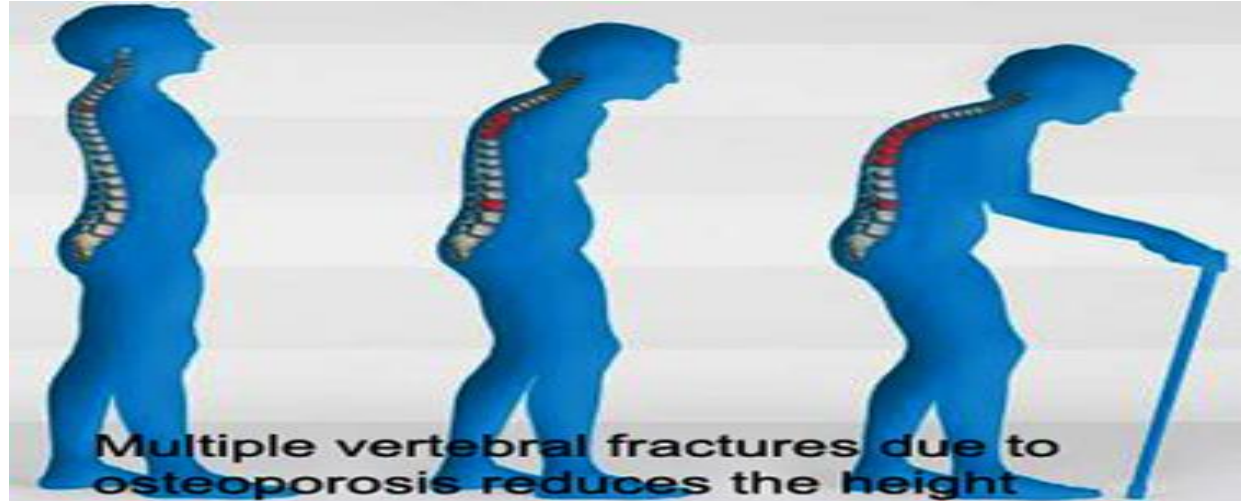


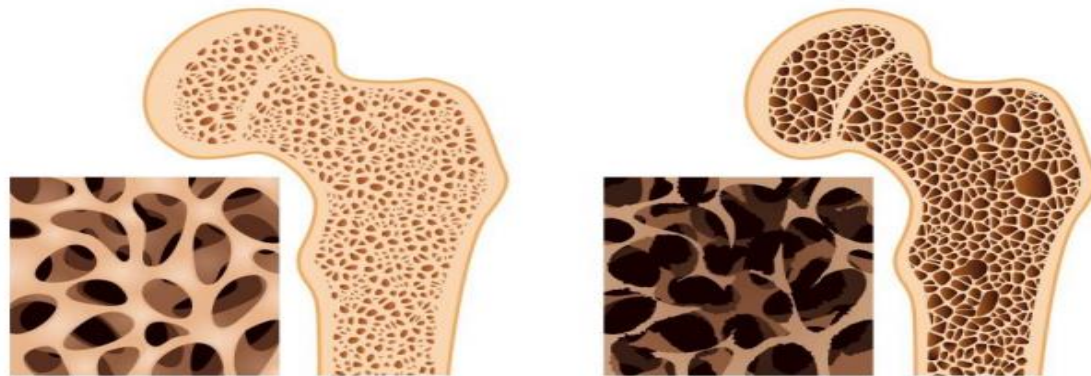
FARMAKOTERAPI

OSTEOPOROSIS



Definisi

- *osteo* = tulang, *porous* = berlubang-lubang atau keropos.
- ialah peny metabolik - me↓ massa tulang, krn matriks dan mineral tulang ↓ disertai kerusakan mikroarsitektur jar tulang.
- T.u pd tulang trabecular (proses resorpsinya lbh cpt drpd tulang lain)
- Dampak : kekuatan tulang ↓, tulang mdh patah
- Wanita > pria, percepatan menjelang menopause

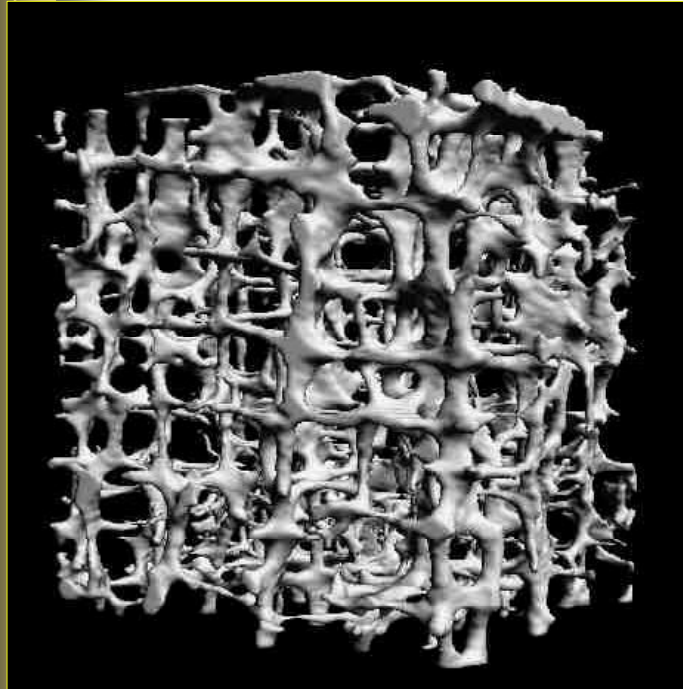


Healthy bone

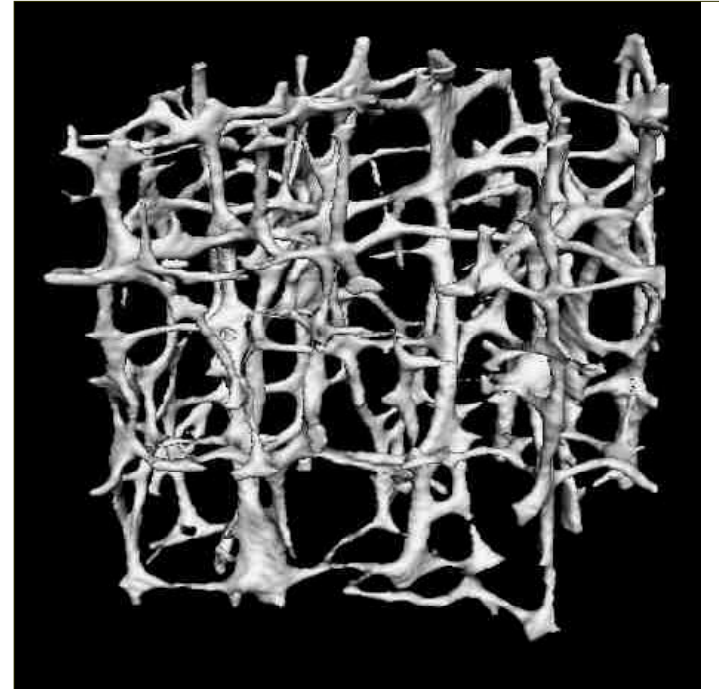
Osteoporosis

Hilangnya arsitektur trabekulasi vertebra dalam Micro CT-3 Dimensi

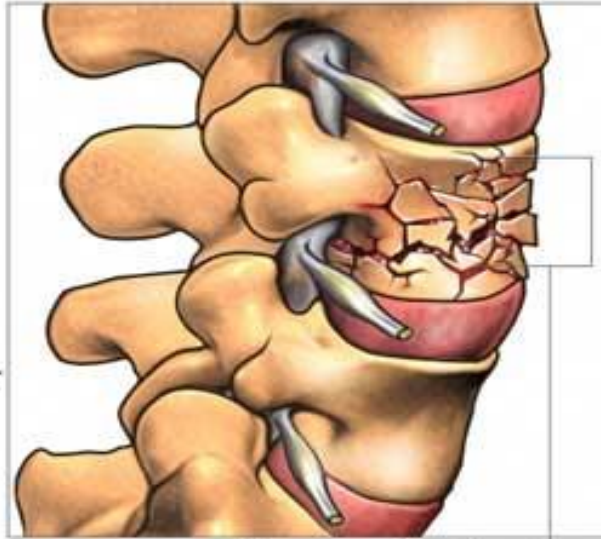
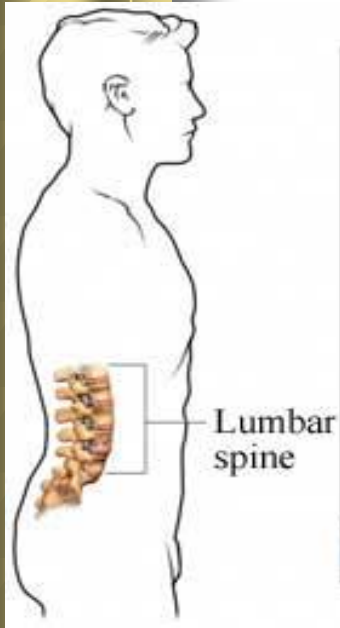
Wanita normal



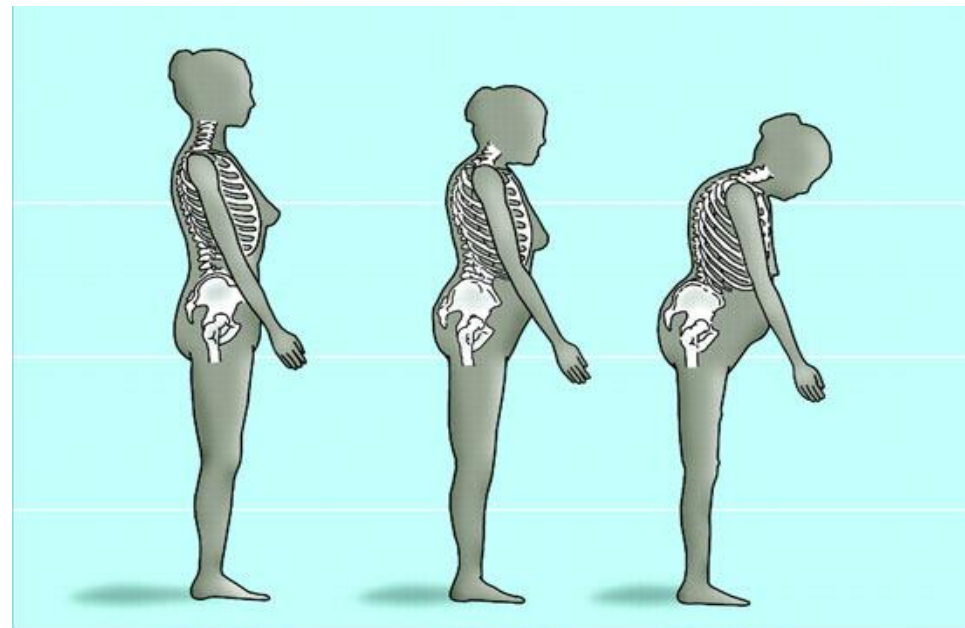
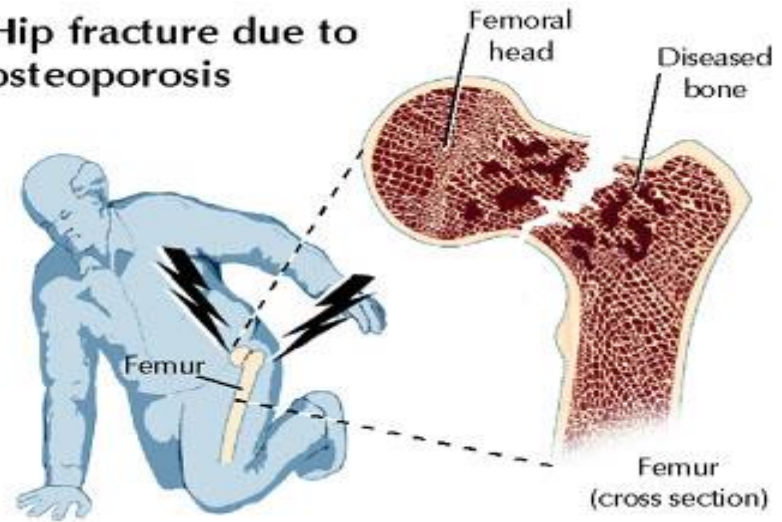
**Wanita Osteoporosis
(dg. fraktur vertebra)**



Loss of bone mass and horizontal trabeculae



Hip fracture due to osteoporosis



BMD

- **berkurang dg pertamb usia**

karena :

