Drugs affecting bone mineral homeostasis. Treatment strategy of osteoporosis

Dr. Erzsébet Kató

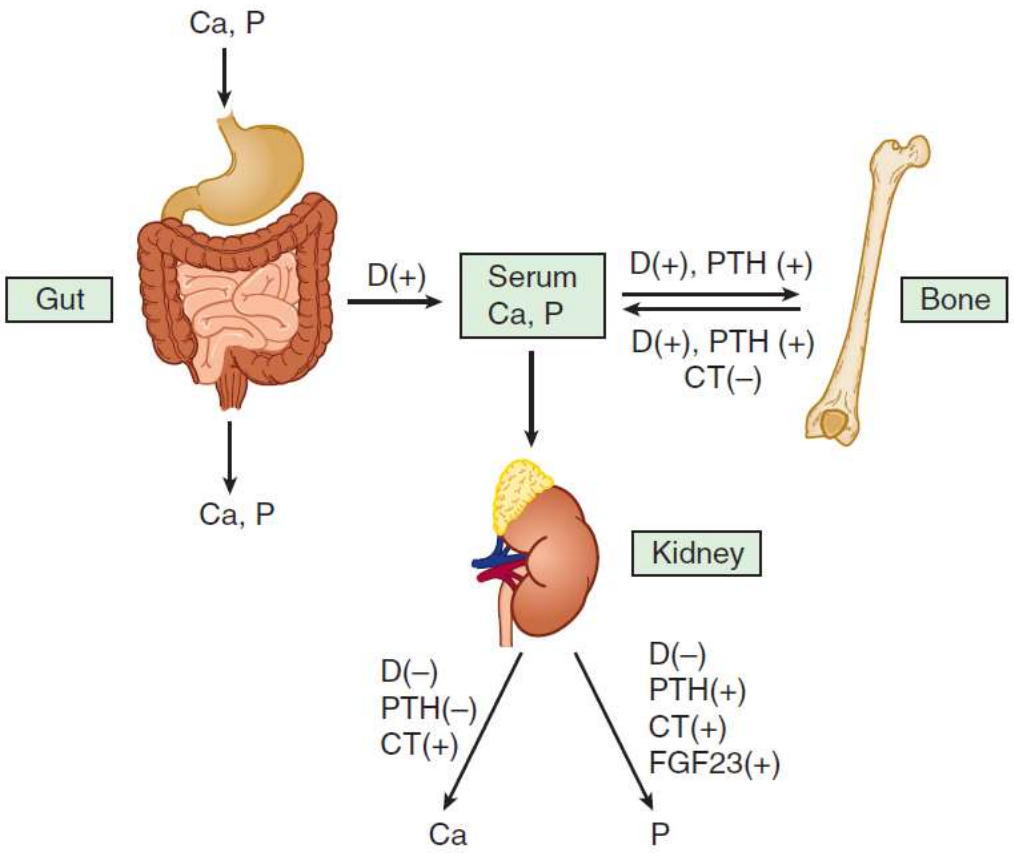
kato.erzsebet@med.semmelweis-univ.hu

http://semmelweis.hu/pharmacology/en/

If **love** makes the human world go round, $[Ca^{2+}]i$ does the same for **cells**.

Rang &Dale's Pharmacology

Mechanisms contributing to bone mineral homeostasis



Serum calcium (Ca) and phosphate (P) concentrations are controlled principally by three hormones: 1,25 –dihydroxyvitamin D (1,25[OH]$_2$D, D), fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH), through their action on absorption from the gut and from bone and on renal excretion. Calcitonine (CT) in pharmacological concentrations can reduce serum Ca and P by inhibiting bone resorption and stimulating their renal excretion.

B. G. Katzung, Basic and clinical Pharmacology

Principal hormonal regulators of bone mineral homeostasis

1. Parathyroid hormone (PTH)

- reduces Ca but increases P renal excretion

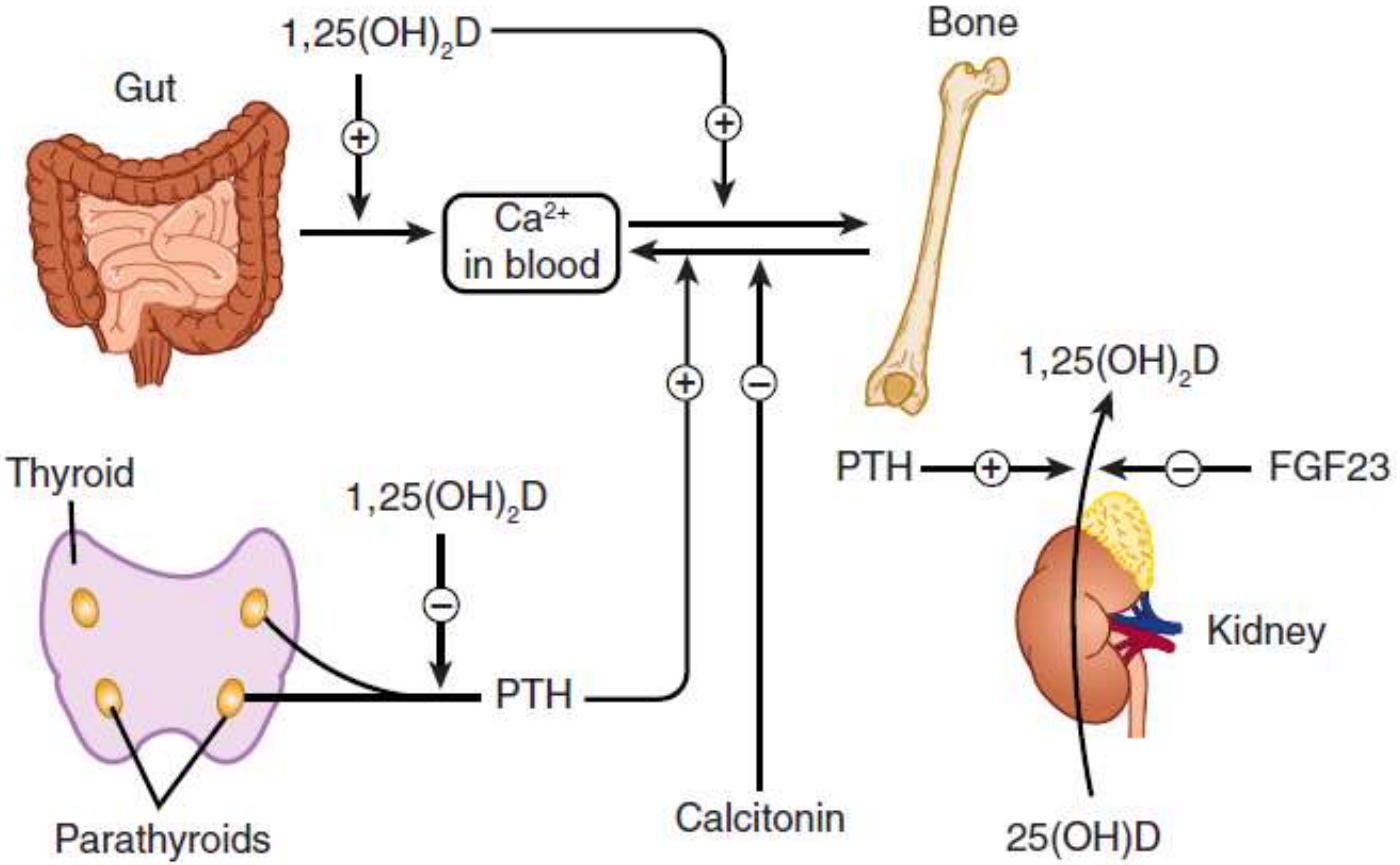
2. Vitamin D → $1,25[OH]_2$D, calcitriol (D)

