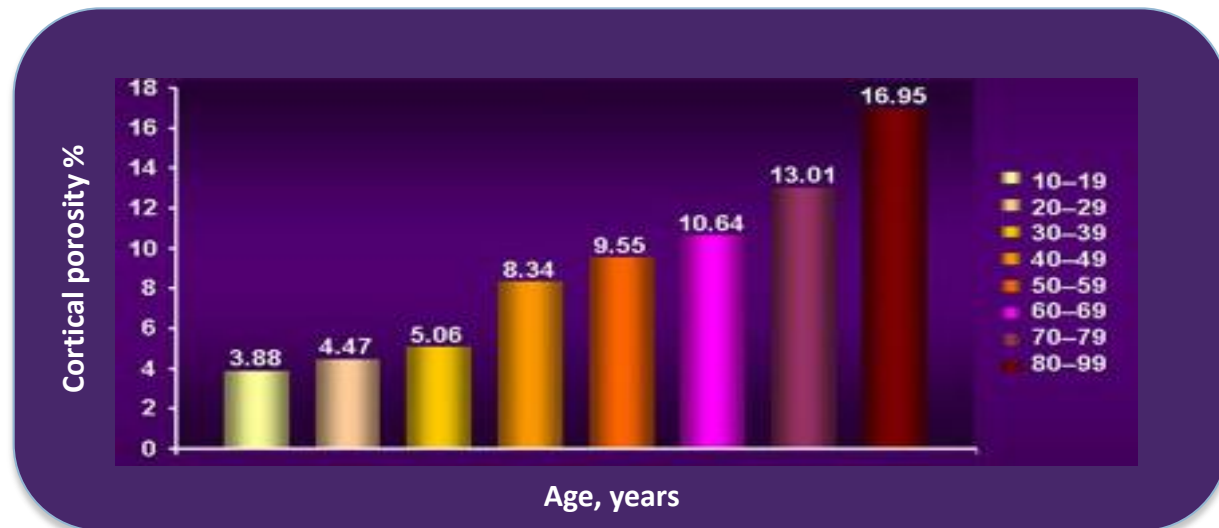
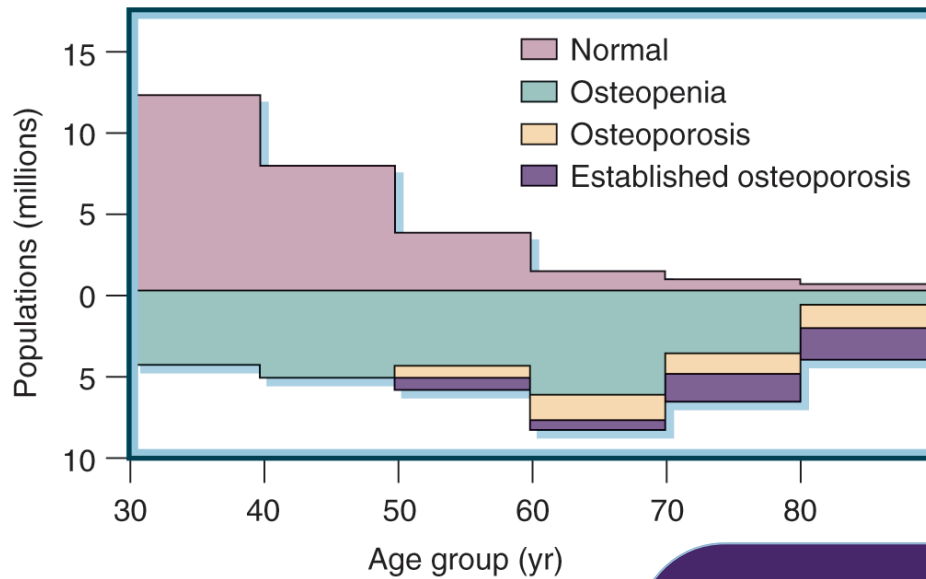


Definition and diagnosis of osteoporosis

It is ABC to remember!

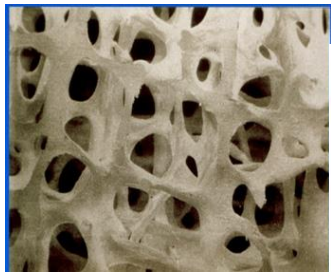


BMD and porosity changes during aging

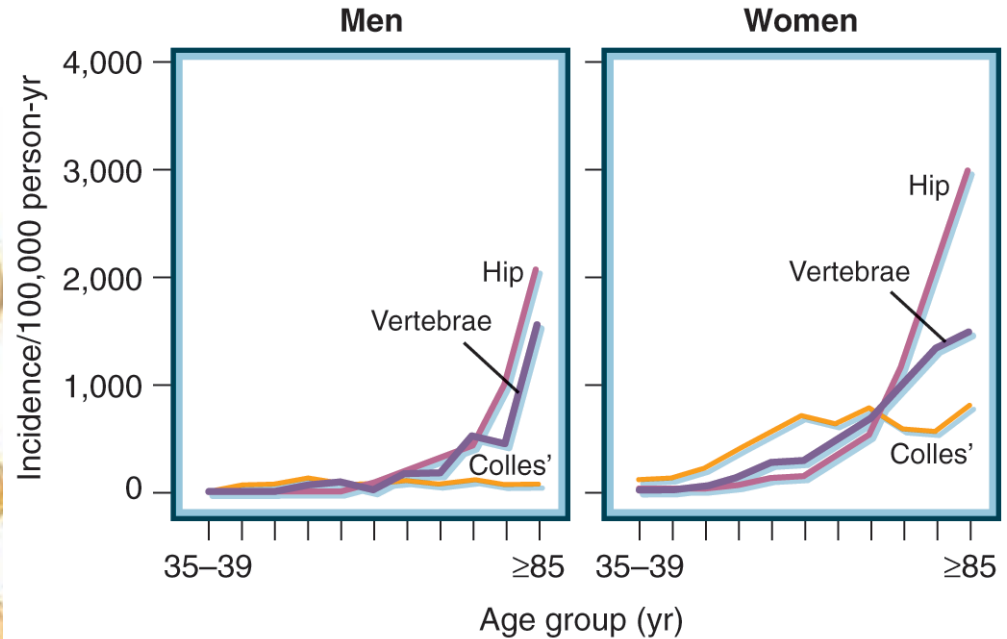
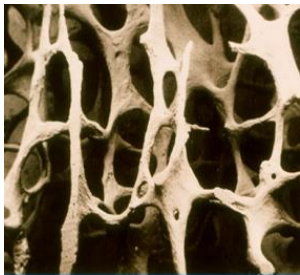


Osteoporosis is a systemic skeletal disease with increased fracture risk in whole skeleton

NORM



OSTEOPOROSIS



- OP is a systemic skeletal disease characterized by low bone density and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility
- OP is one of the biggest reasons for disability due to chronic diseases and health care problems (IOF)
- Millions of women suffer with OP having increased risk of fractures with an impact to life expectancy and working ability (WHO)

Bone risk factors

□ RF:

- Age
- Low BMD
- Previous fractures
- Low BMI
- Fractures in family history
- Smoking
- Alcohol abuse
- Rheumatoid arthritis
- Glucocorticoid treatment



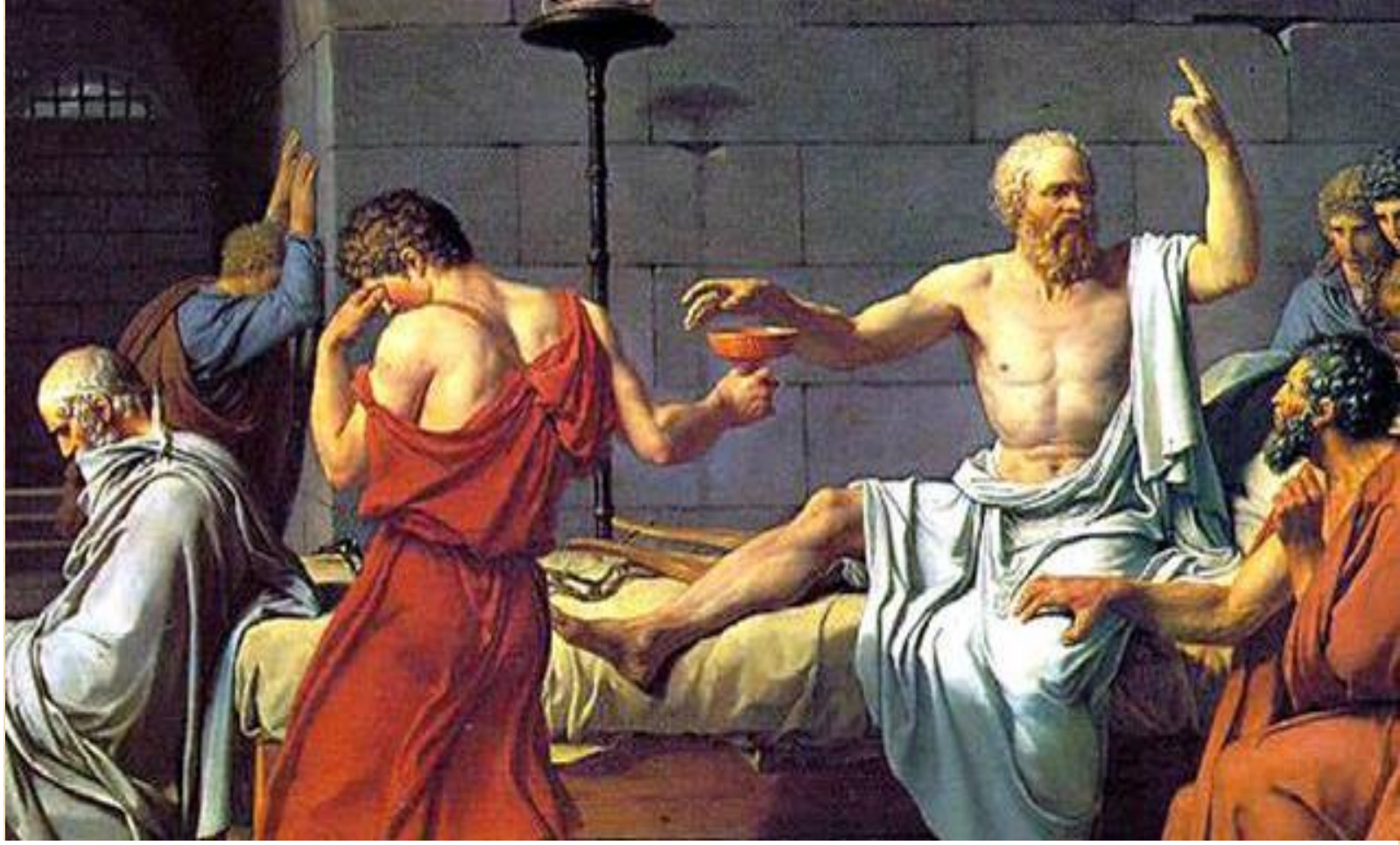
Medical conditions and drugs which increase fracture risk