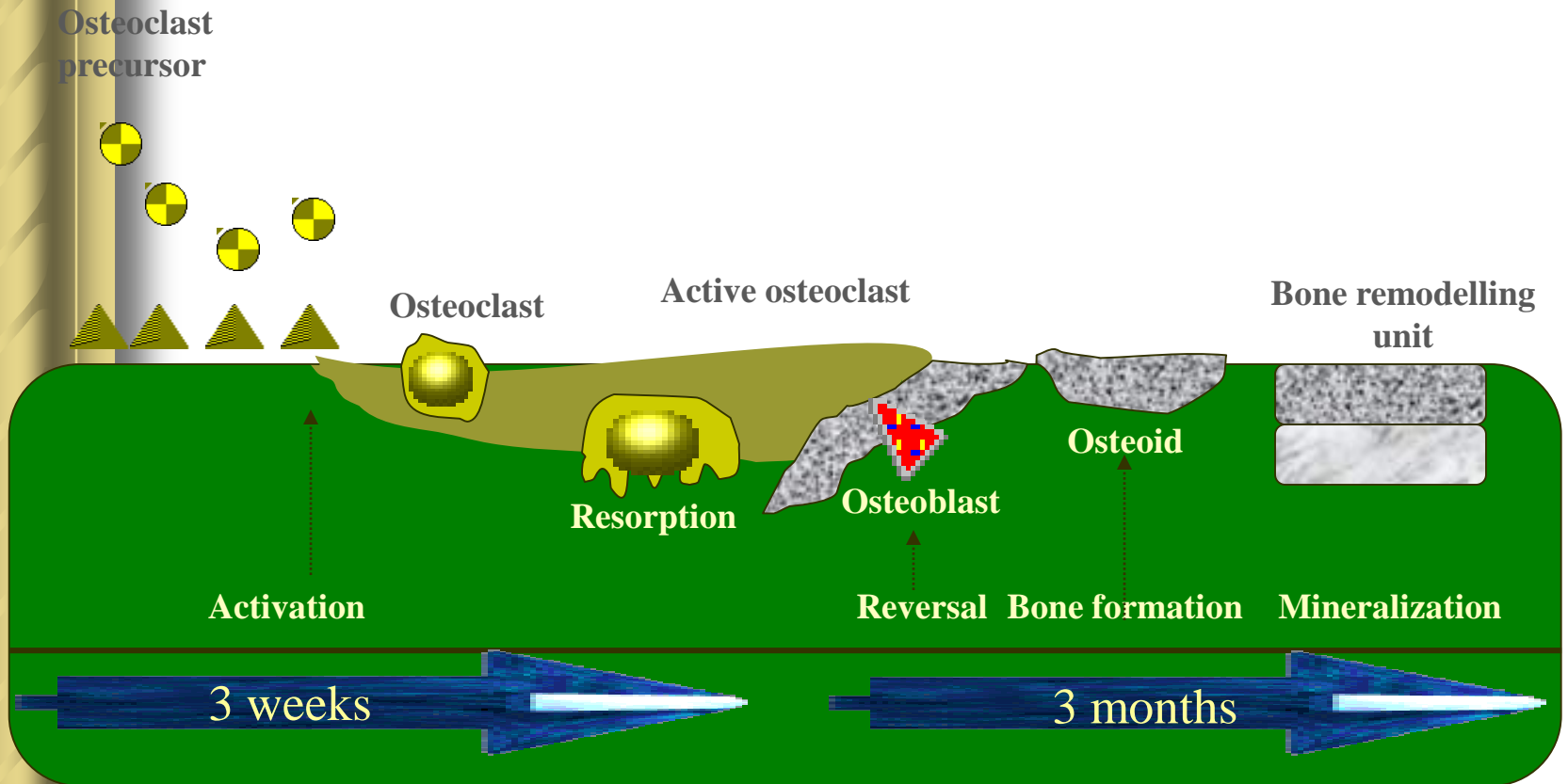
- Absorpsi kalsium di usus dan penggunaannya ↓
- me↑ kadar hormon paratiroid di serum
- Aktivasi vit D ↓
- Diet rendah kalsium, rendah vit D

Sumber Vitamin D = brokoli, kacang-kacangan, ikan teri, ikan salmon, susu, kuning telur, hati, sardine, sinar matahari

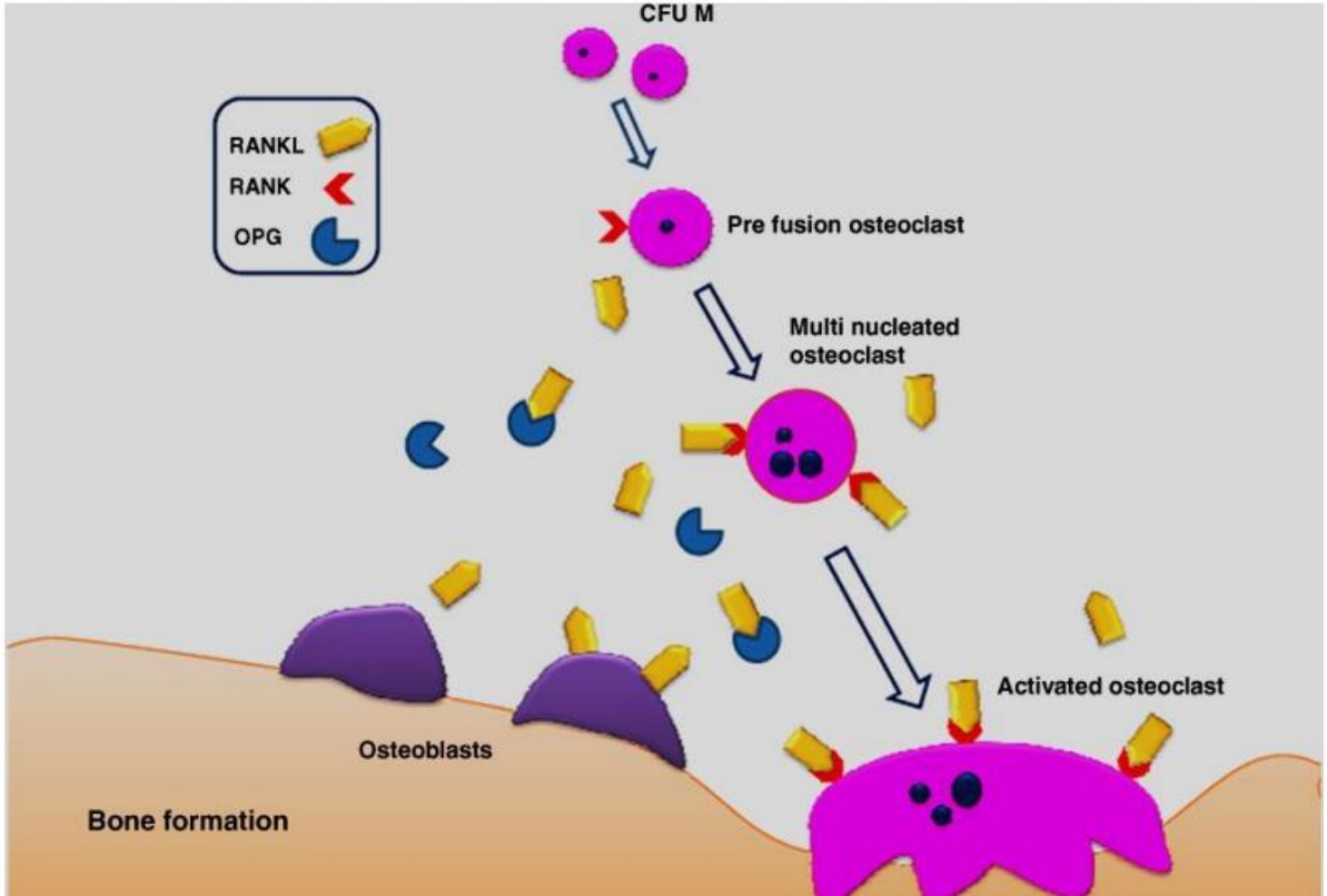
Remodelling Tulang

- Osteoblast = bertanggung jwb pd pembent tulang (bone formation)
- Osteoklast = bertanggung jwb pd penyerapan tulang (bone resorption)
- Osteoporosis = Abn bone turnover. Bone resorption > bone formation
- Tulang organ dinamis, selalu berubah dan mengalami pembaruan
- Pembaruan mulai dgn proses pengeroposan tulang (sel osteoclast) diikuti proses pembentukan tulang (sel osteoblast) ditempat pengeroposan, dilanjutkan mineralisasi shg diganti oleh tulang baru yg kuat
- Proses pengeroposan dan pembaruan berjalan seimbang →
Remodelling

Remodeling Cycle

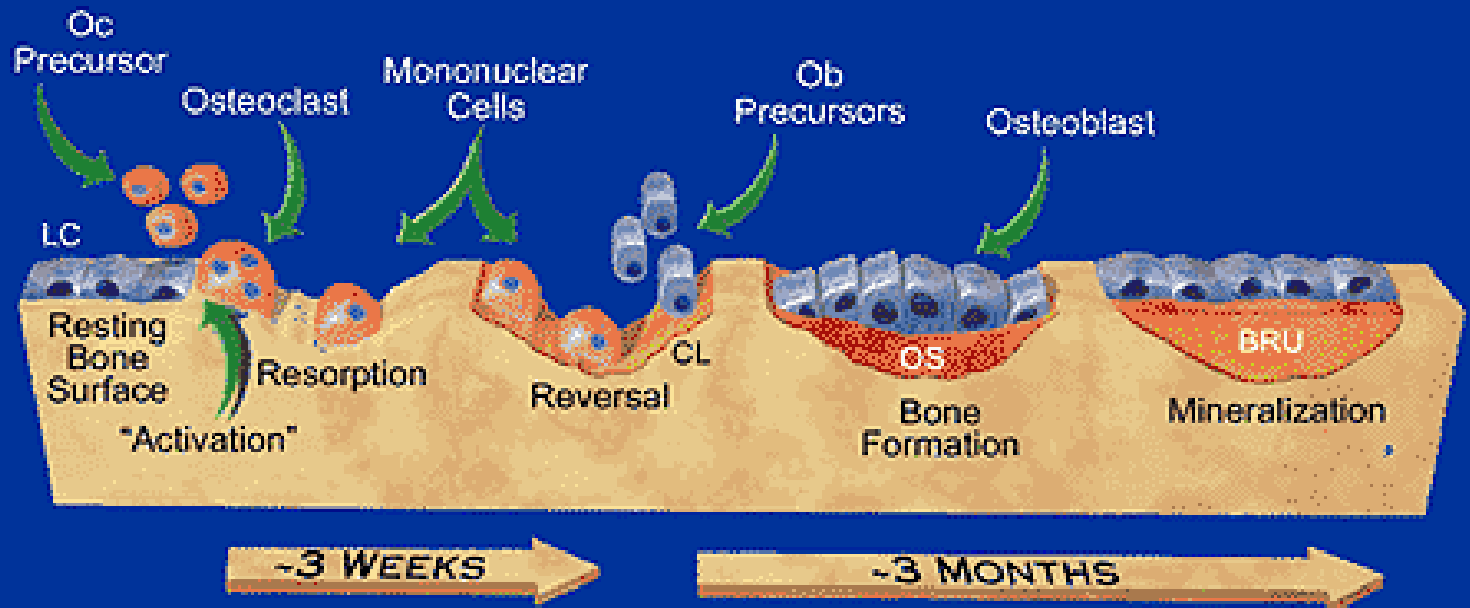


- *Receptor activator of nuclear factor kappa B ligand* (RANKL) adalah sitokin terkait TNF yang diproduksi oleh osteoblast, sel T, dan sel stromal.
- RANKL menstimulasi osteoclastogenesis dan sitokin seperti TNF- α , IL-1, atau IL-11, semua diproduksi oleh aktivasi sel T, yang mengarah ke destruksi tulang
- Osteoprotegerin (OPG) adalah anggota dari TNF *receptor super family* dan diproduksi oleh osteoblast. OPG adalah faktor inhibisi osteoclastogenesis yang mencegah fungsi dari RANKL.
- Sistem keseimbangan dari RANKL/OPG mengatur metabolisme tulang