- increases Ca and P absorption from the gut
- decreases excretion of both Ca and P

3. Fibroblast growth factor 23 (FGF23)

- stimulates renal excretion of P

1. Parathyroid hormone (PTH)



PTH consist of 84 amino acids; PTH 1-34 (available as *Teriparatide* and *Abaloparatide*) is fully active.

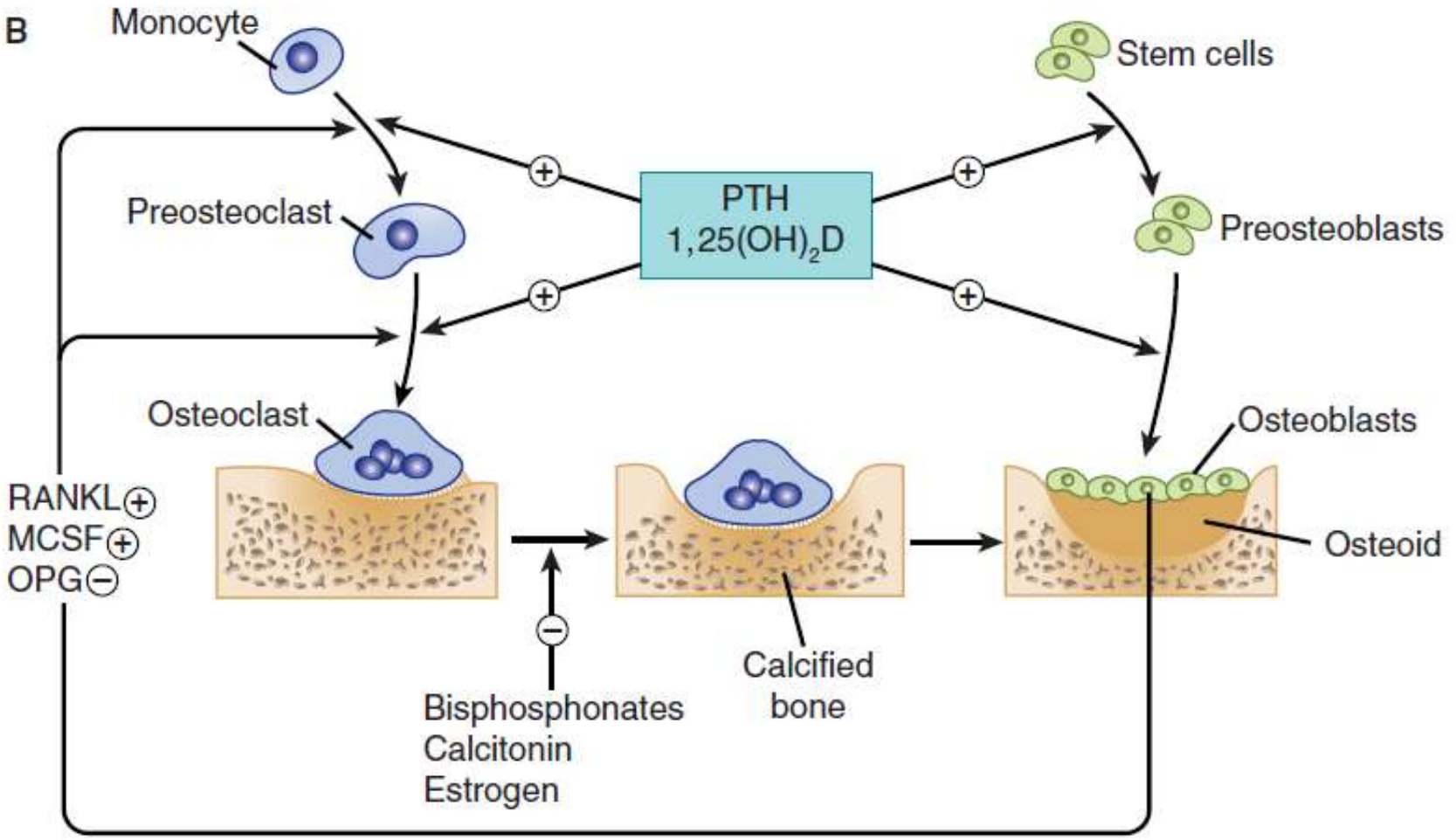
PTH 1-84, *Natpara,* approved recently for hypoparathyroidism

-is regulated - by Ca^{2+} level: Ca^{2+} sensitive protease, Ca^{2+} sensing receptor → reduces PTH secretion

- calcitriol (supresses PTH production)

-effects: increases serum Ca^{2+} / decreases serum phosphate

B. G. Katzung, Basic and clinical Pharmacology



At the level of the bone, both PTH and D stimulate bone formation and resorption.

PTH acts on the osteoblasts which activate osteoclasts by secreting **receptor activating nuclear factor κ ligand (RANKL).** Activation results in bone resorption leading to remodeling