- **Endocrine**
 - **Hyperthyroidism, hyperparathyroidism, Cushing syndrome, diabetes mellitus, hyperprolactinemia, hypercalciuria**
- **Renal:**
 - **CKD, ESRD, renal osteodystrophy**
- **Rheumatologic/connective tissue diseases**
 - **Ankylosing spondylitis, RA, Ehlers Danlos, Marfan syndrome**
- **GIT/liver:**
 - **Gastrectomy, celiac disease, calcium malabsorption, cirrhosis**
- **Infiltrative:**
 - **Multiple myeloma, leucemia, mastocytosis**
- **Nutritional/metabolic:**
 - **Eating disorders, vit.B₁₂ deficiency, vit.D deficiency, increased homocysteine level**
- **GC**
- **Long acting progestins**
- **Aromatase inhibitors**
- **GT-RH agonists**
- **Anticonvulsants**
- **Cytotoxic therapy**
- **Long acting heparine**
- **Lithium**
- **Protone pump inhibitors**

Hodgson SF et al. Endocr Pract 2003;9:544-564

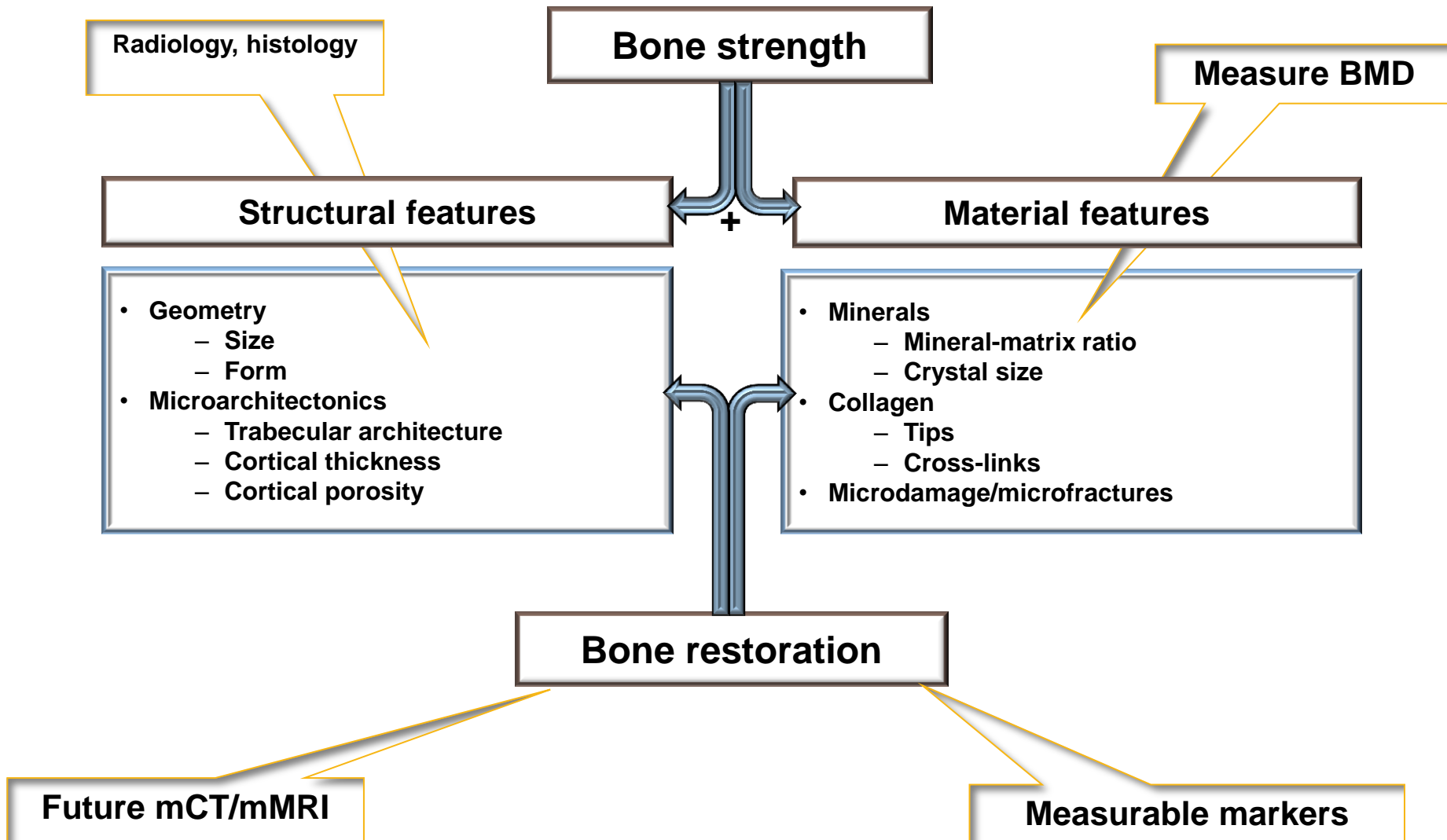
NOF The State of Osteoporosis and Low Bone Mass in the US Washington DC NOF, 2005

Yang Y, Lewis D, Epstein S, Dawid C JAMA 2006;296:2947-2953



Diagnosics of osteoporosis

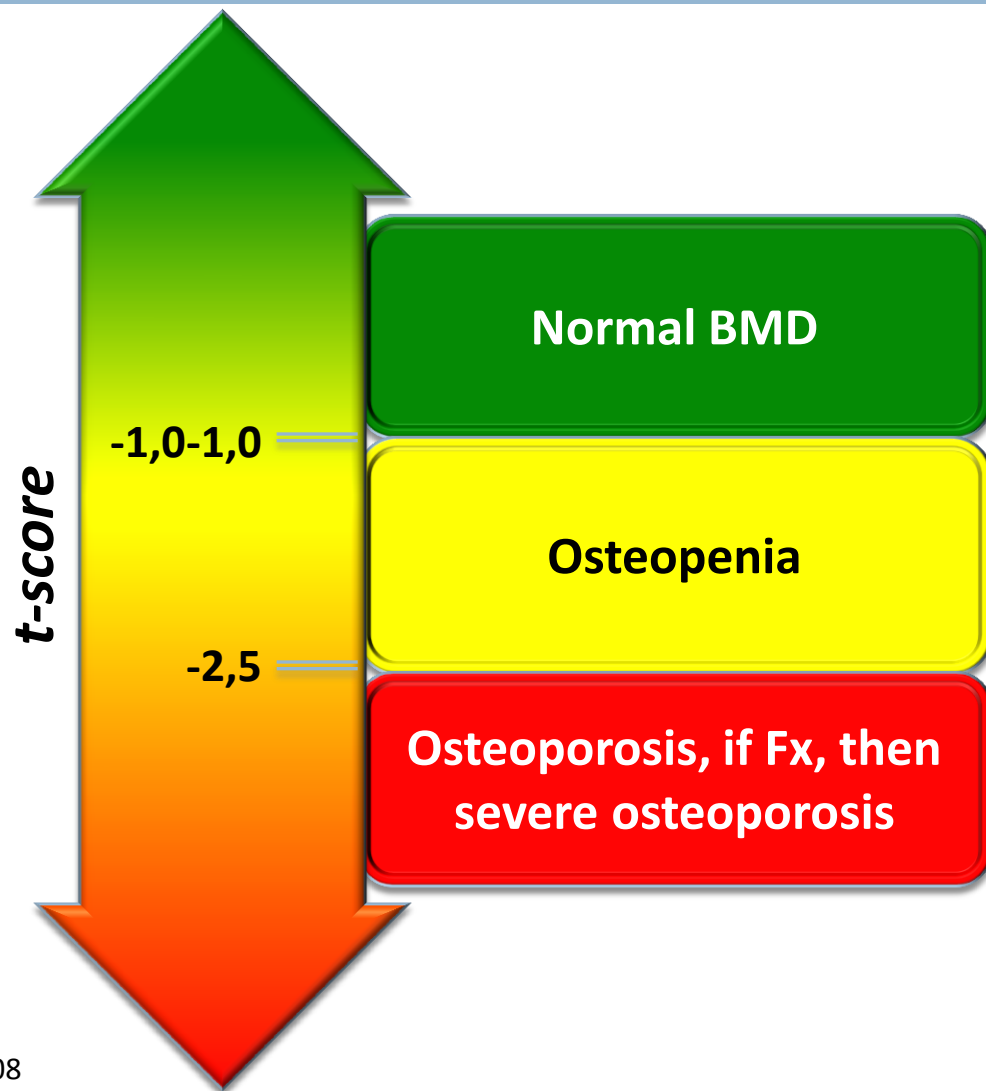
How to detect bone strength?