OSTEOPOROSIS

Bone destruction > formation



LC = Lining Cells CL = Cement Line OS = Osteoid BRU = Bone Remodeling Unit

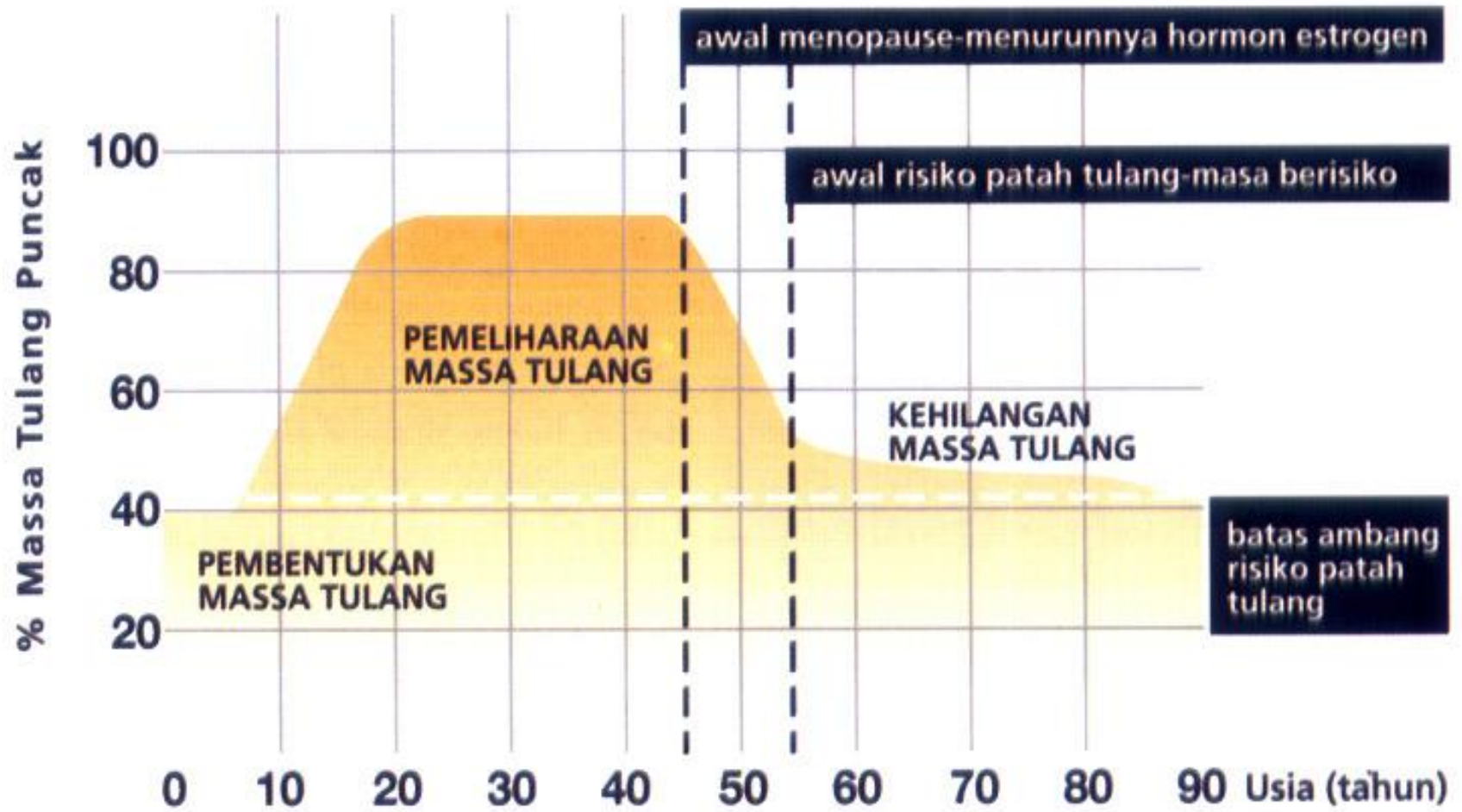
Klasifikasi Osteoporosis

(Riggs and Melton, 1983)

- **Osteoporosis Primer**
 - Tipe 1 → Osteoporosis pd wanita pasca menopause
 - Tipe 2 → Osteoporosis senil /penuaan
- **Osteoporosis Sekunder**
 - ➔ Osteoporosis oleh penyakit, efek samping obat, kondisi yg mengakibatkan kelainan tlg



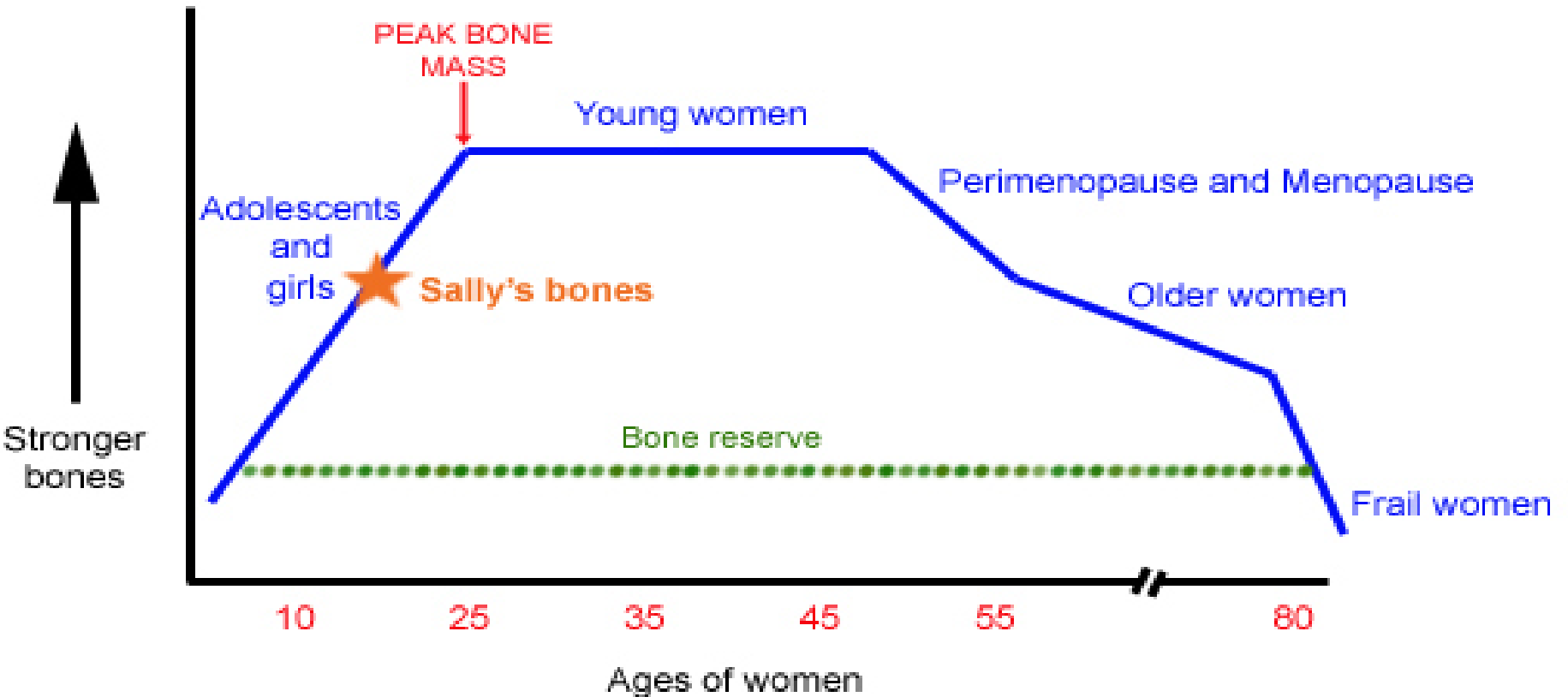
Tabel Massa Tulang Puncak



Puncak Massa Tulang yang Tinggi Dipengaruhi :

- **Latihan fisik yang baik, benar, terukur dan teratur (BBTT)**
- **Diet seimbang, kaya akan kalsium, cukup vitamin D dan zat-zat lain utk tulang**
- **Hindari gaya hidup tak sehat : merokok, alkohol, kafein dll.**