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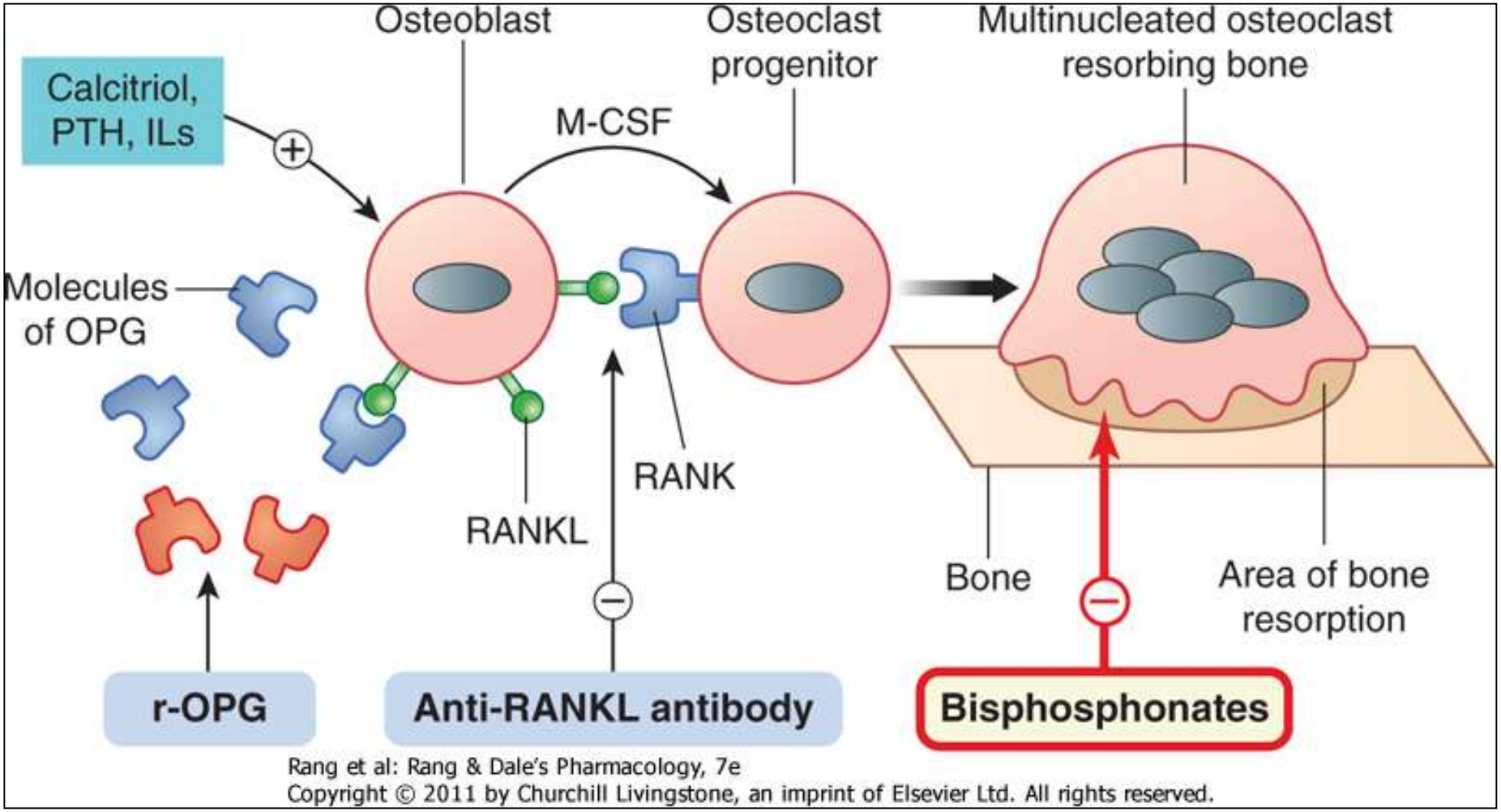
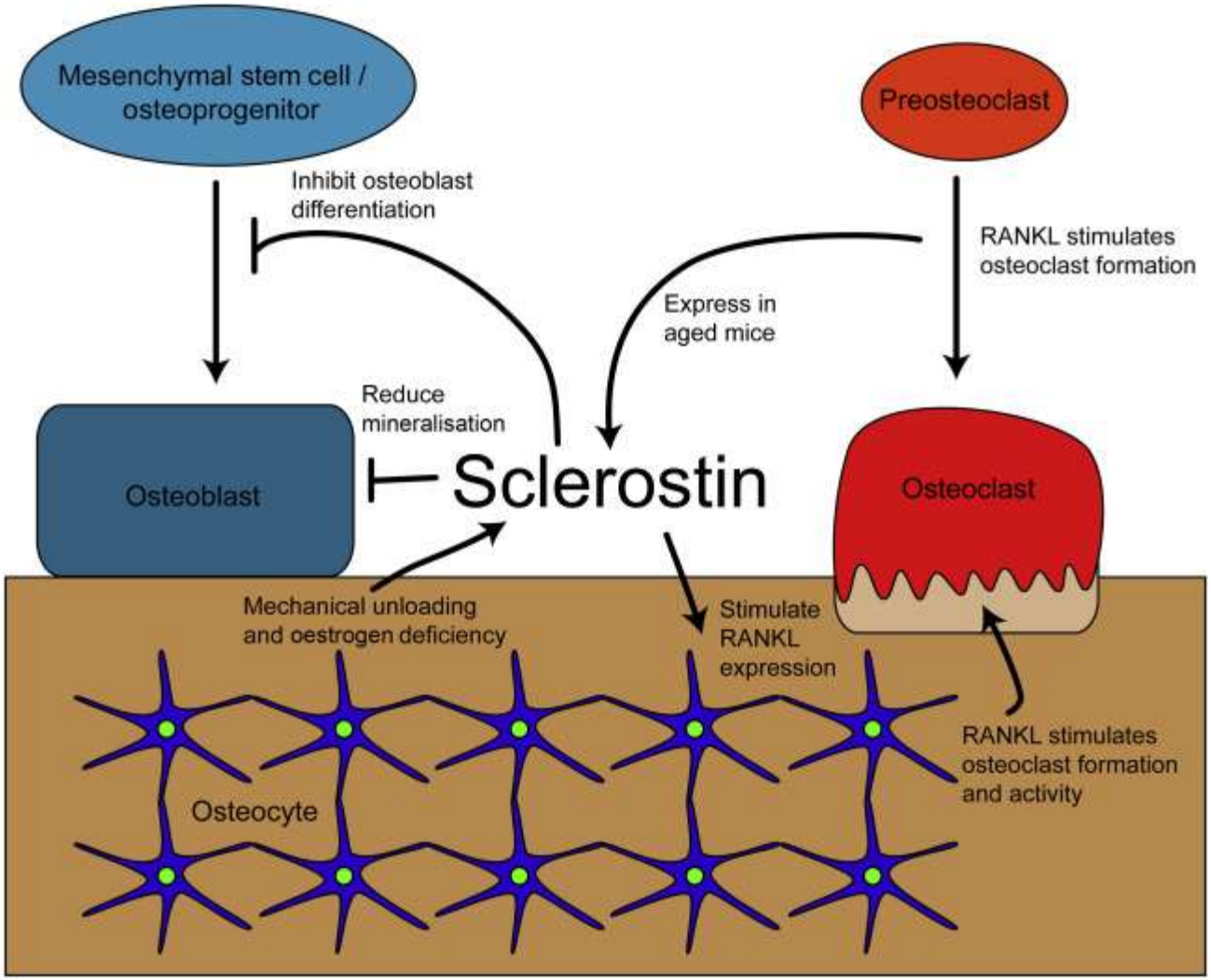
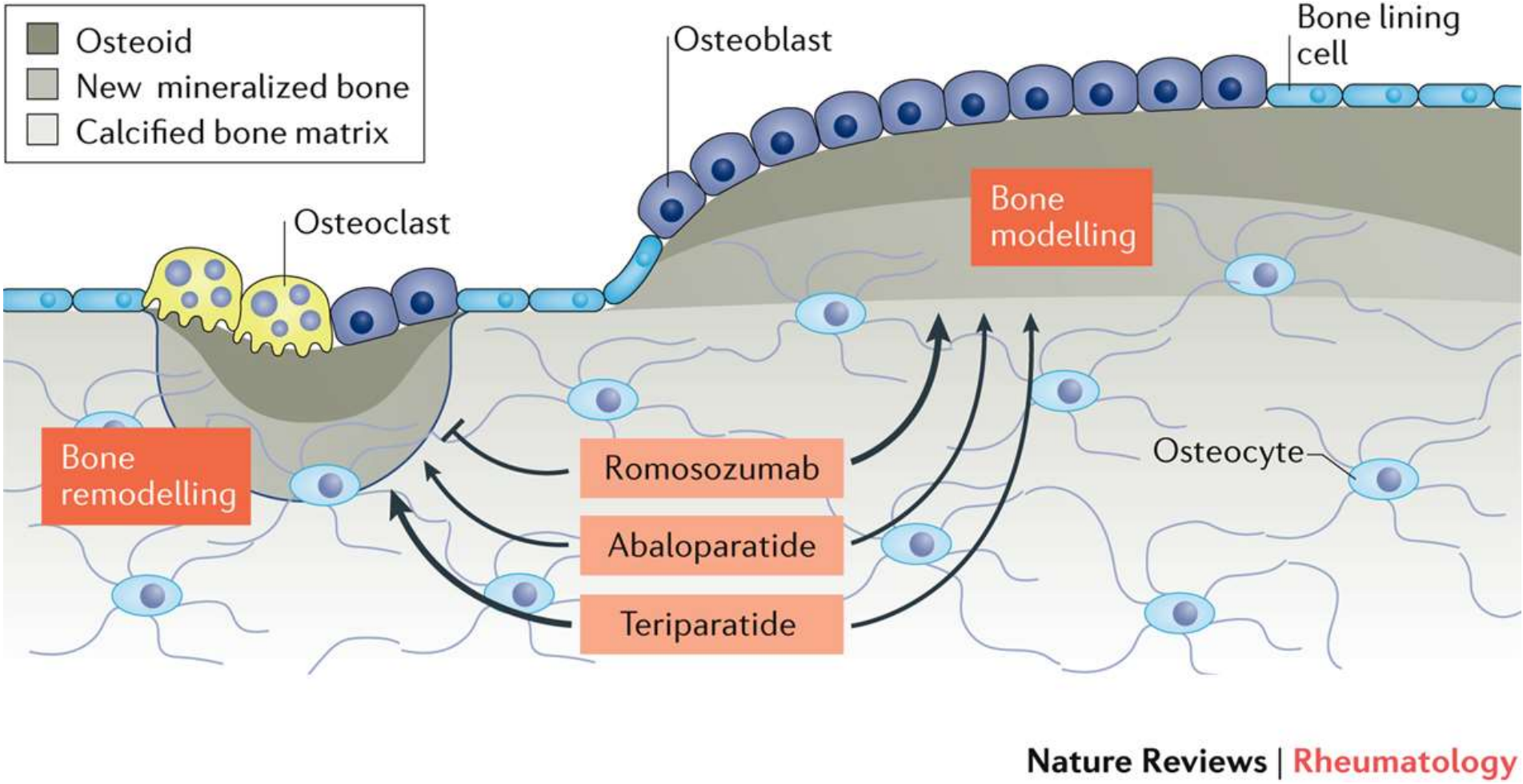