Diagnostics of osteoporosis



- DXA – Dual Energy X-ray Absorptiometry
- Used for OP diagnostics
- Measures BMD mostly in LL vertebrae and hip
- Compares patient's BMD *T-score* with healthy young person's BMD (population reference)

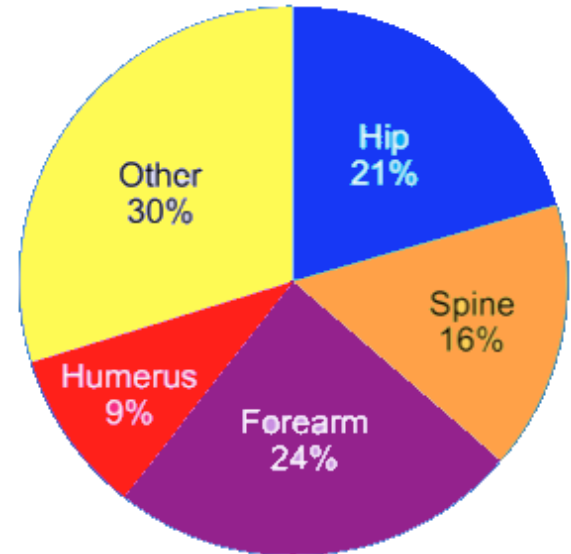




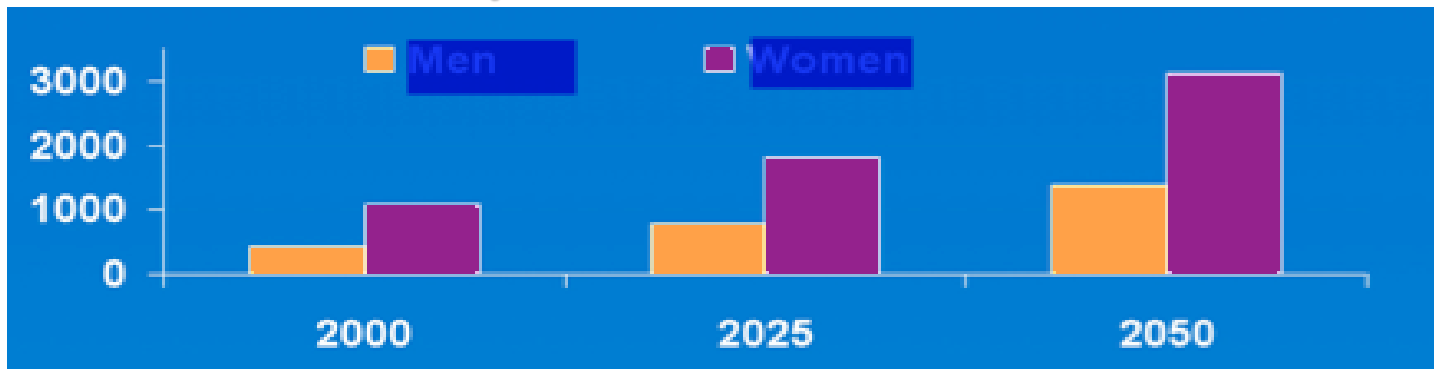
Burden of osteoporosis

Osteoporosis – more than 200 million people

- 30% postmenopausal women have osteoporosis
- Main osteoporosis complication is fracture
- Risk of lifelong possibility for radial, vertebral or hip fracture reaches 40%, nearly similar to CHD risk



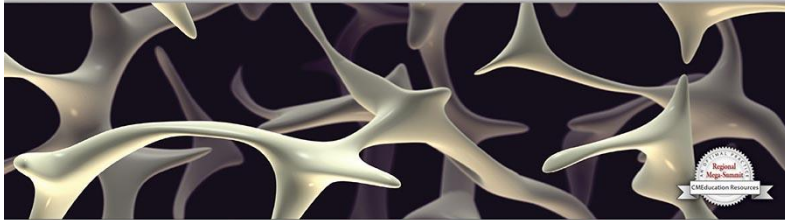
Hip fracture rate increases



The Science and Medicine of

Comprehensive New Dimensions Practice Advances OSTEOPOROSIS MANAGEMENT

New Dimensions, Novel Strategies, and Landmark Practice Advances in Fracture Reduction — Screening, Monitoring, and Therapy: *The Primary Care Perspective*

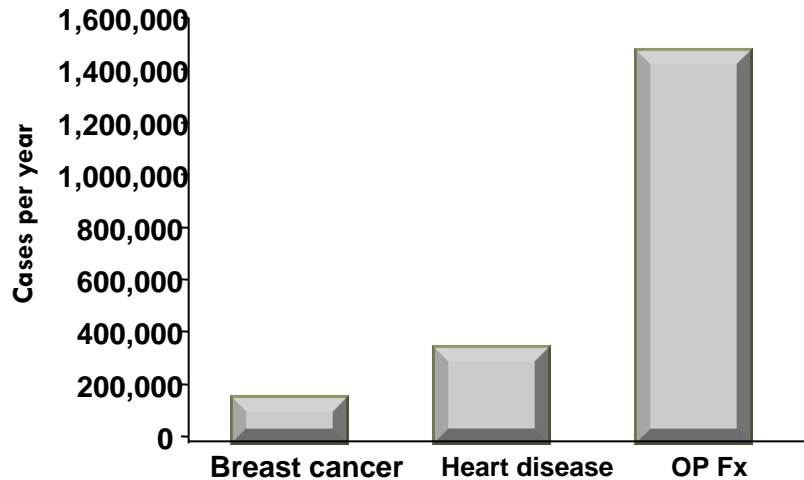


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NOVARTIS



Osteoporotic fractures



Vittore Carpaccio, 1457



A. Rodin,
1885

“Dowager’s «hump»”

Fractures change patient's life tremendously

Vertebral fracture

- ❑ Back pain
- ❑ Height reduction
- ❑ Deformation and immobility
- ❑ Reduced lung function
- ❑ Increased fracture risk

Hip fracture

- ❑ Chronical pain
- ❑ Reduced mobility
- ❑ Increased further fracture risk
- ❑ Increased morbidity and lethality
- ❑ 10–20% of patients are in need of care



Hip fractures cause substantial clinical, social and economic burden



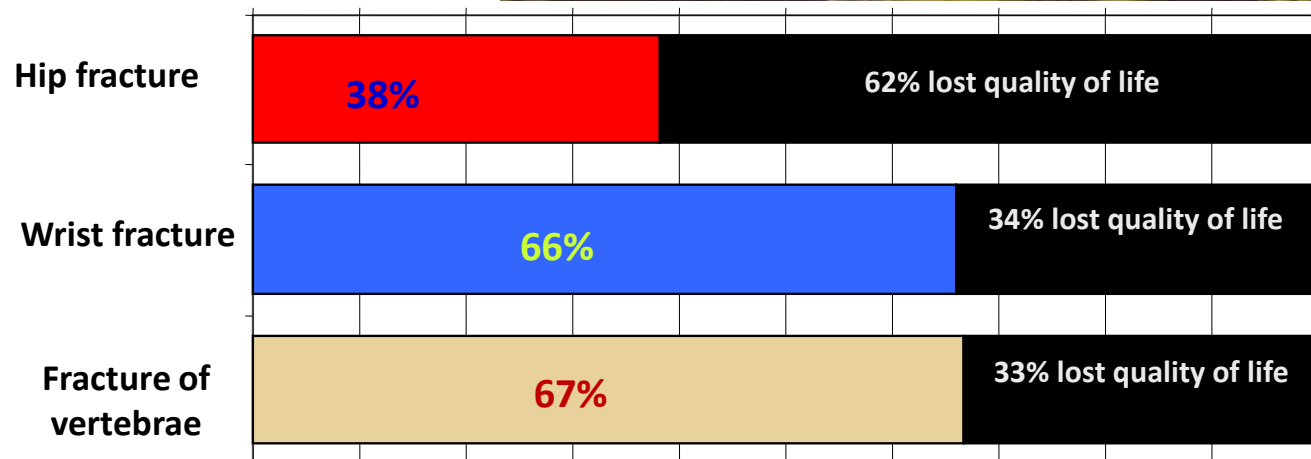
- Hip fractures significantly increase mortality, even in the age group under 65 year¹
- 40% of women who fracture a hip will never be able to walk again without assistance, and less than 20% will recover to their pre-fracture competence in activities²
- Hip fractures are the most important factor contributing to the cost burden of osteoporosis, including hospitalisations³