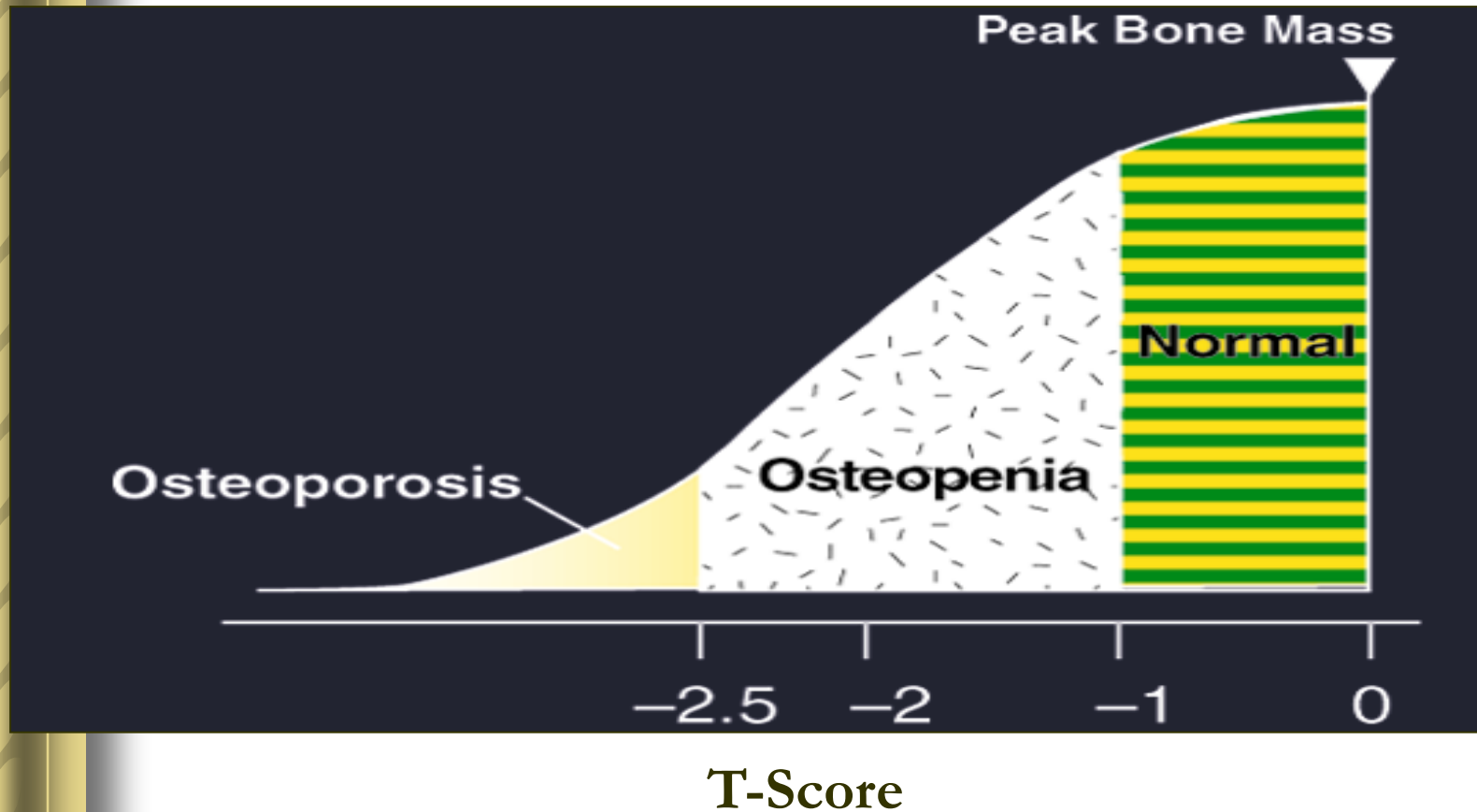
Life Cycle of Bone - Women



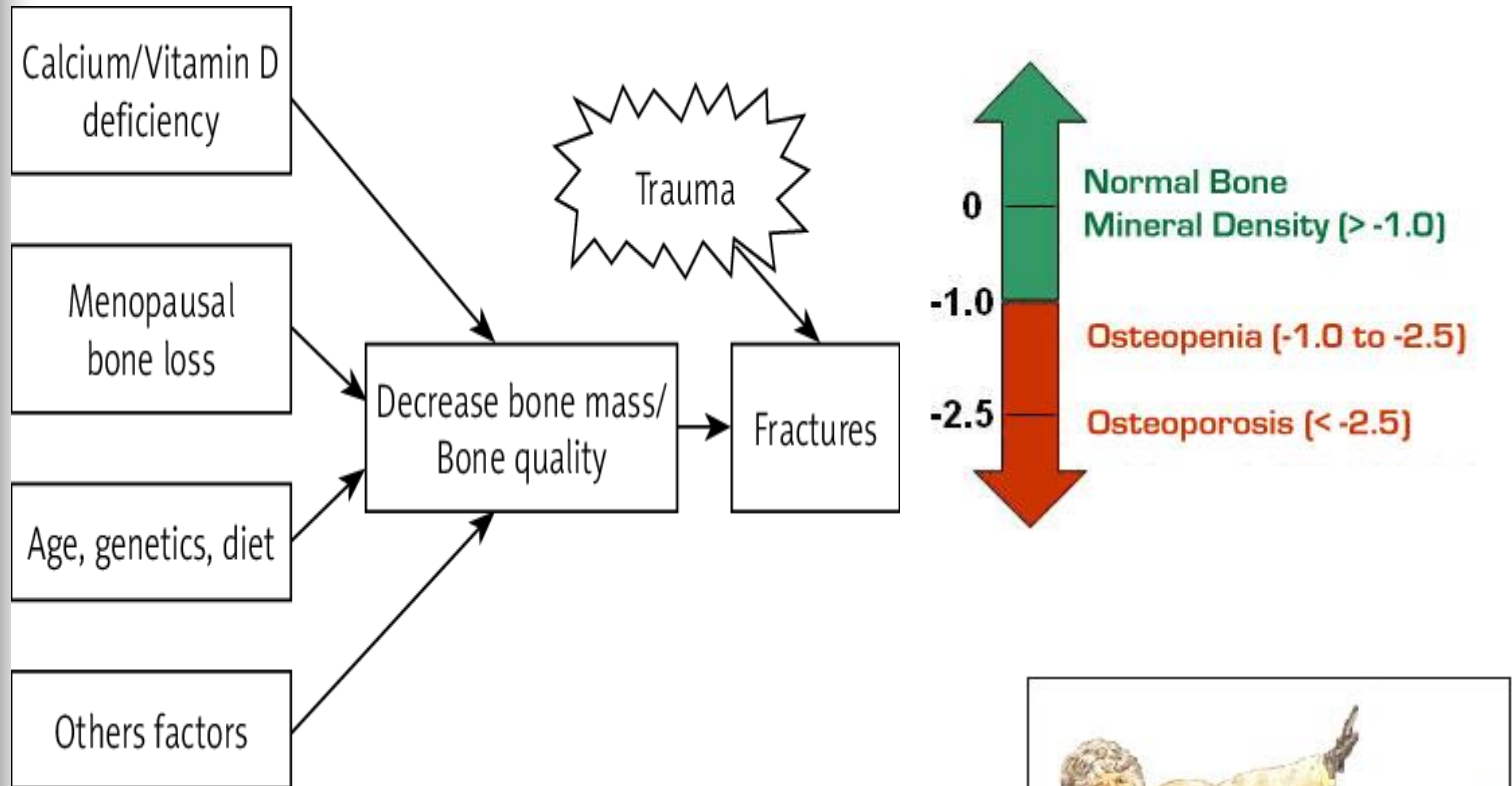
JcPrior 2007

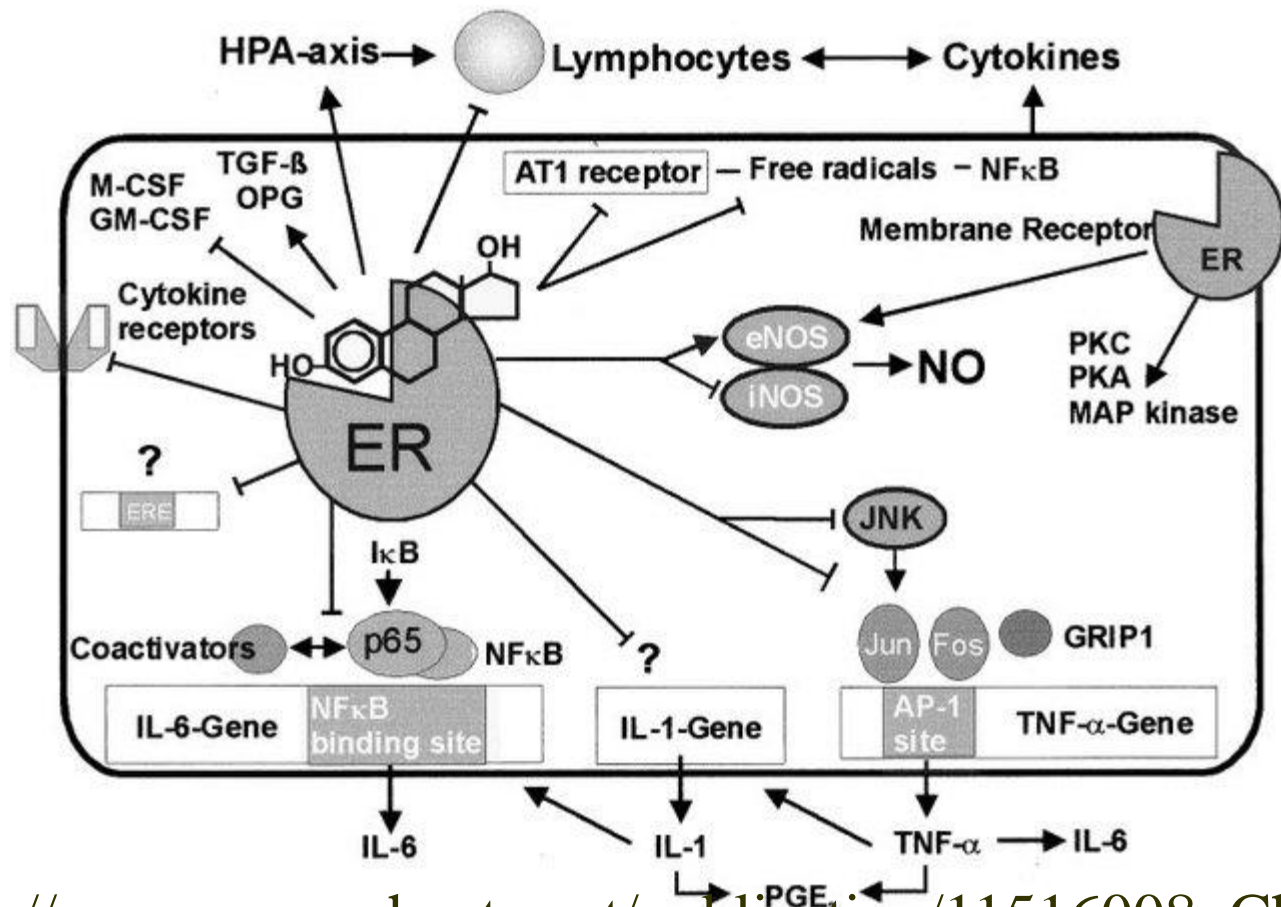
WHO Osteoporosis Guidelines

(Berdasarkan hasil pemeriksaan kepadatan mineral tulang dgn alat Bone Densitometer)

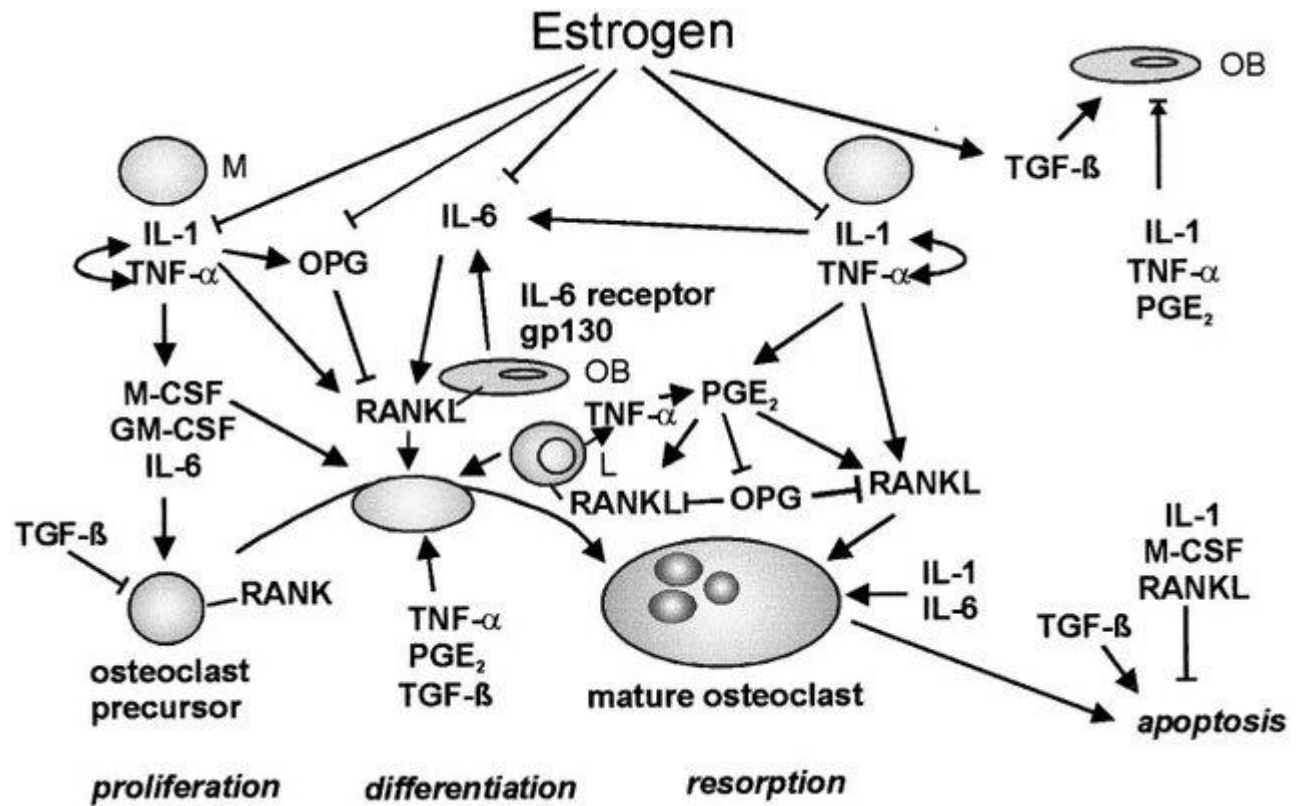


Osteoporosis & Fraktur



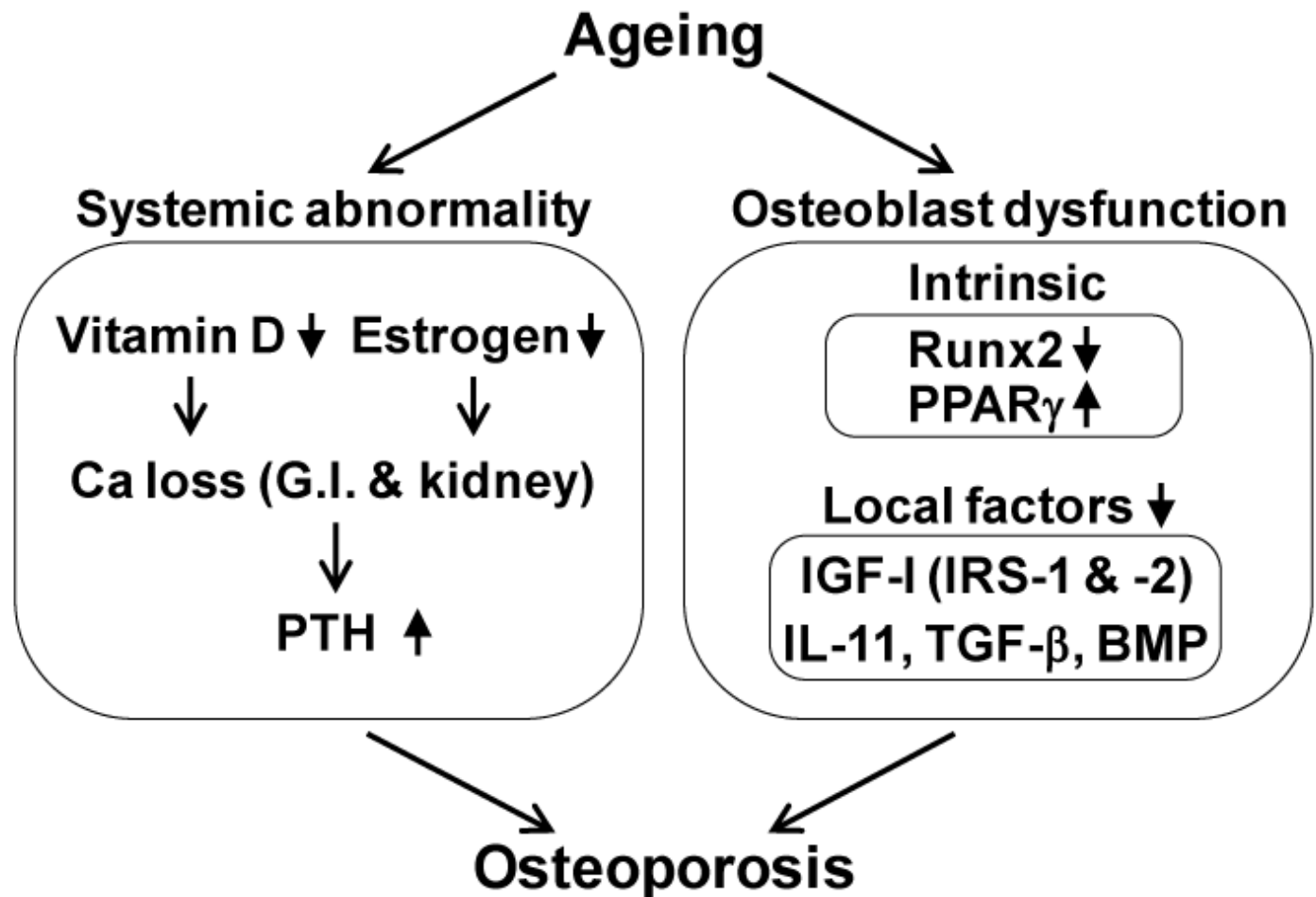


https://www.researchgate.net/publication/11516008_Changes_in_Proinflammatory_Cytokine_Activity_after_Menopause/figures