The osteoblast is stimulated by D, PTH and cytokines to express a surface ligand, the RANK ligand (RANKL) → acts on the osteoclast at RANK (receptor activator of nuclear factor kappa B) → differentiation and activation of the osteoclast progenitors → multinucleated bone-resorbing cells → bone remodeling. The osteoblast releases osteoprotegerin (OPG), which functions as a decoy receptor, inhibits RANKL.



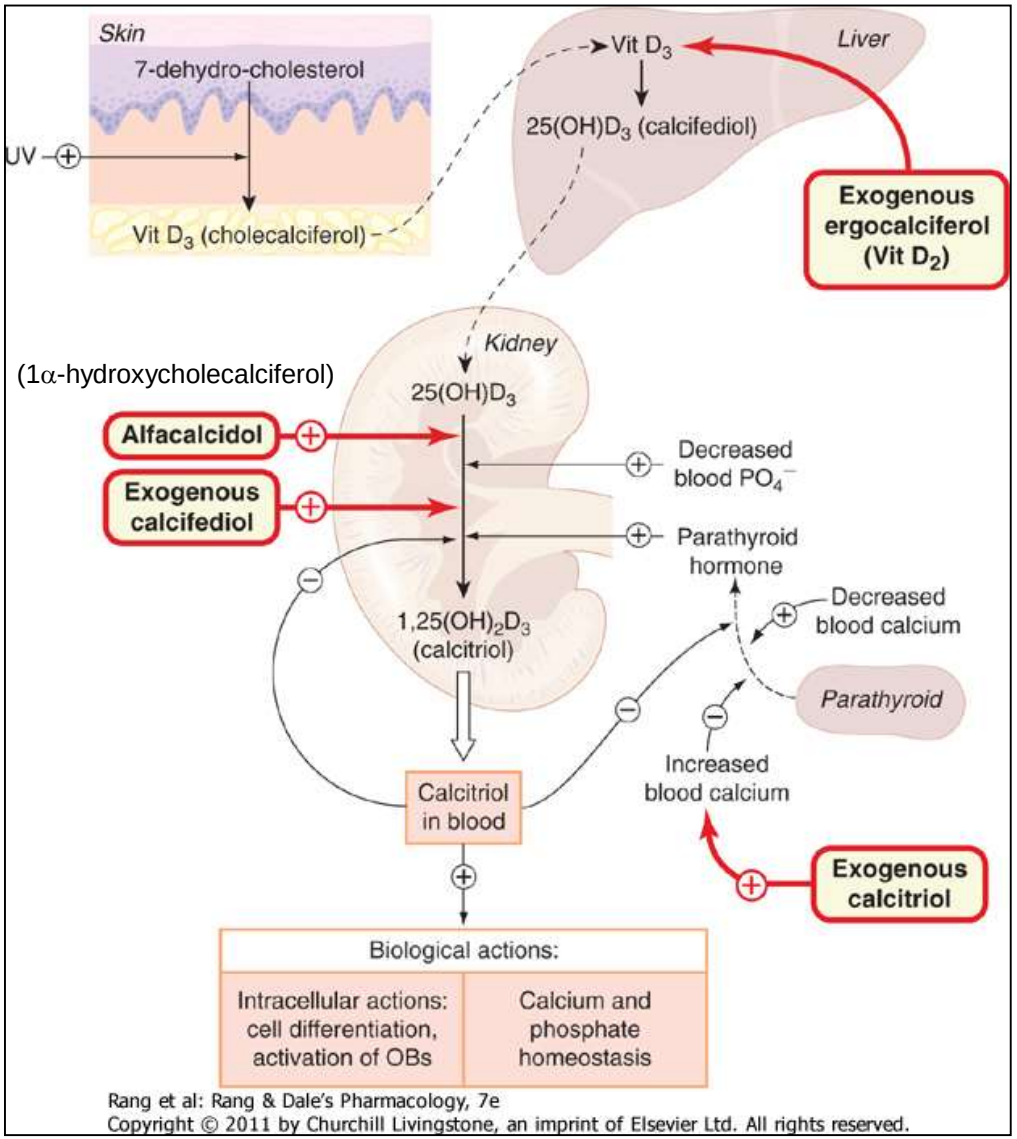
PTH also inhibits SCLEROSTIN which inhibits osteoblast's proliferation. ROMOSOZUMAB, an antibody against sclerostin was aproved recently