Functional status of patients before and after hip fracture

Ability to	Before fracture (%)	6 months after fracture (%)
dress without assistance	86	49
reach something without assistance	90	32
walk without assistance	75	15
climb stairs	63	8
walk at least 900m	41	6

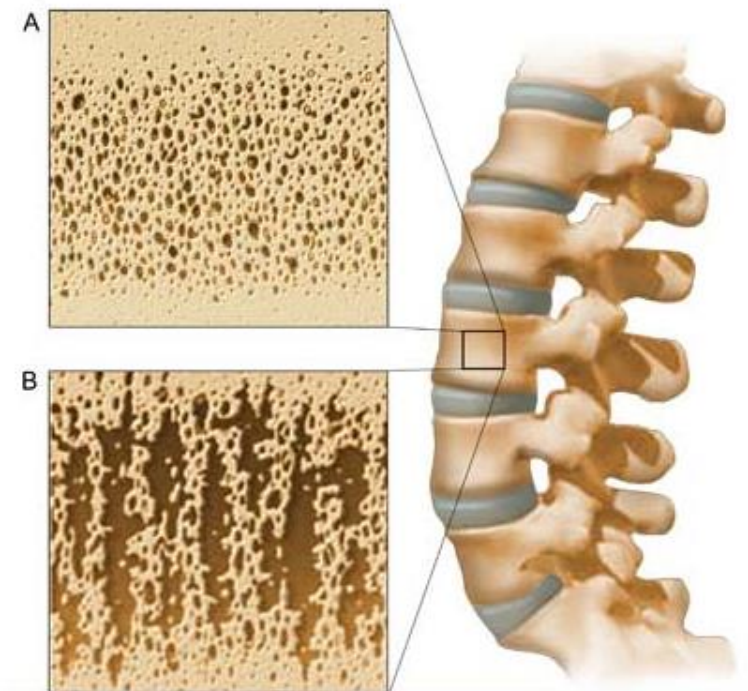


L.M. Cooney, 1993



A prior fracture is a precursor of subsequent fracture

- In women a fracture increases the risk of subsequent fracture by 86%¹
- for 1 in 5 postmenopausal women with prior vertebral fracture, subsequent fracture is expected within a year²
- prior fragility fracture is reported in between 45% and 52% of women with hip fracture³⁻⁵
- women with prior fracture have an approximately 2-fold higher risk of suffering a hip fracture

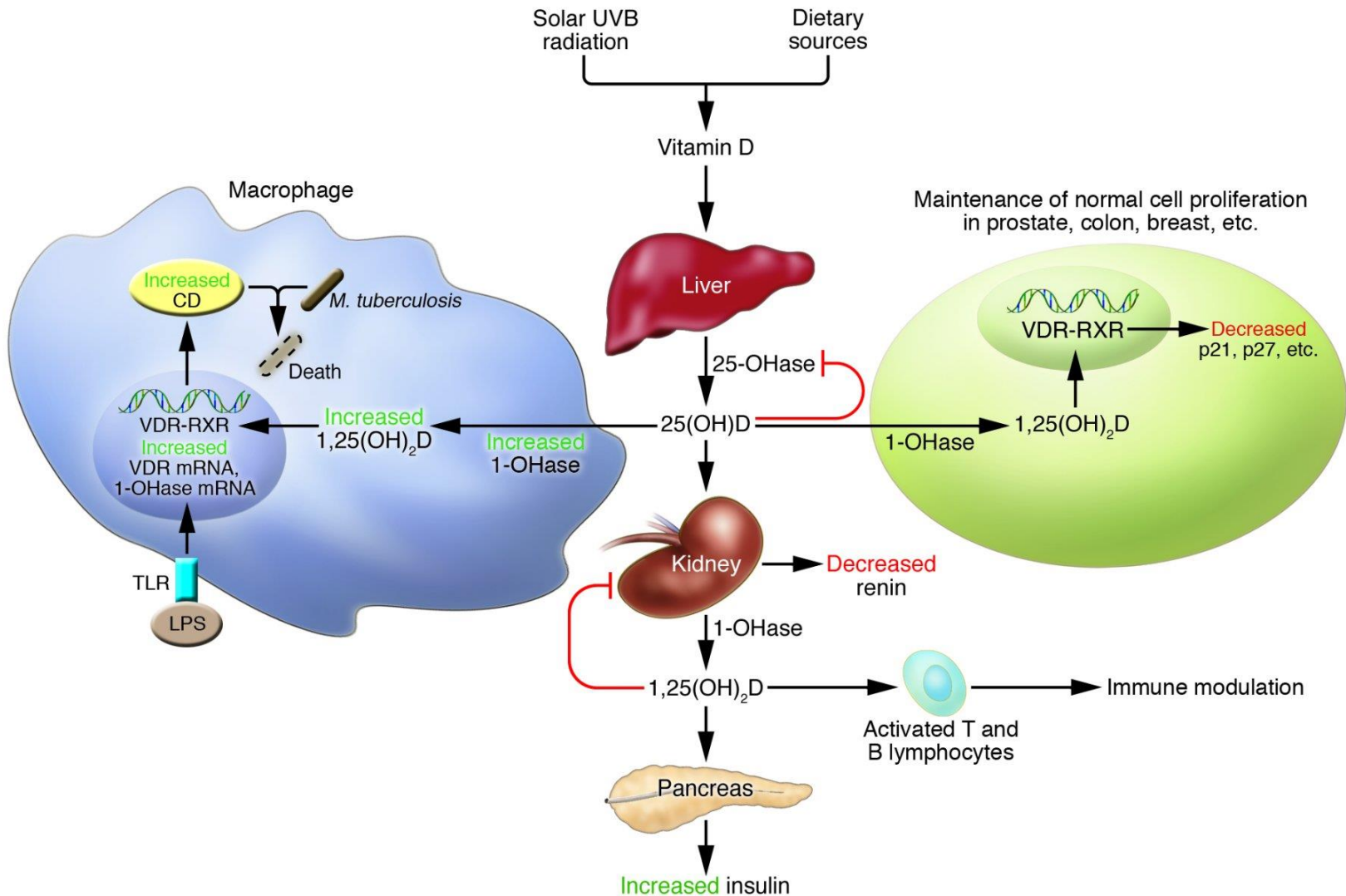


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¹Kanis JA et al. Bone 2004;285:375-382. ²Lindsay R et al. JAMA 2001;285:320-323. ³Lyles KW et al. ASBMR 2008. ⁴Edward BJ et al. Clin Orthop Rel Res 2007;225-230. ⁵McLellan AR et al. (2004) Effectiveness of Strategies for the Secondary Prevention of Osteoporotic Fractures in Scientific Group 99030 NHS Quality Improvement Scotland. ⁶Klotzbuecher CM et al. J Bone Min Res 2000;15:721-739