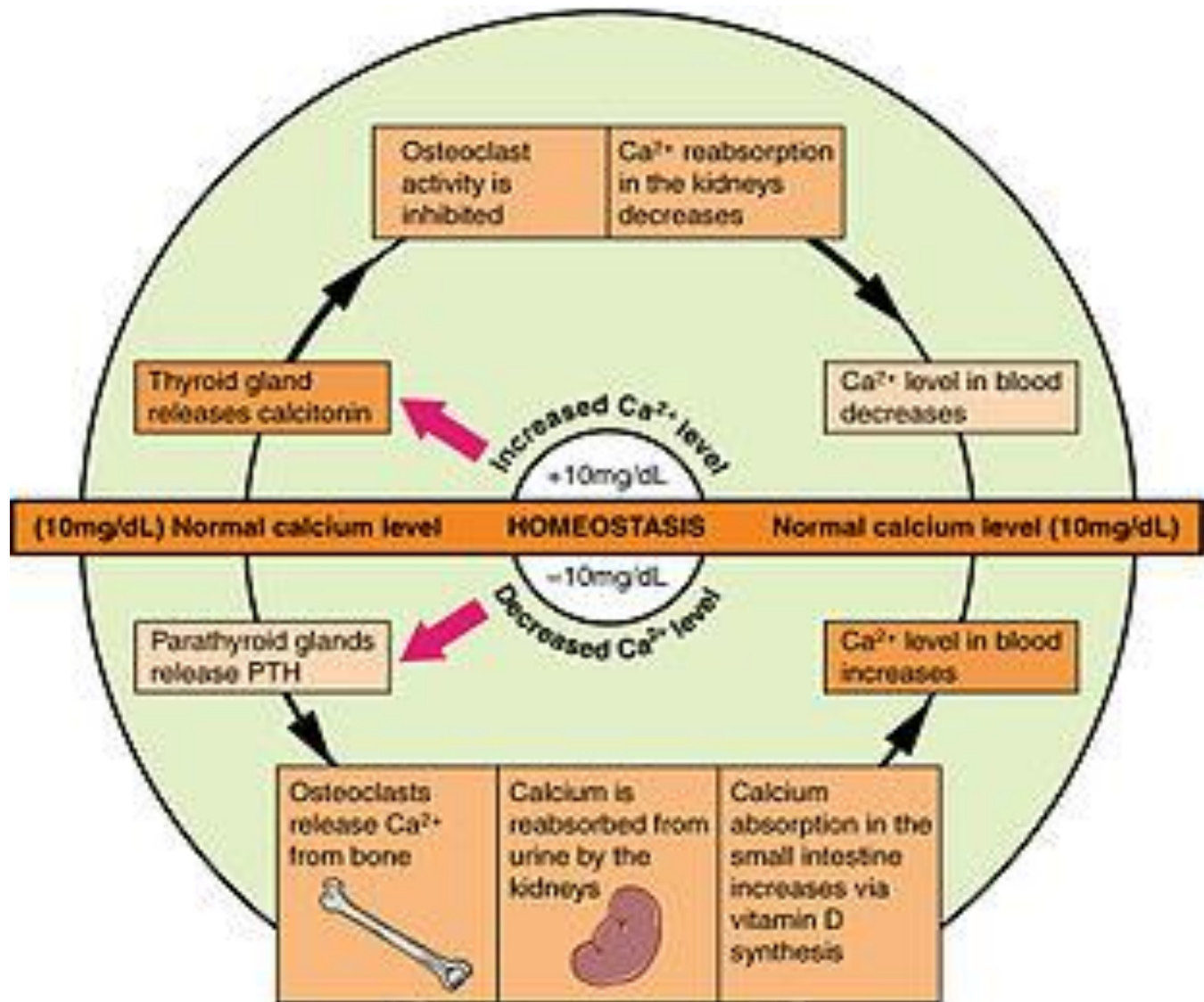


https://www.researchgate.net/publication/11516008_Changes_in_Proinflammatory_Cytokine_Activity_after_Menopause/figures

Osteoporosis and Aging

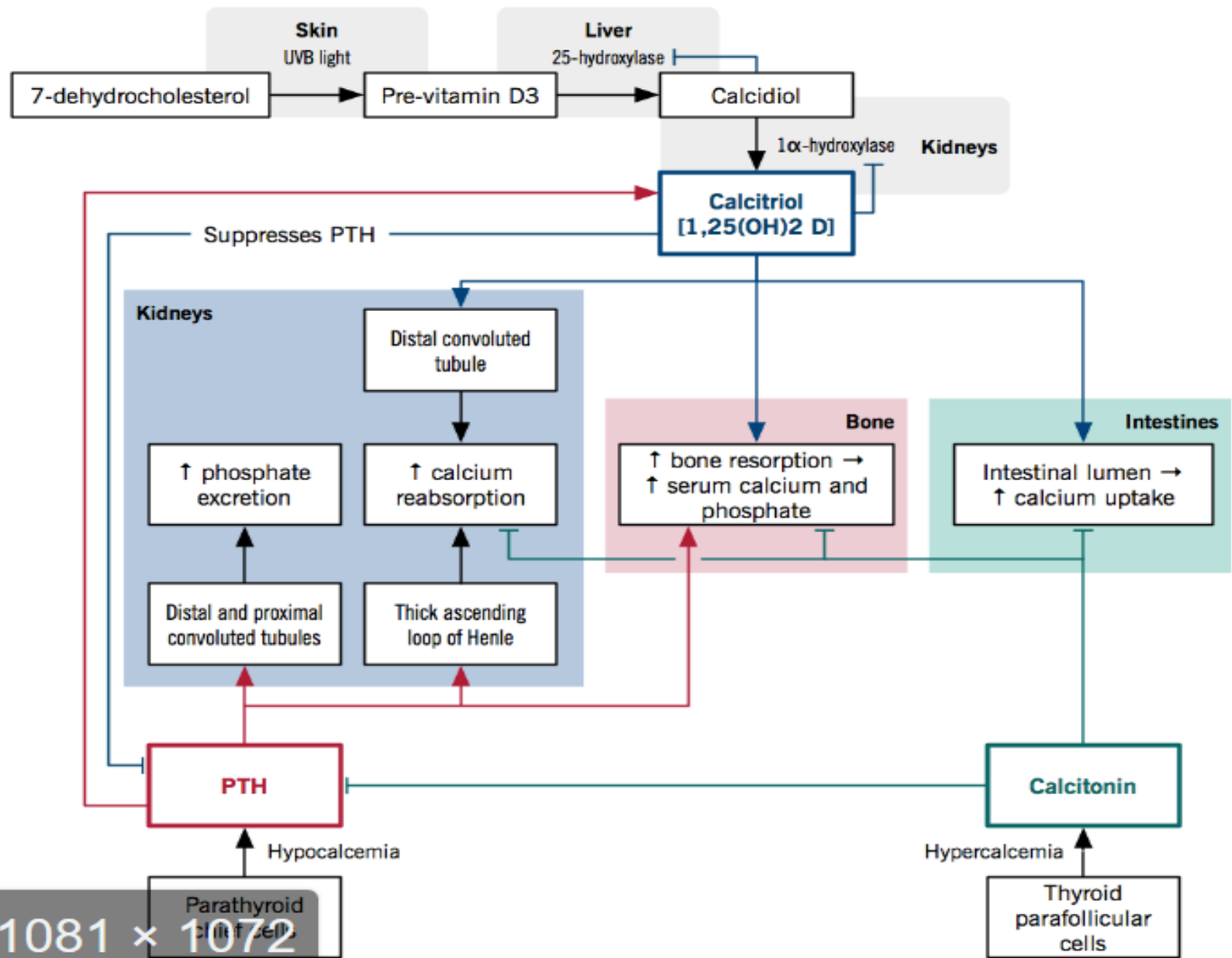


Homeostasis Ca^{2+}



Why is less calcium absorbed

- **Lower intake vitamin D rich foods.** Vitamin D maintains plasma calcium concentrations by increasing its intestinal absorption and mobilising calcium from bones
- **Conversion of vitamin D to its active form decreases in the elderly.** This is due to an age related decrease in the production of 7-dehydrocholesterol, the immediate precursor of vitamin D during adulthood
- Cholecalciferol (vitamin D3) formed in the skin by exposure to ultraviolet light also prevents osteoporotic fractures
- Calcium absorption also impaired in chronic renal and liver disease



1081 × 1072

Risk factors

Primary

- **genetics (up to 80%)**
- Female –post menopausal
- Increasing age
- Low BMI
- Caucasian ethnicity
- Poor nutrition, poor dietary intake Ca and Vit D
- Smoking
- Sedentary lifestyle
- Untreated premature menopause
- inadequate physical activity
- low weight/BMI

Secondary

- Renal impairment
- Chronic liver disease
- Rheumatoid arthritis
- Long term corticosteroid use
- hyperthyroidism