Ferrari, S. L. (2018) Romosozumab to rebuild the foundations of bone strength
Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2018.5

ROMOSOZUMAB, an antibody against sclerostin was aproved recently. In the Fracture Study in Postmenopausal Women with Osteoporosis (FRAME) trial, which included 7,180 postmenopausal women with osteoporosis, 1 year of treatment with romosozumab increased spine and hip bone mineral density (BMD) from baseline by 13.3% and 6.8%, respectively

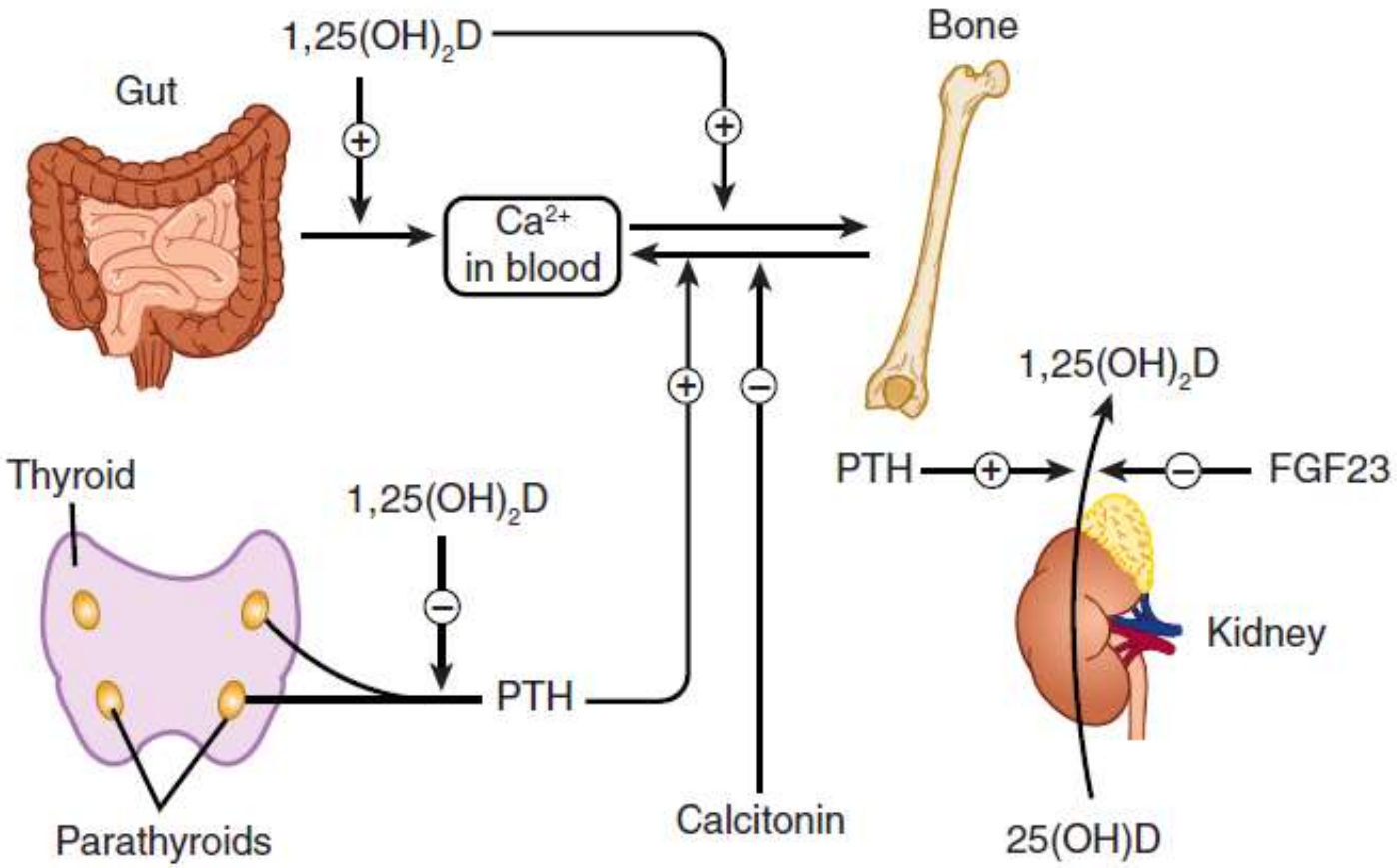
2. Vitamin D (→1,25[OH]$_2$D, calcitriol)



Cholecalciferol is produced from 7-dehydrocholesterol in the skin under ultraviolet radiation

- in the liver calcifediol (25[OH]D) then in the kidney calcitriol, D (1,25[OH]2D) is formed which is the most active metabolite