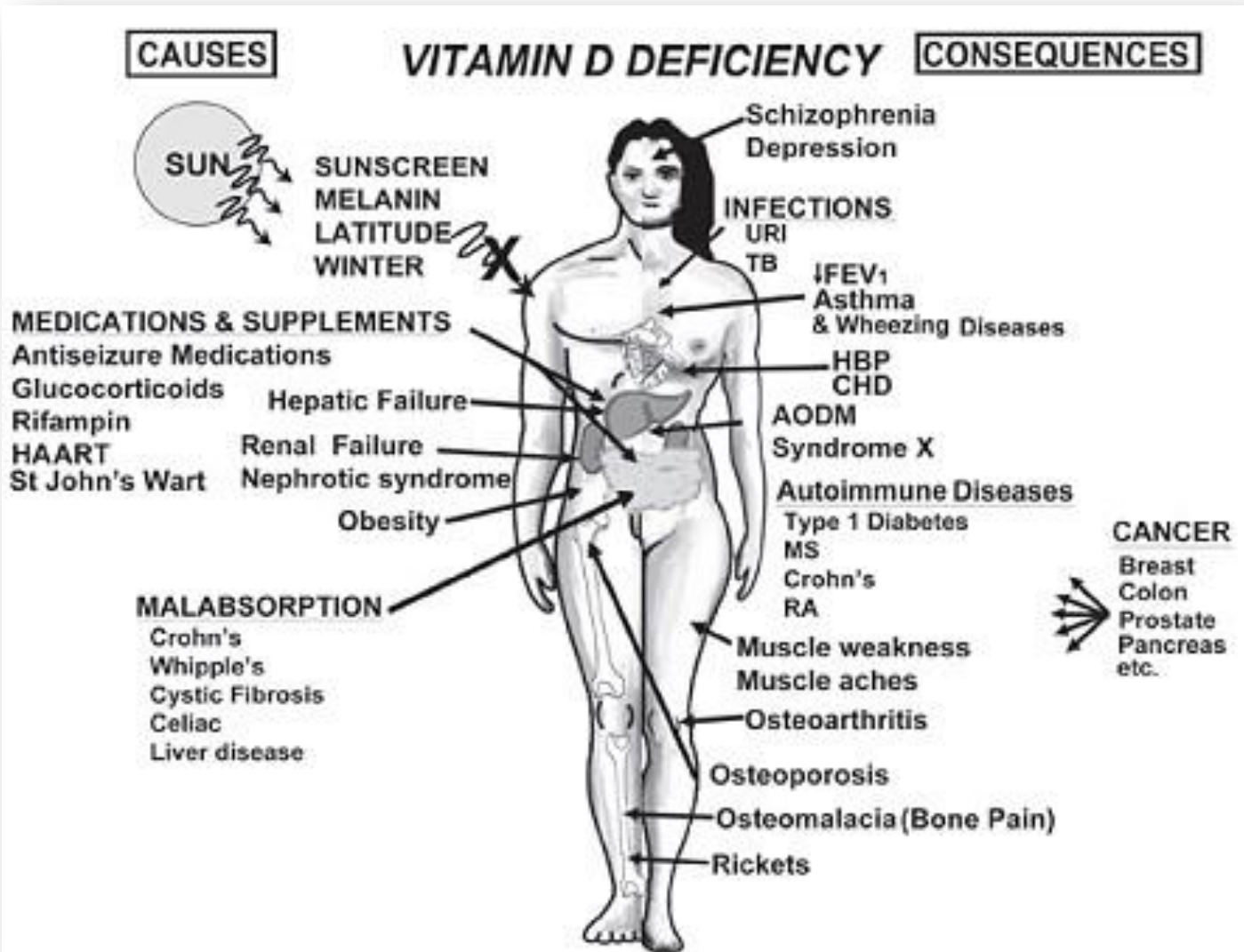
Ode to vitamin D

Multiple roles of vitamin D

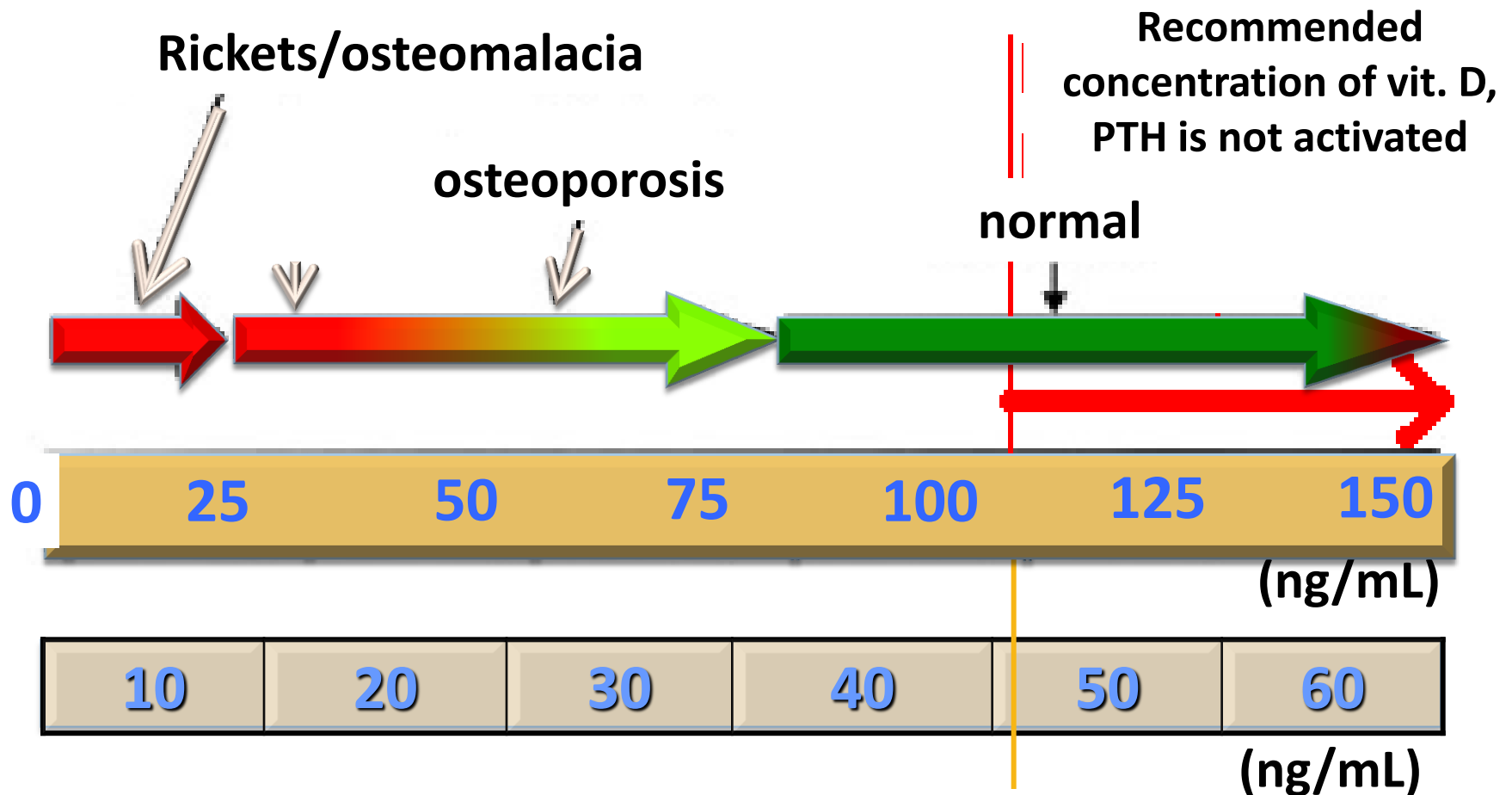


Vitamin D deficiency causes and influences various medical conditions

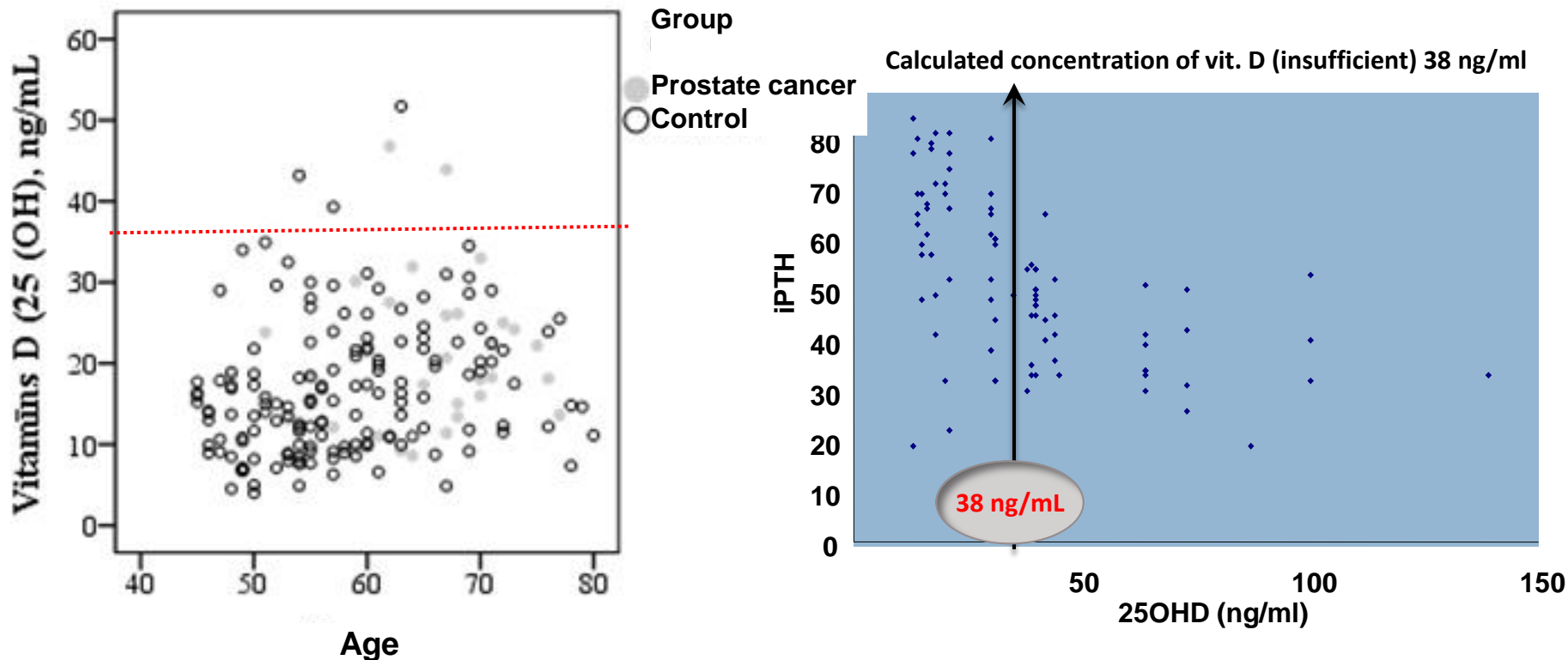
(Michail F Holick, 2008)