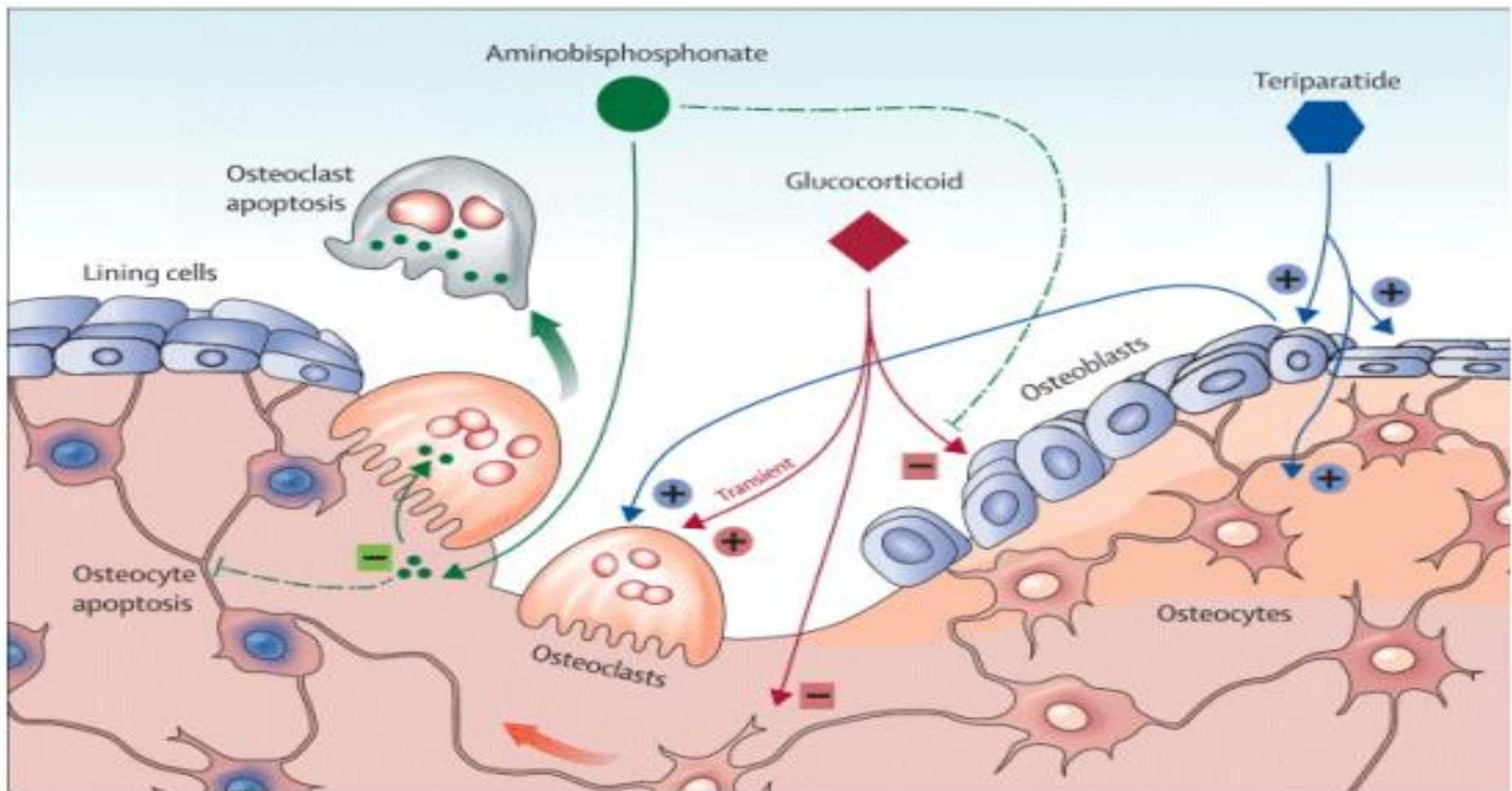


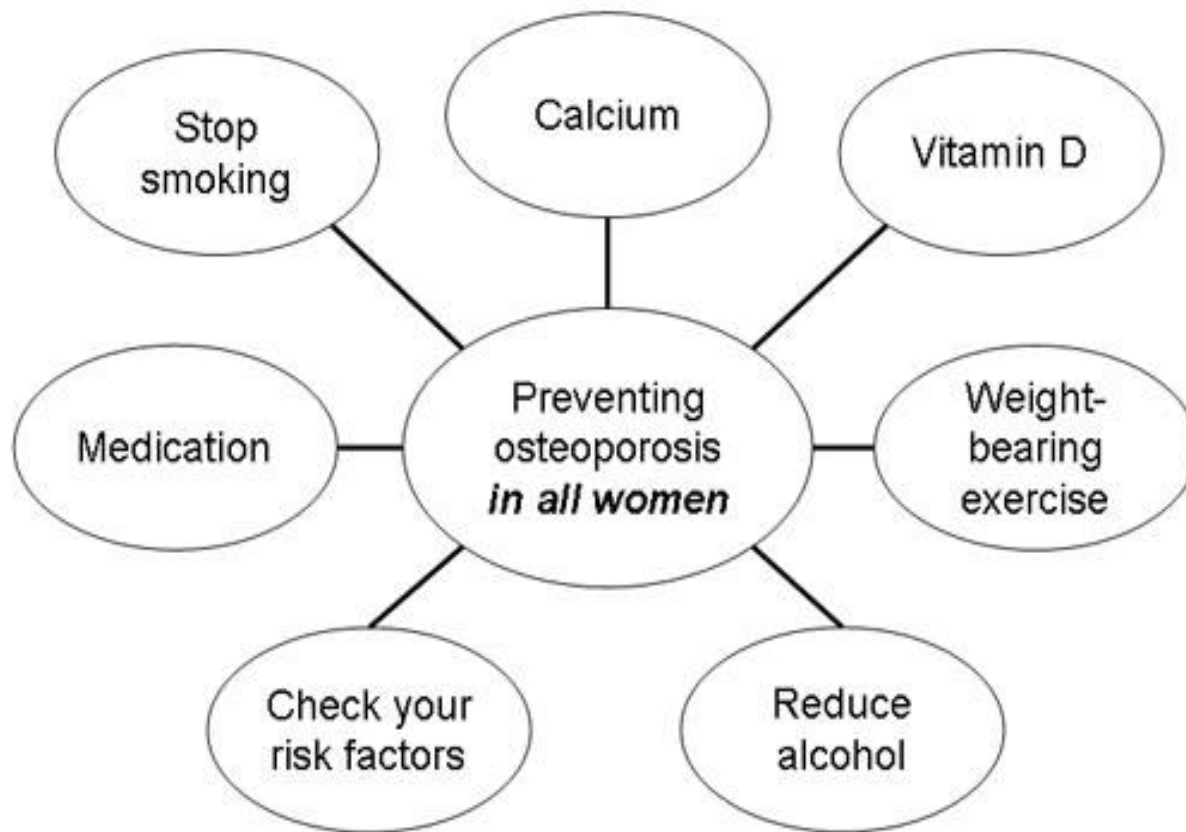
Medical conditions associated with o'porosis

- AIDS/HIV
- Amyloidosis
- Ankylosing spondylitis
- COPD
- Congenital porphyria
- Cushing's
- Eating disorders
- Gastrectomy
- Gaucher's
- Hemochromatosis
- Hemophilia
- Hyperparathyroidism
- Hypogonadism
- Hypophosphatasia
- Idiopathic scoliosis
- Inflammatory bowel disease
- IDDM
- Lymphoma/leukemia
- Malabsorption syndromes
- Mastocytosis
- Multiple myeloma
- Multiple sclerosis
- Pernicious anemia
- Rheumatoid arthritis
- Liver dz (esp PBC)
- Spinal cord transection
- Sprue
- Stroke
- Thalessemia
- Thyrotoxicosis
- PTH secretion due to malignancy
- Weight loss

Drugs associated with increased osteoporosis risk

- Aluminum
- Anticonvulsants (phenobarb/phenytoin)
- Cytotoxic drugs
- Glucocorticosteroids and adrenocorticotropin (up to 10% bone loss in first year of tx with high doses)
- GnRH agonists
- Immunosuppressants
- Lithium
- Long term use of heparin (bone loss in 1/3 of women)
- Long acting parenteral progesterone
- Supraphysiologic thyroxine doses
- Premenopausal use of tamoxifen





Kebutuhan kalsium berdasarkan usia

Usia	Kebutuhan kalsium perhari (mg)
0 to 6 bulan	210
7 to 12 bulan	270
1 to 3 tahun	500
4 to 8 tahun	800
9 to 18 tahun	1,300
19 to 50 tahun	1,000
> 50 tahun	1,200

**Tumbuh
cepat**

Anjuran Pemberian Vitamin D berdasarkan kelompok umur

Kelompok Umur	(IU/hari)	RNI ($\mu\text{g}/\text{har}$)
Usia 0-9 tahun	200	5
Usia 10-18 tahun	200	5
Usia 19-50 tahun	200	5
Usia 51-65 tahun	400	10
Usia 65+ tahun	600	15
Masa kehamilan	200	5
Masa menyusui	200	5

Sumber: FAO/WHO: Human Vitamin and Mineral Requirements, 2002

The truth about exercise

- **Weight bearing exercise has positive effect on skeleton**
- **Insufficient to prevent bone loss in early menopause, but will slow the rate**
- **Impact loading (ie weight lifting) best osteogenic stimulus**
- **Exercise reduces risk of falls, +/- reduces fracture risk in falls that do occur**



Latihan Fisik



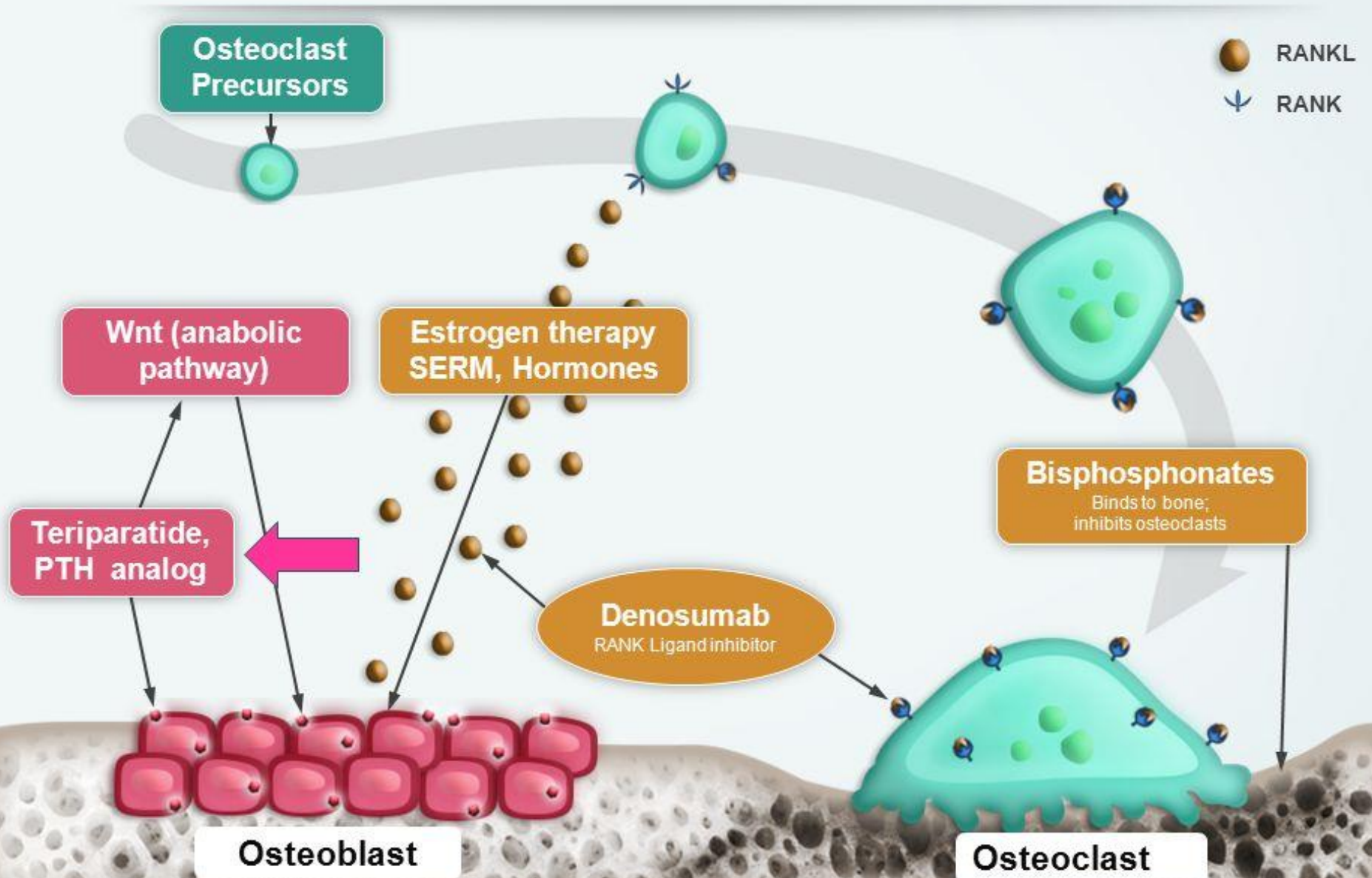
- Latihan pembebanan
- Gerakan dinamis dan ritmis
- Daya tahan (endurans) dlm bent *aerobic low impact*

When to treat



- **First – lifestyle changes (details to follow)**
- **Next – follow guidelines as stated by National Osteoporosis Foundation (NOF); recommend pharmacologic therapy to postmenopausal women with T-scores <-2.0 as measured by central DEXA regardless of risk factors, and <-1.5 if risk factors present**