2. Vitamin D (→1,25[OH]$_2$D, calcitriol)

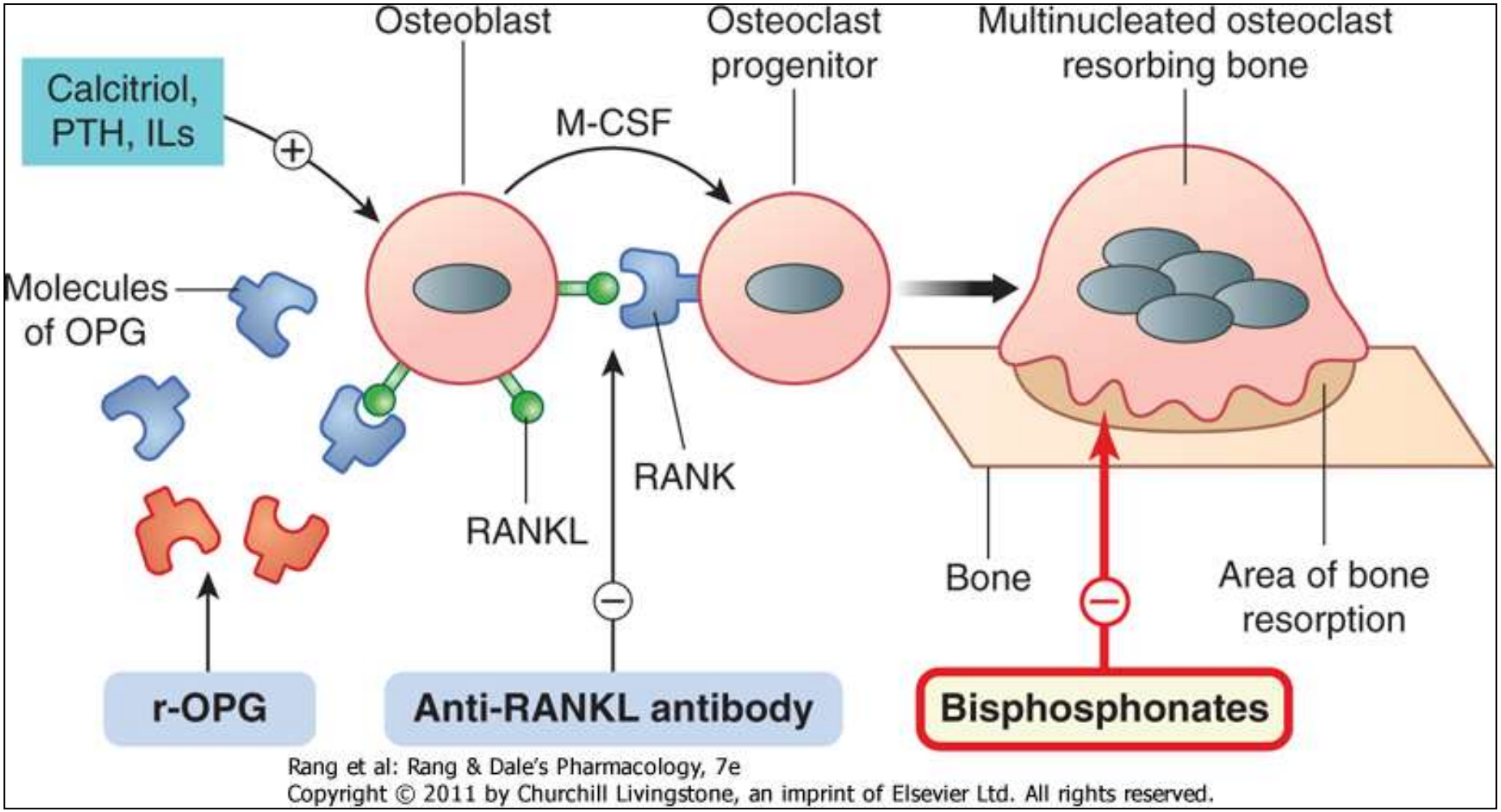


In the body D is produced by the kidney under the control of PTH (stimulates) and FGF23 (inhibits). D in turn inhibits the production of PTH and stimulates FGF23 release from bone. D is the principal regulator of intestinal Ca and P absorption.

- increases Ca and P absorption from the gut

- decreases excretion of both Ca and P

B. G. Katzung, Basic and clinical Pharmacology



Calcitriol altogether with PTH and cytokines stimulates osteoblasts to express RANKL → causes differentiation and activation of the osteoclast progenitors → bone remodeling

Principal hormonal regulators of bone mineral homeostasis

2. Vitamin D (→1,25[OH]$_2$D, calcitriol)

-produced from 7-dehydrocholesterol in the skin under ultraviolet radiation

-in the liver calcifediol (25[OH]D) then in the kidney calcitriol (1,25[OH]$_2$D) is formed which is the most active

-PTH stimulates, FGF23 inhibits the formation of calcitriol in the kidney

-Calcitriol: - increases Ca and P absorption from the gut

- decreases excretion of both Ca and P

- induces RANKL in osteoblasts

- Role in the immune system: vitamin D receptor is expressed on immune cells (B- and T cells, antigen presenting cells). Deficiency in vitamin D is associated with increased autoimmunity as well as an increased susceptibility to infection. (Vitamin D and the Immune System, C. Aranow, J Investig Med. 2011, 59(6):881-886).

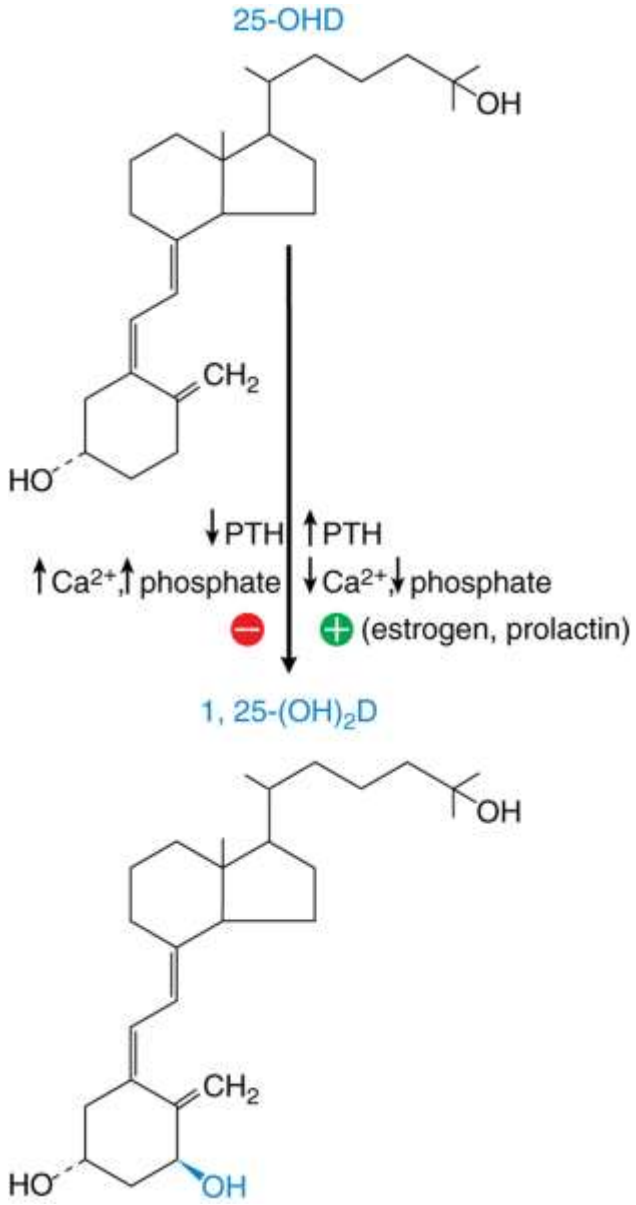
Secondary hormonal regulators of bone mineral homeostasis