Recommended concentrations of 25(OH)D3 in serum



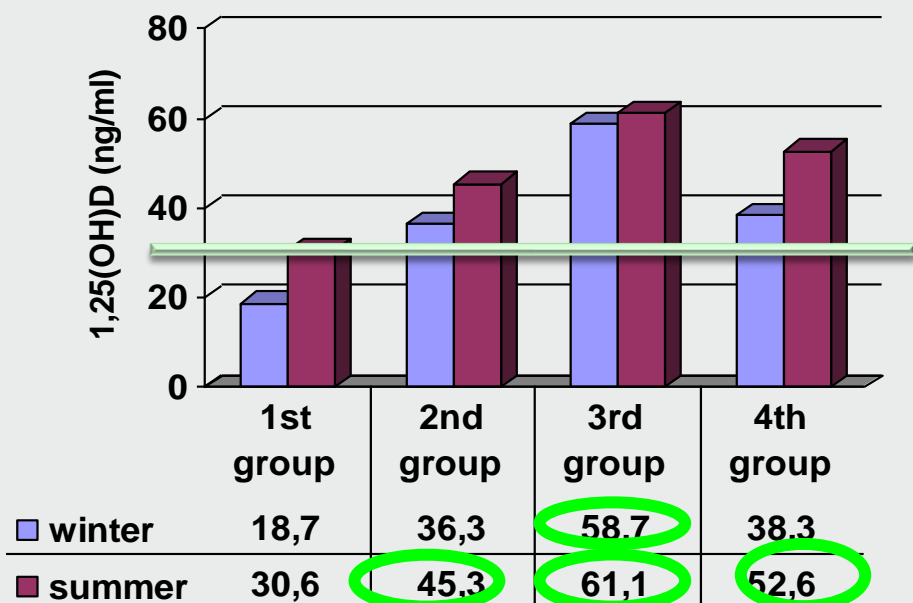
Correlation of age and vitamin D concentration in PC and control group males and vitamin D concentration in Latvia when synthesis of PTH is influenced



Conclusions:

Deficit of vit. D can be found in both PC and control group males. Nutrition does not provide the necessary intake of vitamin D. In order to assess the preventive effect of vit. D against PC it is suggested to use inactive forms of vitamin D, thus, increasing vit. D concentration in serum and enabling further prospective research.

Concentration of vit. D in summer and winter in Latvia



1.	<ul style="list-style-type: none"> ■ PM women ■ No intake vitamin D supplements ■ Do not visit solarium
2.	<ul style="list-style-type: none"> ■ Women in childbearing age ■ No intake vitamin D supplements ■ Do not visit solarium
3.	<ul style="list-style-type: none"> ■ Women in any age ■ Use vitamin D supplements and/or visit solarium
4.	<ul style="list-style-type: none"> ■ males

Conclusions:

- In order to avoid increased PTH stimulation, the optimum vit. D concentration in Latvia has to be at least 38 ng/mL.
- 70,4% of all healthy women had vit. D deficiency in winter and 59,8% in summer.
- The highest rate of vit. D deficiency both, in winter and summer was found in postmenopausal women who don't take additional vit.D supplementation



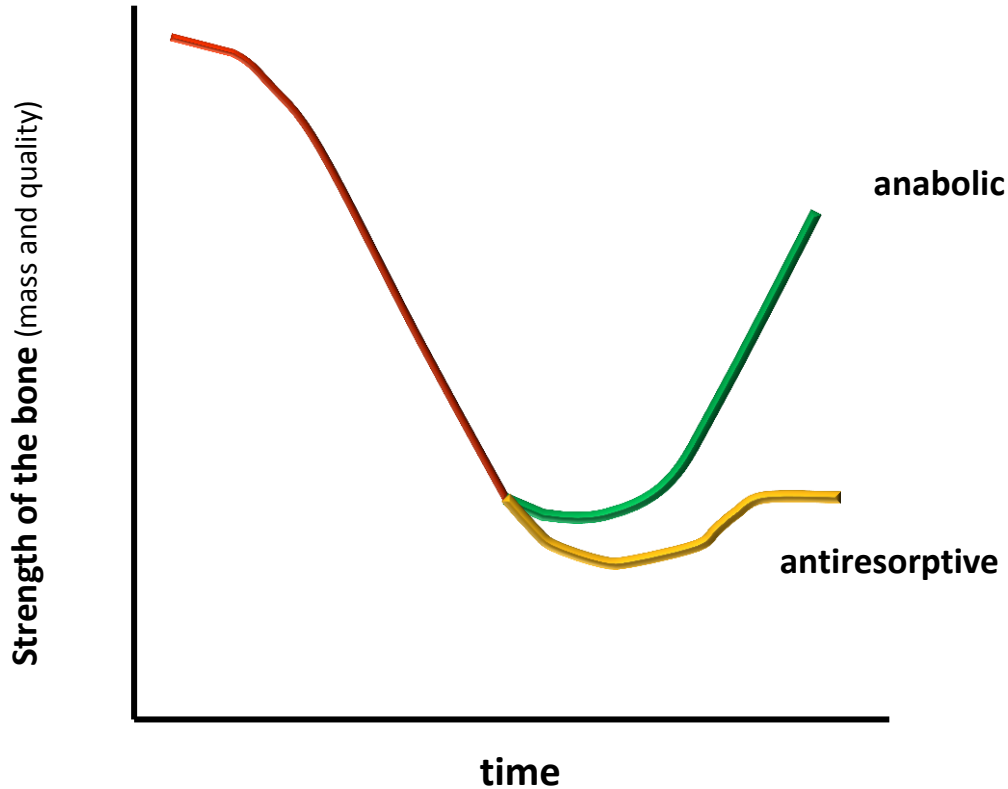
Osteoporosis is curable

Main principle of antiosteoporotic therapy – to avoid first and subsequent minimal trauma bone fractures

- Increase BMD
- Improve skeletal architectonics
 - ▣ Increase bone size and dimensions
 - ▣ Increase amount and thickness of trabeculae
 - ▣ Renew trabecular net binding
- Improve material features of the bone
 - ▣ Reduce bone turnover
 - ▣ Increase mineralisation
- Microdamage correction

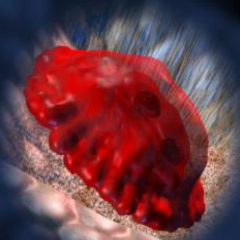


Drugs for treatment of osteoporosis



Antiresorptive agents

OsCl



Catepsin-K inhibitors

Calcitonin

DENOSUMAB

Stroncium Ranelate
(dual action)

Estrogen

SERMs

Raloxifene

Bisphosphonates

Alendronate

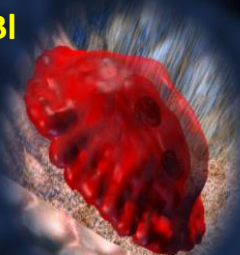
Risedronate

Ibandronate

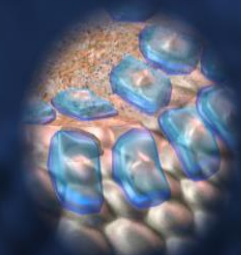
Zoledronic Acid

Anabolic agents

OsBl

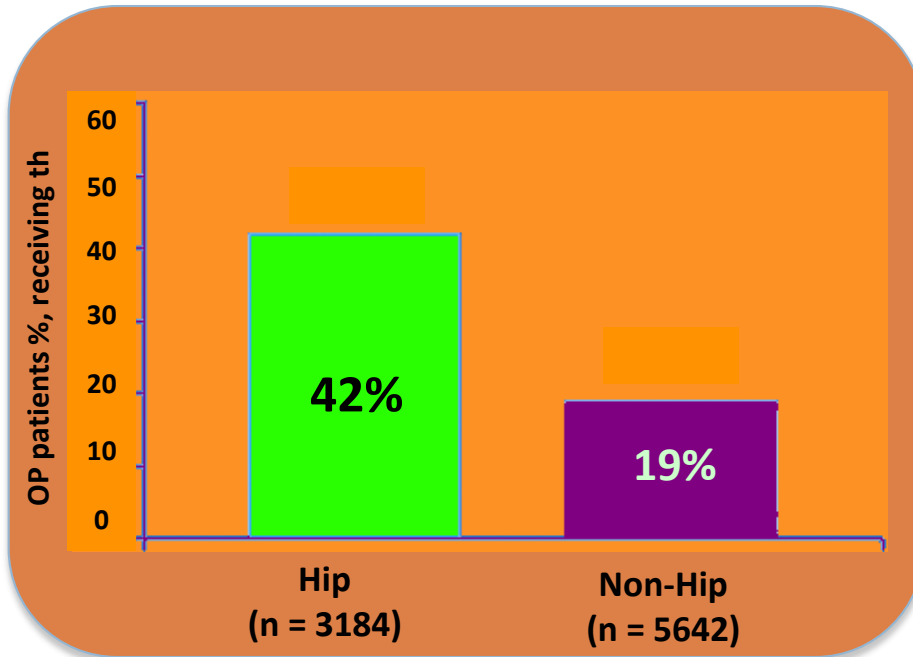


iPT
(Preatact, Forsteo)



Calcium and vit. D!!!