Mechanism of Action of Available Osteoporosis Therapies



Drug Treatments for Osteoporosis

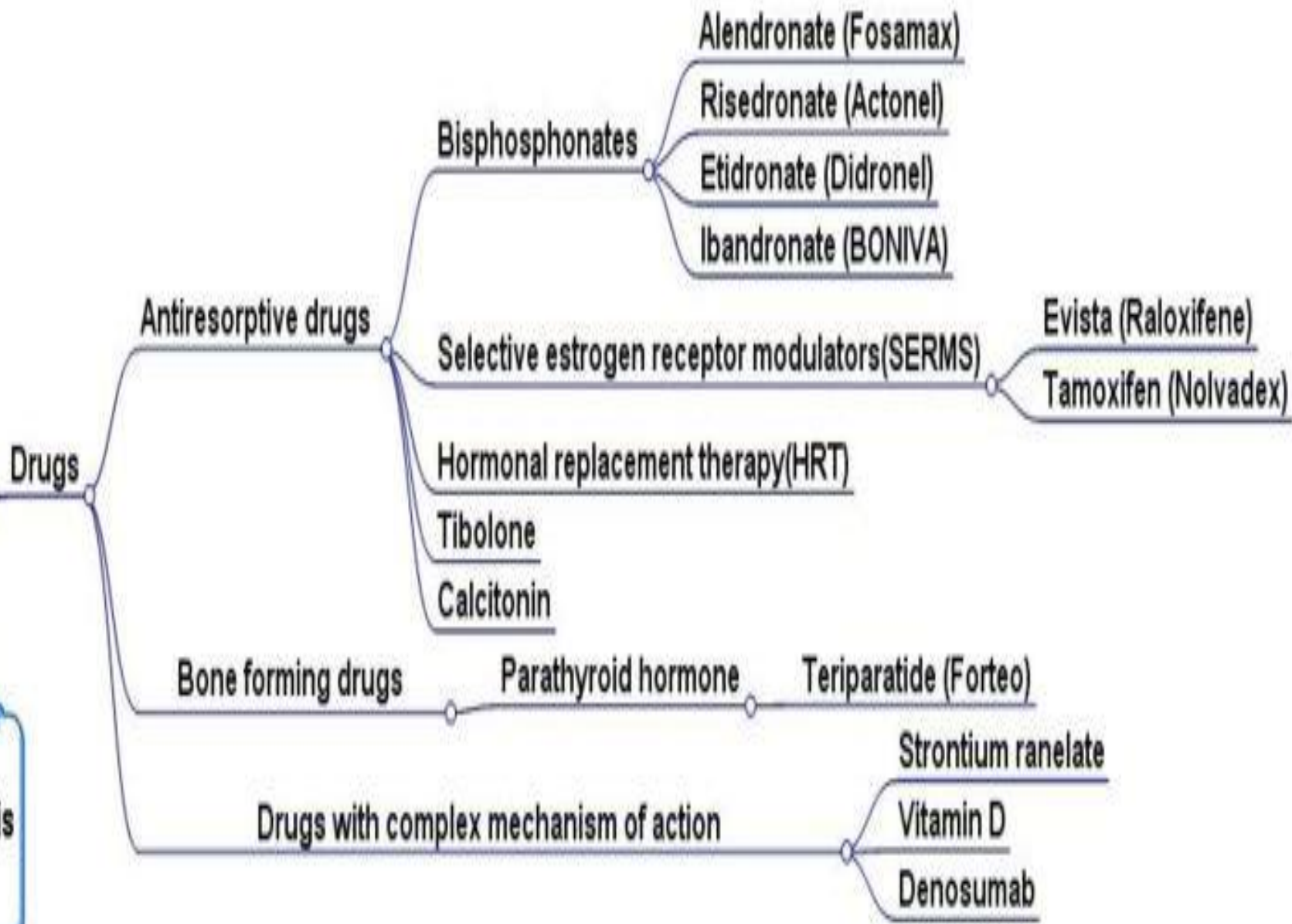
Antiresorptive

- Bisphosphonates
alendronate, risedronate, ibandronate, etidronate
- SERMs (Selective estrogen receptor modulators)- raloxifene
- Calcitonin
- Estrogen

Anabolic

- PTH -Teriparatide

Osteoporosis



Treatment of Postmenopausal Osteoporosis

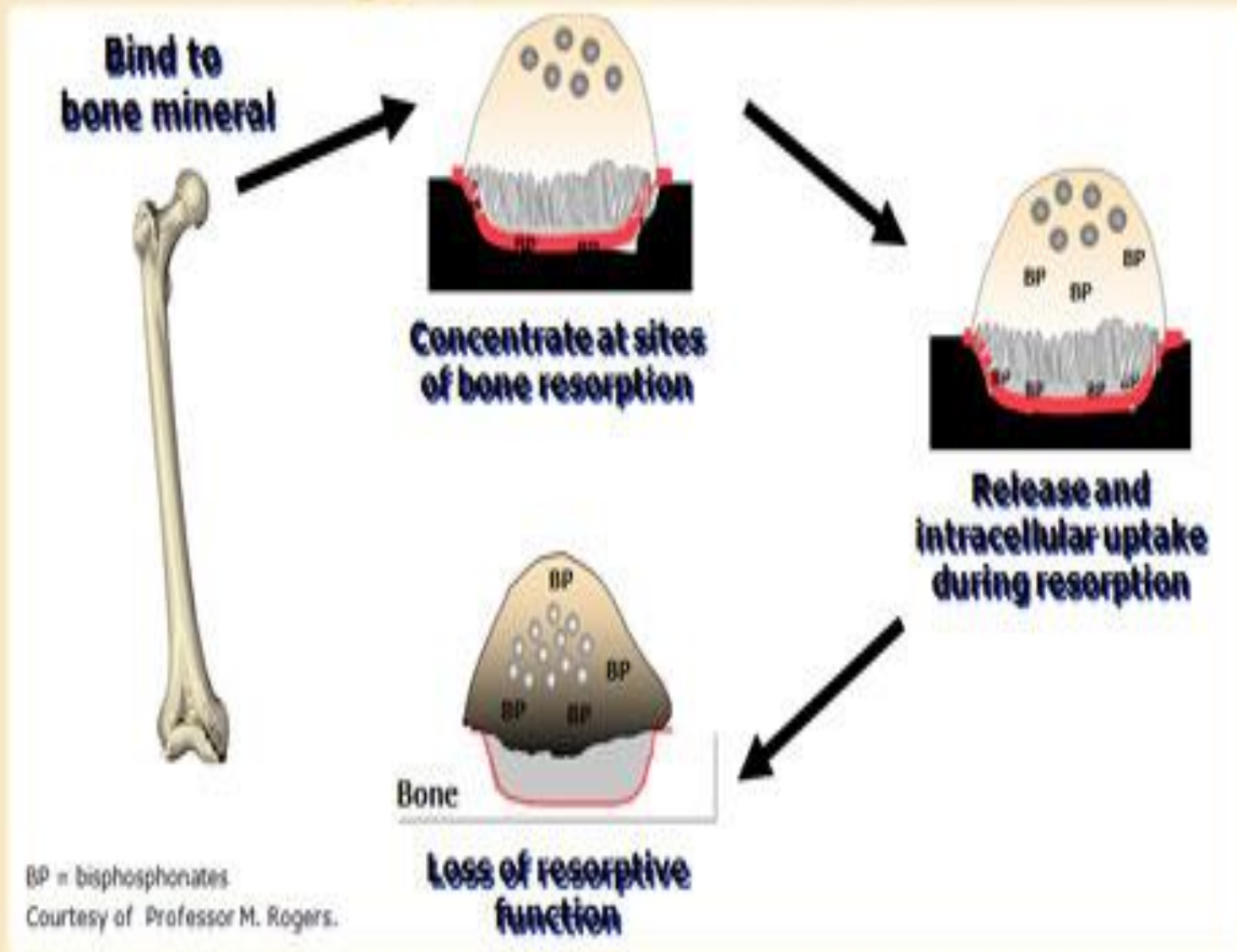
FDA Approved Indications

	Prevention	Treatment
Alendronate (Fosamax)	Yes	Yes
Risedronate (Actonel)	Yes	Yes
Calcitonin (Miacalcin)	No	Yes
HT	Yes	No
Raloxifene (Evista)	Yes	Yes
PTH (Forteo)	No	Yes

Bisphosphonates

- Ada 2 kelas :
 - Non-nitrogenous bisphosphonates (clodronate, etidronate, tiludronate)
 - Pro-drug, dimetab di dlm sel osteoclast menghasilkan metabolit aktif yg sitotoksik dan menyebabkan kematian sel osteoklast
 - Nitrogenous bisphosphonates (pamidronate, Alendronate, risendronate, ibandronate)
 - Menghamb farnesyl diphosphate synthase (FDPS) pd jalur mavalonate, shg menghilangkan fungsi GTPase small→regulasi fungsi osteoklast terganggu
- Effective for tx and prevention of osteoporosis
- Low oral bioavaibility, highly polar, high molecular weight, paracellular route absorbtion
- Precautions – avoidance of pill induced esophagitis (CI with reflux, GERD, other esophageal abnormalities); must take on empty stomach, with 1 glass water and remain upright for 30 min

Action of Bisphosphonates Depends on Mineral Binding and Effects on Osteoclasts

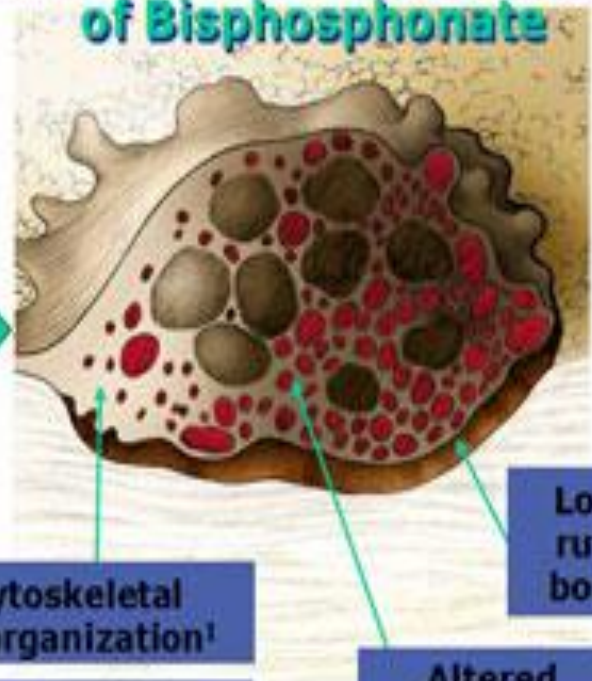


Effects of Bisphosphonates on Osteoclast Function

Normal Osteoclast



Osteoclast Following Uptake of Bisphosphonate



Cytoskeletal disorganization¹

Cell death by apoptosis²

Altered vesicular trafficking³

Loss of ruffled border¹

1. Sato, M, et al. *J Clin Invest.* 1991;88:2095-2105.
2. Hughes DE, et al. *J Bone Miner Res.* 1995;10:1478-1487.
3. Rogers M. *Curr Pharm Des.* 2003;9:2643-2658.

Generasi Biphosphonate

Bisphosphonate	Relative potency
<i>First generation BPNs</i>	
Etidronate	1
*Tiludronate	10
<i>Second generation BPNs</i>	
Pamidronate	100
Alendronate	100–500
*Ibandronate	500–1000
<i>Third generation BPNs</i>	
Risedronate	1000
Zoledronate	5000

<i>Bisphosphonates</i>	<i>Points to consider</i>
Alendronate (oral) & Risedronate (oral)	<ul style="list-style-type: none"> • Post-menopausal women: prevents vertebral, non-vertebral, and hip fractures^{31,32} • Men: Some evidence of decreased risk of vertebral fractures;^{27,28} some evidence of increased hip bone density, but no significant hip fracture reduction • Glucocorticoid induced osteoporosis (GIO): Some evidence of decreased vertebral fracture risk
Etidronate (oral)	<ul style="list-style-type: none"> • Post-menopausal women: prevents vertebral fractures³³ • GIO: maintains BMD in GIO although data is limited; Health Canada approved indication is for GIO prevention only (not treatment)²⁹
Zoledronic acid (intravenous)	<ul style="list-style-type: none"> • Post-menopausal women: prevents vertebral, non-vertebral, and hip fractures³⁴ • Men: Data is limited; Some evidence of decreased risk of vertebral and non-vertebral fractures (study included those with prior hip fracture and only 24% men);³¹ • GIO: maintains BMD • Cost effectiveness may limit use • Consider for high-risk patients who are unable to tolerate oral therapy or have poor adherence

SERMs



- **Mixed estrogenic and antiestrogen properties depending on tissue**
- **Raloxifene**
 - Besides increasing BMD, also lowers risk of breast Ca without stimulating endometrial hyperplasia. However can increase risk of vasomotor symptoms (hot flashes, etc). Decreases LDL without noticeable effect on CVD.
- **Tamoxifen**
 - Not typically rx for osteoporosis alone, but if already being used for breast cancer can provide effective bone protection

<i>Drug</i>	<i>Points to consider</i>
Raloxifene (oral)	<ul style="list-style-type: none"> • Post-menopausal women: reduces the incidence of vertebral fractures • May be considered in post-menopausal women who are unable to tolerate bisphosphonates and have no history of thromboembolic disease • Caution: Significantly increases the risk of venous thromboembolic disease and stroke

RANK Ligand Inhibitor:

Denosumab

Denosumab =injeksi monoklonal Ab thd R/activator dari nuklei faktor - kB ligan (RANK-L).Mek kerja : menghambat resorpsi tulang oleh osteoclast dg cara memblok interaksi antara RANKL dg R/ RANK yg tdp di perm osteoclast

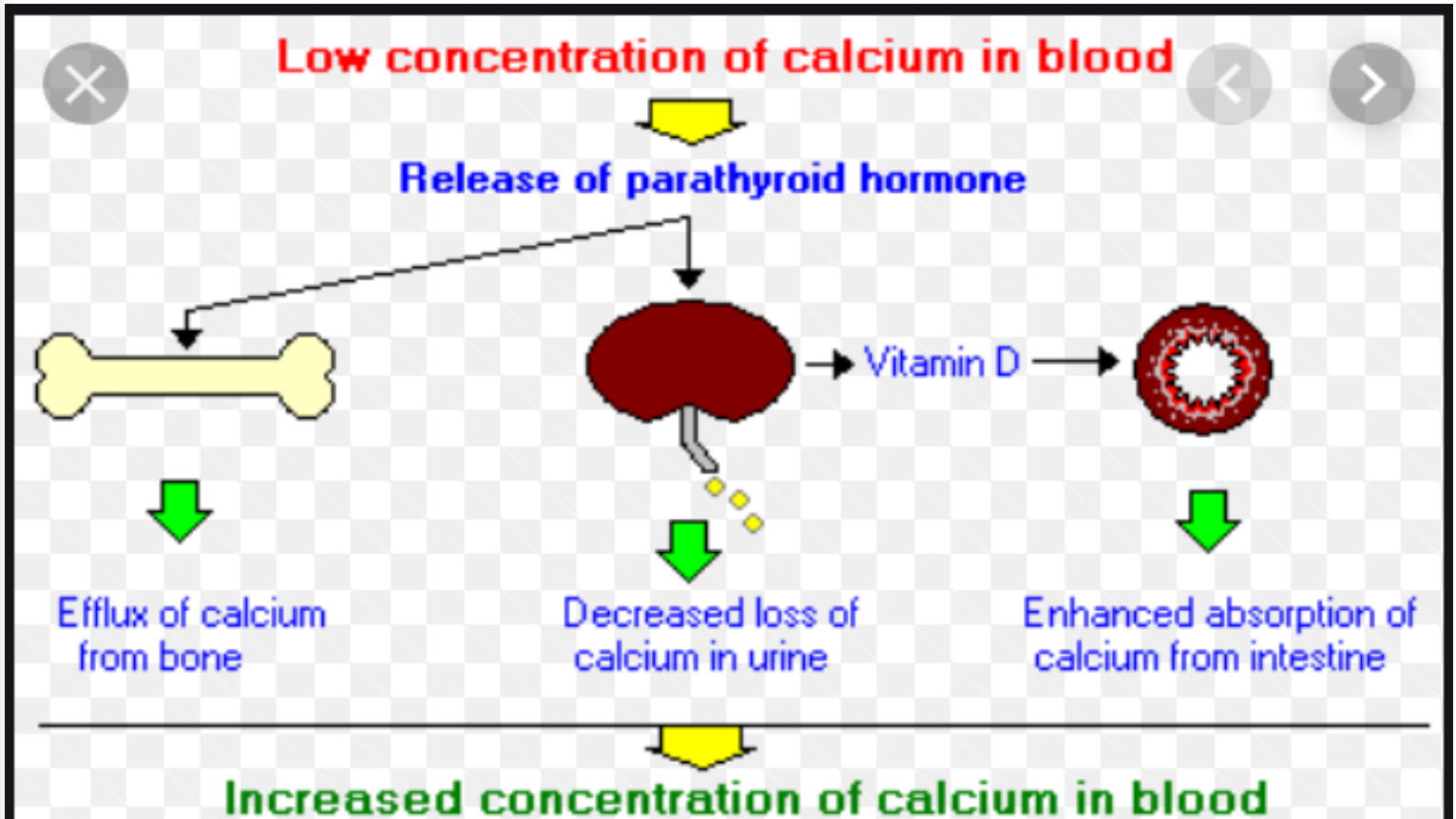
<i>Drug</i>	<i>Points to consider</i>
Denosumab (subcutaneous)	<ul style="list-style-type: none"> • Postmenopausal women: prevents vertebral, non-vertebral, and hip fractures • Cost and lack of long term safety data may limit use

Calcium/Vitamin D

- **Should be considered adjuvant therapy for all individuals (esp >65 y/o)**
- **WHI study – modest benefit in bone health. Statistically significant only with FULL doses and in older population. Otherwise – small increase in BMD with small decrease in hip fractures.**
- **NIH recs:**
 - **Premenopausal: 1000 mg**
 - **Postmenopausal <65 y/o using estrogen: 1000 mg**
 - **Postmenopausal not using estrogen: 1500 mg**
 - **All women >65: 1500 mg**

4.2.4 Synthetic Parathyroid Hormone: Teriparatide is an anabolic agent that improves bone quality, quantity, and increases bone strength. ^{22-24,30,36}

<i>Drug</i>	<i>Points to consider</i>
Teriparatide (subcutaneous)	<ul style="list-style-type: none">• Post-menopausal women: prevents vertebral and non-vertebral fractures in postmenopausal women with severe OP• Men: increases BMD; currently no fracture data available• GIO: Some evidence of benefit in the treatment of GIO• Cost and need for daily subcutaneous injection may limit use• Consider for patients at increased risk of fracture or lack of response to other therapies• Maximum lifetime exposure is 24 months• Bisphosphonates must be discontinued prior to treatment• Gains in BMD decline once treatment with teriparatide is discontinued; consider anti-resorptive therapy after completing treatment course



4.2.5 Calcitonin Peptides: Calcitonin Salmon is an inhibitor of bone resorption; available in parenteral and nasal spray formulations. Although calcitonin does not build bone, in women > 5 years beyond menopause, it appears to slow bone loss and increase spinal bone density. ^{26,37,38}

Drug	Points to consider
Calcitonin (nasal)	<ul style="list-style-type: none">• Post-menopausal women: Reduces incidence of vertebral fractures however evidence for benefit is limited• Consider as an alternative when other more effective drugs cannot be used• Effective in decreasing acute pain associated with vertebral osteoporotic fractures• Calcitonin injection is currently not approved for the treatment of OP; it is sometimes prescribed for patients who have pain due to acute vertebral fractures (See <i>Appendix D - Prescription Medication Table for Osteoporosis</i>)• Nasal route of administration has the most data for use in OP and is more commonly used due to convenience and tolerability

4.2.6 Hormone Replacement Therapy [HRT] (estrogen with or without progesterone): HRT is primarily indicated for the management of moderate to severe menopausal symptoms in women.^{22,24-26,35} A beneficial effect has been seen on BMD and fracture risk due to the significant anti-resorptive activity of estrogen.

<i>Drug</i>	<i>Points to consider</i>
HRT (oral or transdermal)	<ul style="list-style-type: none">• Post-menopausal women: Shown to prevent vertebral, hip and non-vertebral fractures• Is not recommended for the sole indication of OP prevention and for long term use for this indication; consider benefits versus risks (See <i>Appendix D - Prescription Medication Table for Osteoporosis</i>)• May be appropriate for OP prevention when it is already being used for the management of menopausal symptoms

The Guidelines and Protocols Advisory
Committee on

Hormones

- **Estrogen + medroxyprogesterone reduced risk of hip and clinical vertebral fractures by 34%, and overall fractures by 24%**
- **Another study showed positive bone changes after unopposed estrogen for 24 months – without induction of endometrial hyperplasia**
- **Initial recommendations – start hormone therapy within 5-10 years after menopause**

Hormones – cont'd

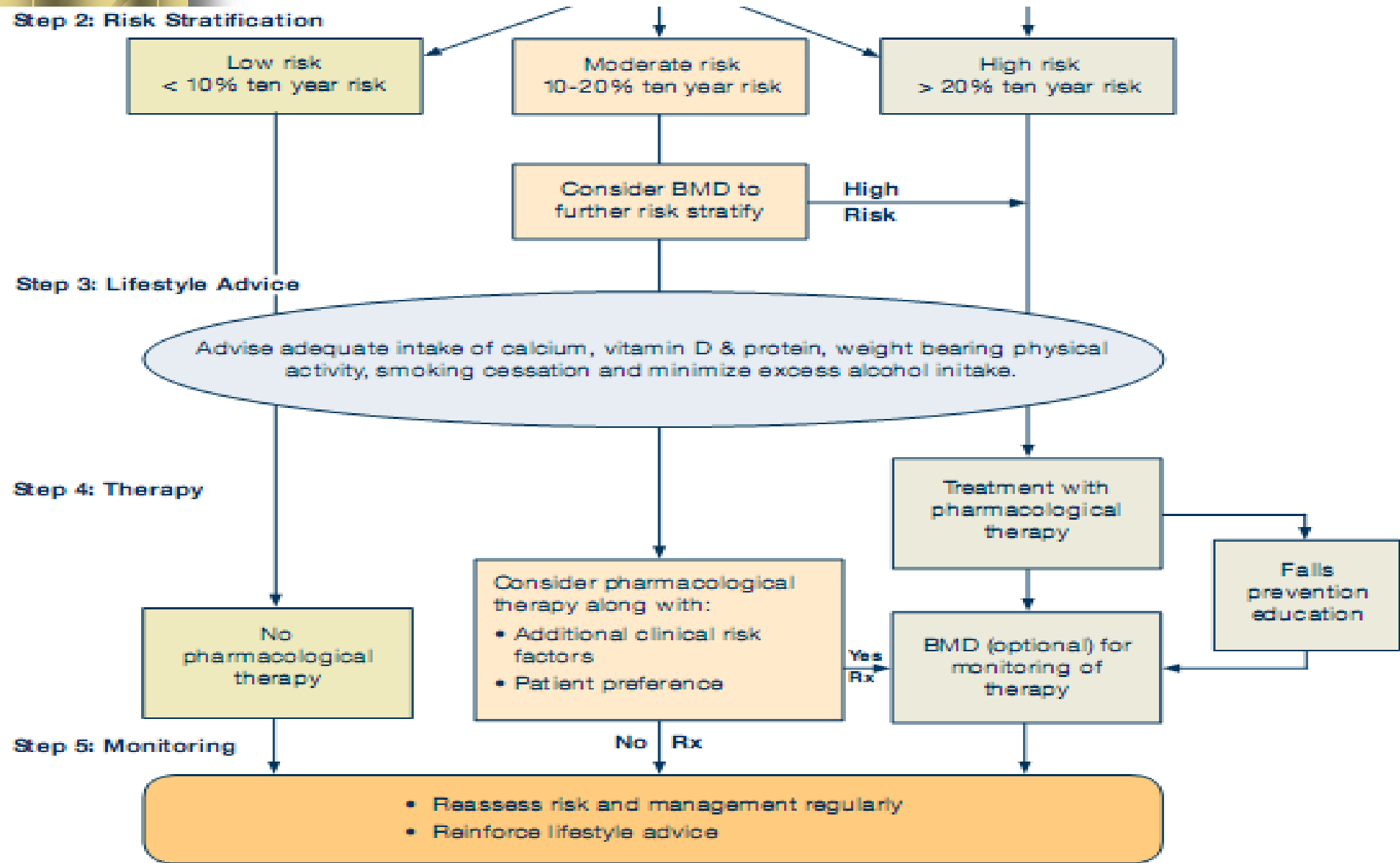


- **However, as of recent WHI study, estrogen-progesterone therapy *no longer* first-line approach for osteoporosis treatment in postmenopausal women due to increased risk of breast cancer, stroke**
- **Indications: persistent menopausal symptoms, inability to tolerate other options, failure to respond to other options.**

Why not try...

- PTH – daily subcutaneous injections can favor bone formation over resorption. Use should be limited to high risk/refractory patients. Should not be combined with bisphosphonates.
- Calcitonin – nasal formulation, concern over tachyphylaxis, less effective; use suggested in pts with painful osteoporotic fractures for analgesic action
- Calcitrol – must monitor for hypercalcemia, hypercalciuria, renal insufficiency. Lack of consistent benefit.
- Vitamin K – required for carboxylation of osteocalcin (needed in mineralization). Perhaps only beneficial when Vit K deficiency present.
- Sodium fluoride – not recommended – “hardens” teeth but increased bone brittleness.

Guideline Tx Osteoporosis



* Review available lateral thoracolumbar x-ray for evidence of fragility fracture

Sekian.....