1. Calcitonin (CT)

- secreted by the parafollicular cells of the thyroid gland
- lowers serum Ca and phosphate
- inhibits osteoclastic bone resorption
- at long term inhibits both bone *formation* and *resorption*

2. Glucocorticoids

- decrease Ca absorbtion, enhance Ca excretion, block bone formation
- their prolonged administration is a common cause of osteoporosis

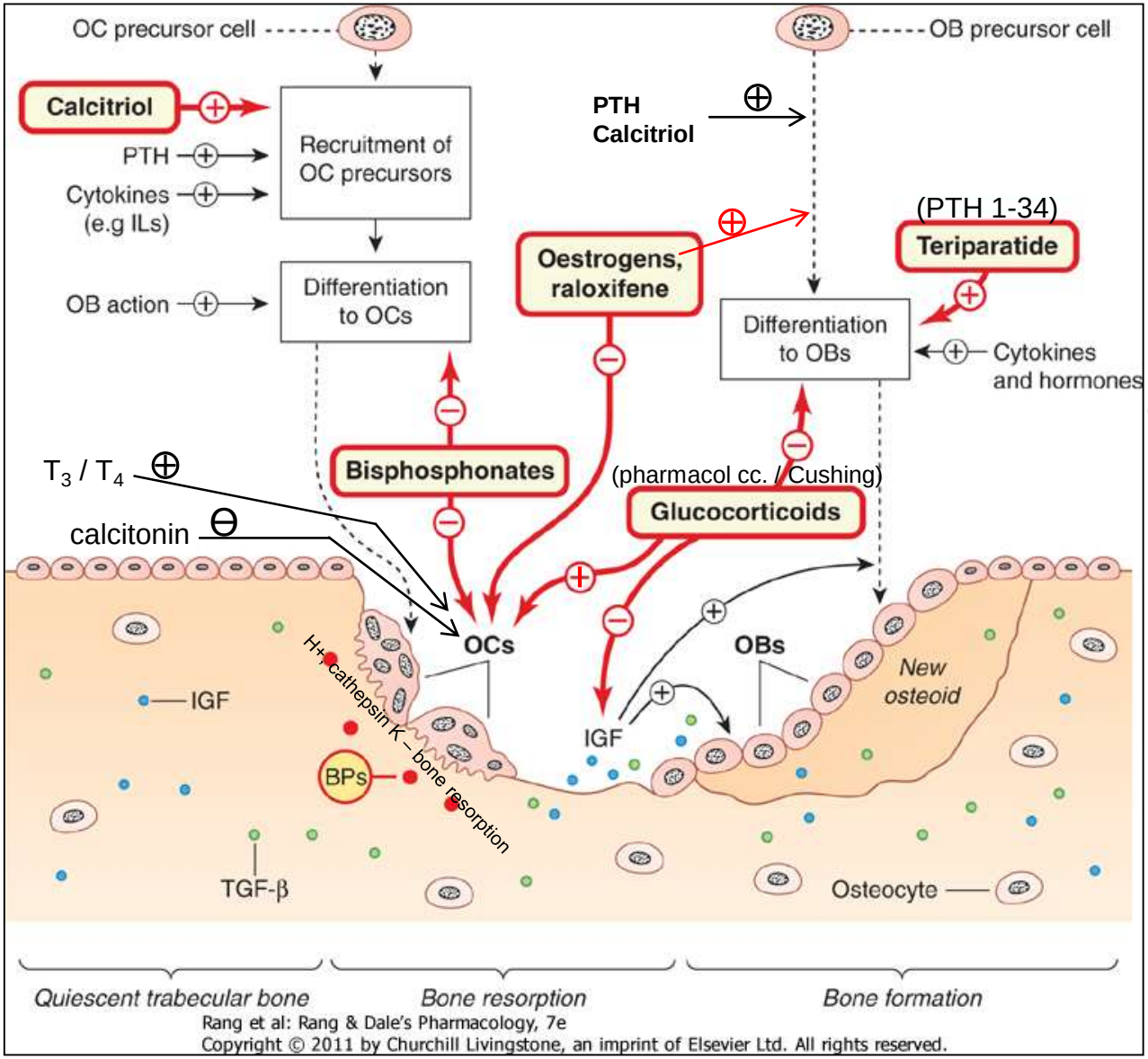


3. Estrogens

- can prevent postmenopausal bone loss

- reduce bone resorbing action of PTH

- increase calcitriol blood level (by complex mechanism)