Women with osteoporosis often do not receive proper antiosteoporotic therapy for prolonged time

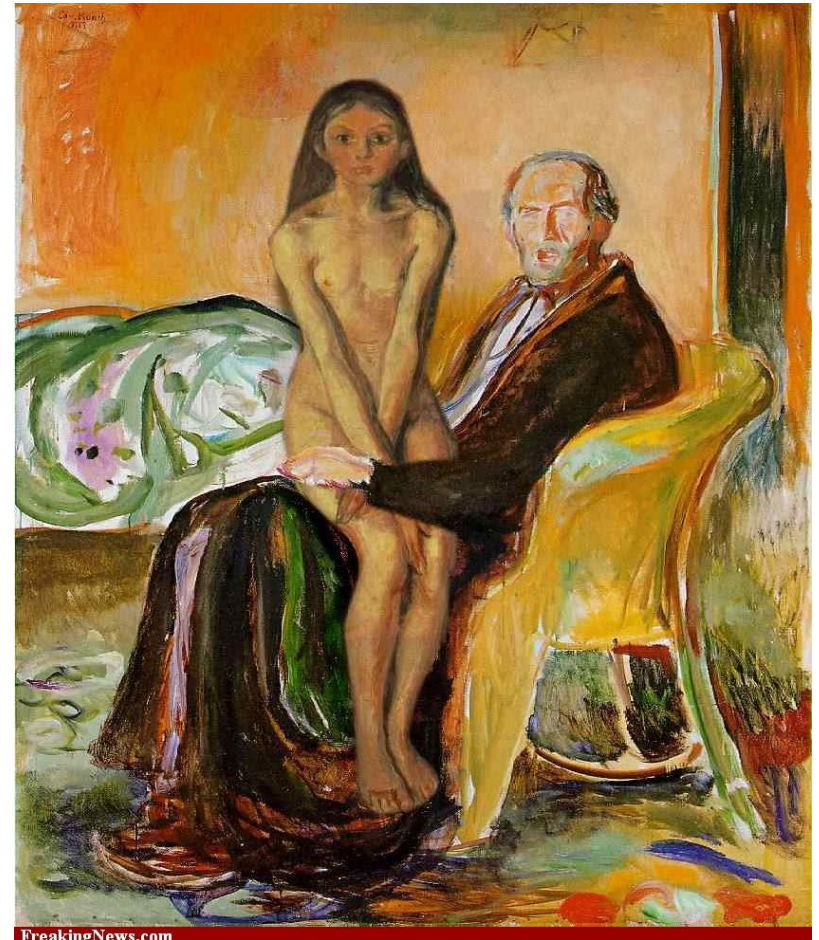


National Clinical Audit of Falls and Bone Healths (2007)

<http://sitik.wordpress.com/2010/10/28/mengenal-tulang-berisiko-osteoporosis/>

Bisphosphonate (BP) effects

- ↓ bone turnover
- ↑ BMD in lumbar vertebrae and proximal hip
- ↓ vertebral fracture risk
- Various effects on hip fractures
- Quick effects on BMD and bone markers
- Quick effects on bone fracture risk
- Persuasive effect if used for prolonged periods
- Good research results in treatment of osteoporosis
- Safe to use for prolonged periods



Edvard Munch

Possible side effects of BP

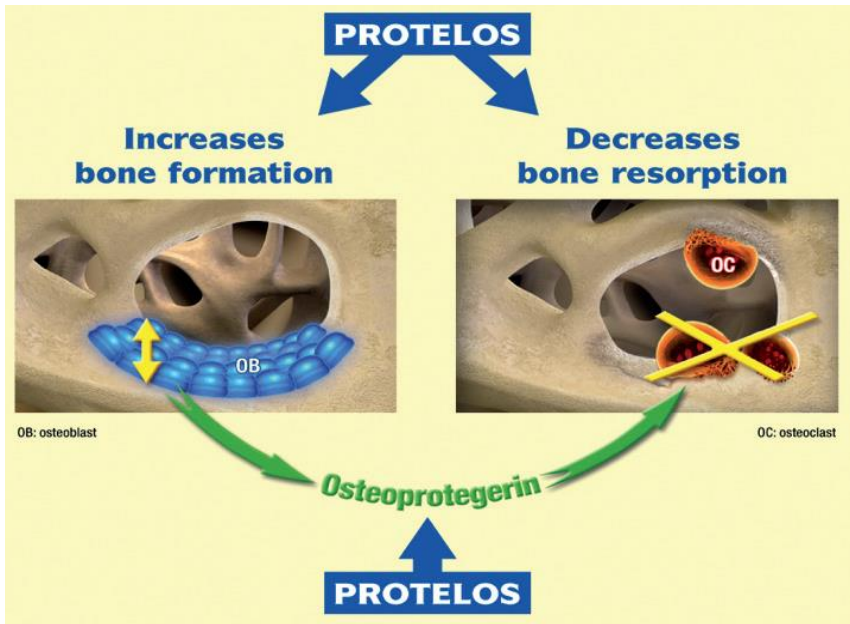
- **Necrosis of jaw**
- **Oesophageal ulcer, Ca**
 - **Do not subscribe BP to patients with:**
 - Barrett esophagus
 - Erosive gastritis
 - stomach ulcer
- **Subtrochanteric fractures of femoral neck**
- **AF (seldom)**



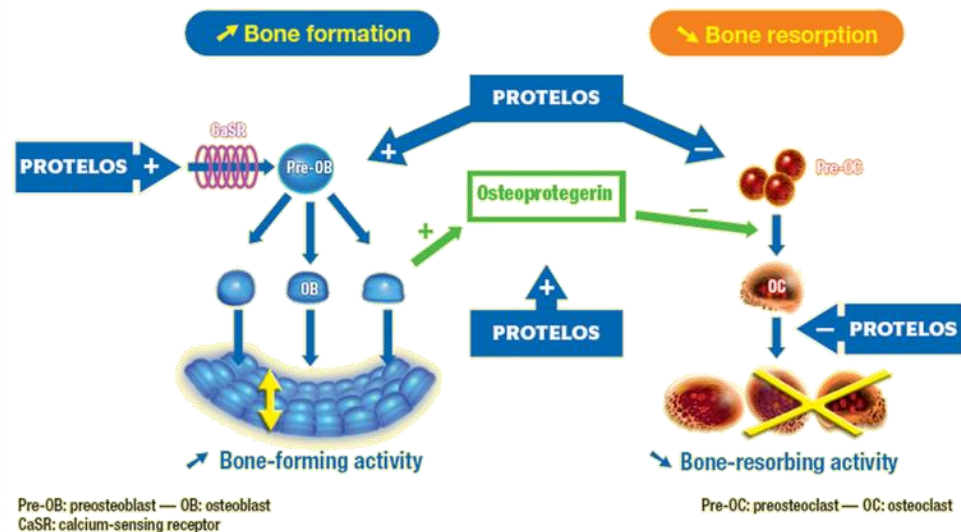
Vincent Van Gough. Old Man

Strontium ranelate action principle

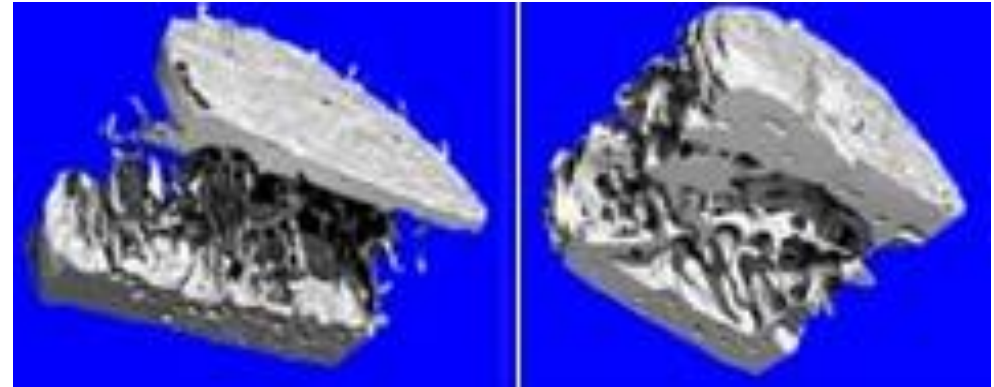
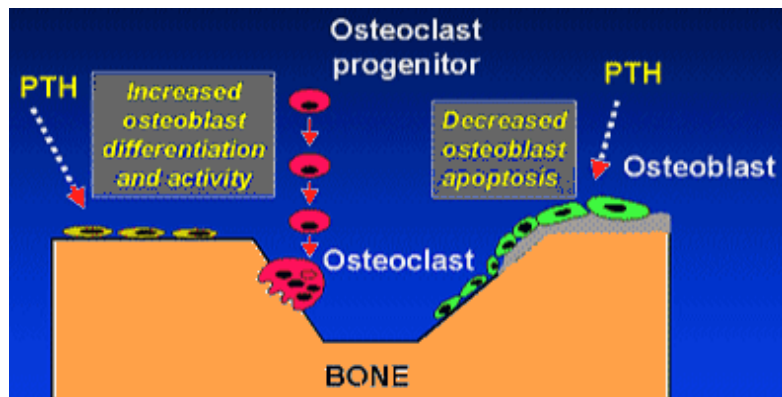
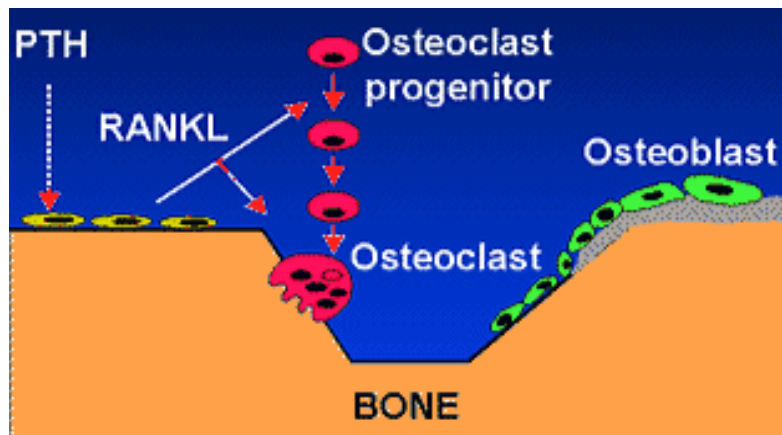
(currently restricted)



- Increases bone formation
- Reduces bone resorption
- Promotes growth of new bone tissue
- Increases level of osteoprotegerin, a protein reducing bone resorption



Constant intake of high dose PTH promotes bone resorption, but intermittent low dose promote bone formation

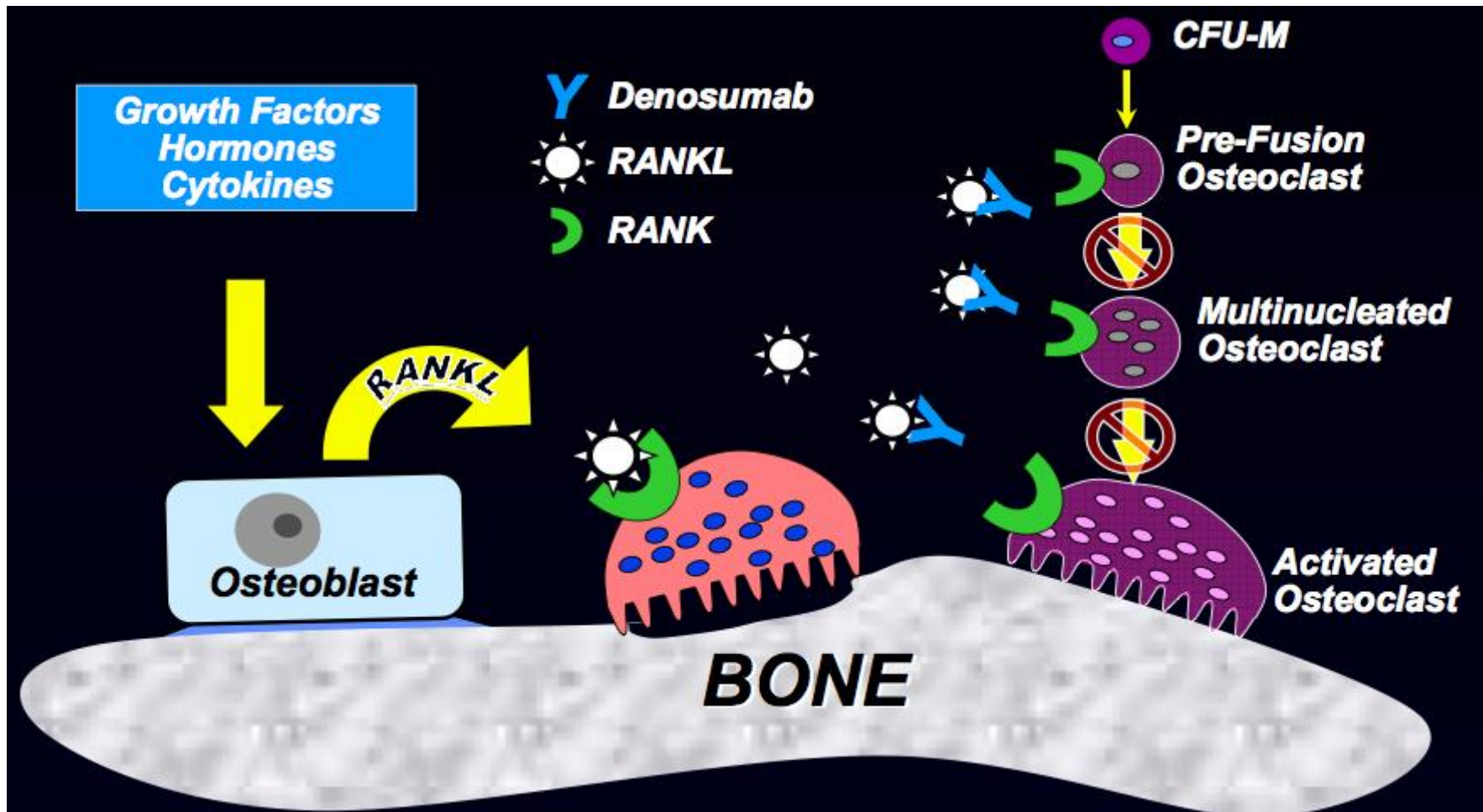


Before

After

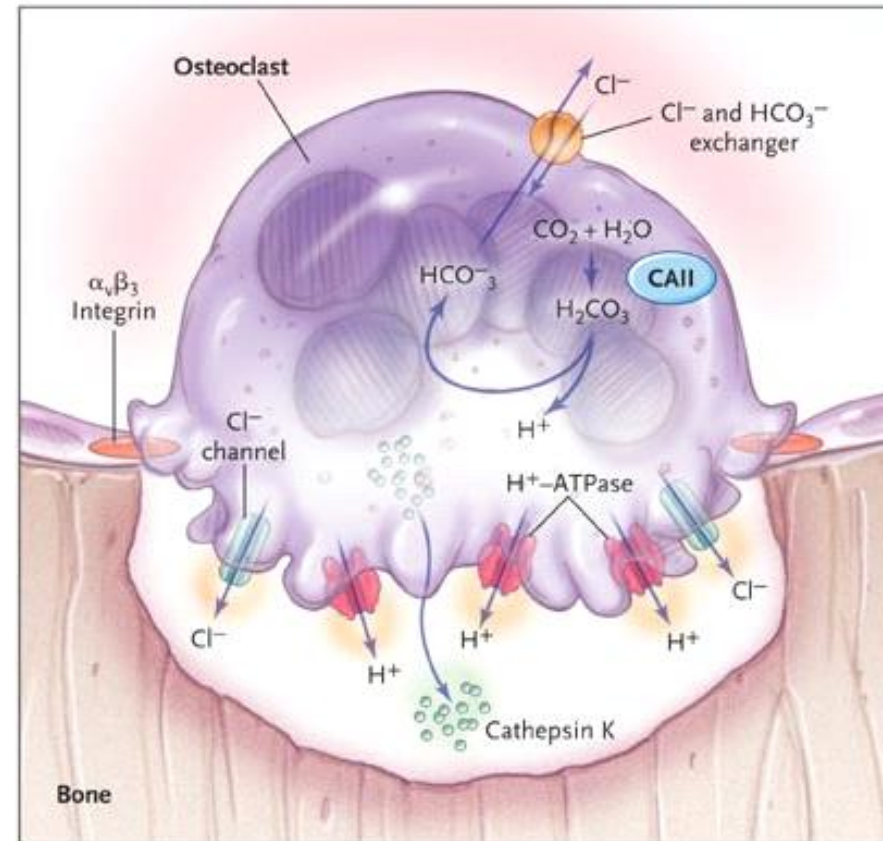
- **Increases bone resorption**
 - Large doses, prolonged intake
- **Promotes bone formation**
 - Intermittent low doses
 - Increases differentiation and activity of osteoblasts
 - Decreases apoptosis of osteoblasts
- **Increases thickness and amount of trabeculae**
- **Renew binding of trabeculae**
- **Increases diameter and strength of cortical bone**

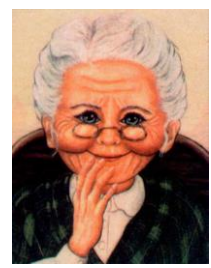
Denosumab – human IgG antibody against RANKL, controls differentiation, activation and survival of osteoclasts



Odanacatib (Cathepsin-K inhibitor) – new osteoporosis drug

- Cathepsin-K – enzyme responsible for collagen type 1 degradation
- CatK – cysteine protease, with high influence on OsCl
- In mice reduced CatK synthesis causes increase of BMD and cortical bone surface
- During bone formation CatK concentration is 4-6 times higher
- CatK blocks bone formation
- Reduced synthesis of CatK increases BMD, but bone formation is not decreased





Take home message

- ❑ Osteoporosis is an important society health problem
- ❑ Consider secondary causes of bone loss
- ❑ Lifestyle modification recommended
- ❑ Cortical bone porosity and thickness are important features
- ❑ Long-term osteoporosis treatment is safe and effective



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HUMORHOUR.COM

Take a careful look at people!

First impression is important, but not always complete!