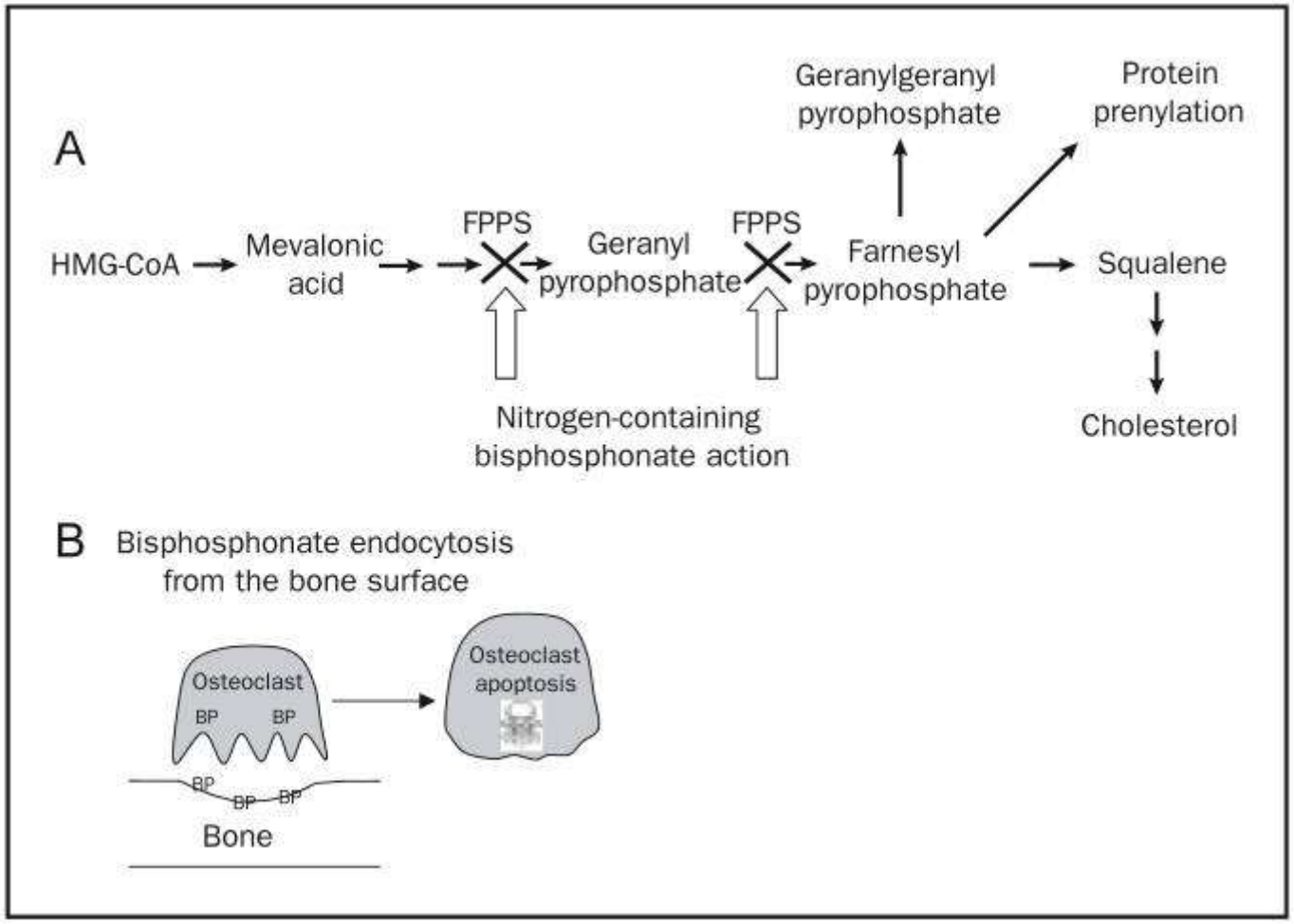


Cytokines such as insulin-like growth factor (IGF) and transforming growth factor (TGF)-beta are embedded in the bone matrix. *Bone resorption*. Osteoclast (OC) precursor cells, recruited by cytokines and hormones, are activated by osteoblasts (OBs) to form mobile multinuclear OCs that move along the bone surface, resorbing bone and releasing the embedded cytokines. *Bone formation*. The released cytokines recruit OBs, which lay down osteoid and embed cytokines IGF and TGF-beta in it. The osteoid then becomes mineralised, and lining cells cover the area. Oestrogens cause apoptosis (programmed cell death) of OCs. Note that pharmacological concentrations of glucocorticoids have the effects specified above, but physiological concentrations are required for OB differentiation. BPs, embedded bisphosphonates-these are ingested by OCs when bone is resorbed; IL, interleukin; PTH, parathyroid hormone.

Nonhormonal agents affecting bone mineral homeostasis

1. Bisphosphonates

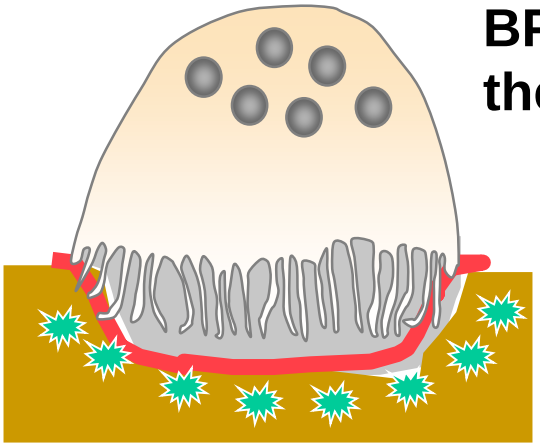
- enzyme resistant analogues of pyrophosphate (P-O-P) and bind to the mineral substance of the bones
- mechanism of action:
  - *non–nitrogen*-containing bisphosphonates (etidronate, clodronate, and tiludronate) become incorporated in ATP → cytotoxic effect
  - *nitrogen*-containing bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid) inhibit the activity of farnesyl pyrophosphate synthase and by this the mevalonic acid pathway
- the trabecular micro-architecture of bone is maintained
- most effective known inhibitors of bone resorption
- *Bisphosphonates decrease bone turnover by decreasing the number of the basic multicellular (remodeling) units (BMUs) responsible for bone remodeling.*
- The decrease of BMUs leads to rapid increase of bone mineral density (BMD) in the first year, later a new equilibrium between bone metabolism and resorption is established



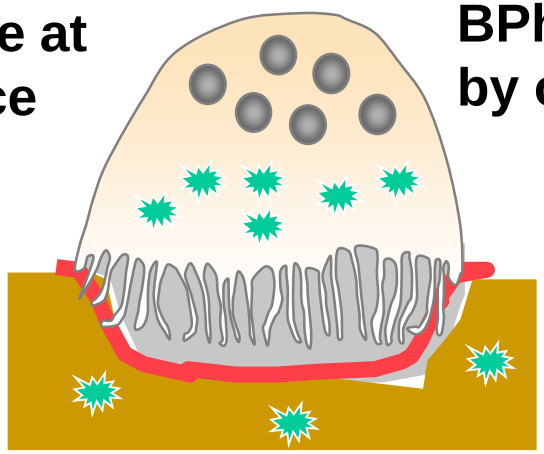
Bisphosphonates: Mechanism of Action and Role in Clinical Practice. Mayo Clin Proc. 2008 Sep; 83(9): 1032–1045.

The mechanism of bone resorption inhibition by bisphosphonates (BPh)

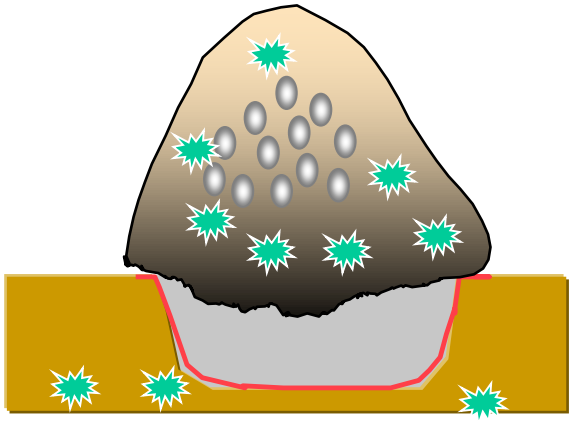
Following Mike Rogers (2005)



BPh accumulate at the bone surface



BPhs are taken up by ostecoclasts



BPh inhibit bone resorption within the osteoclasts. Many osteoclasts undergo apoptosis

BPh

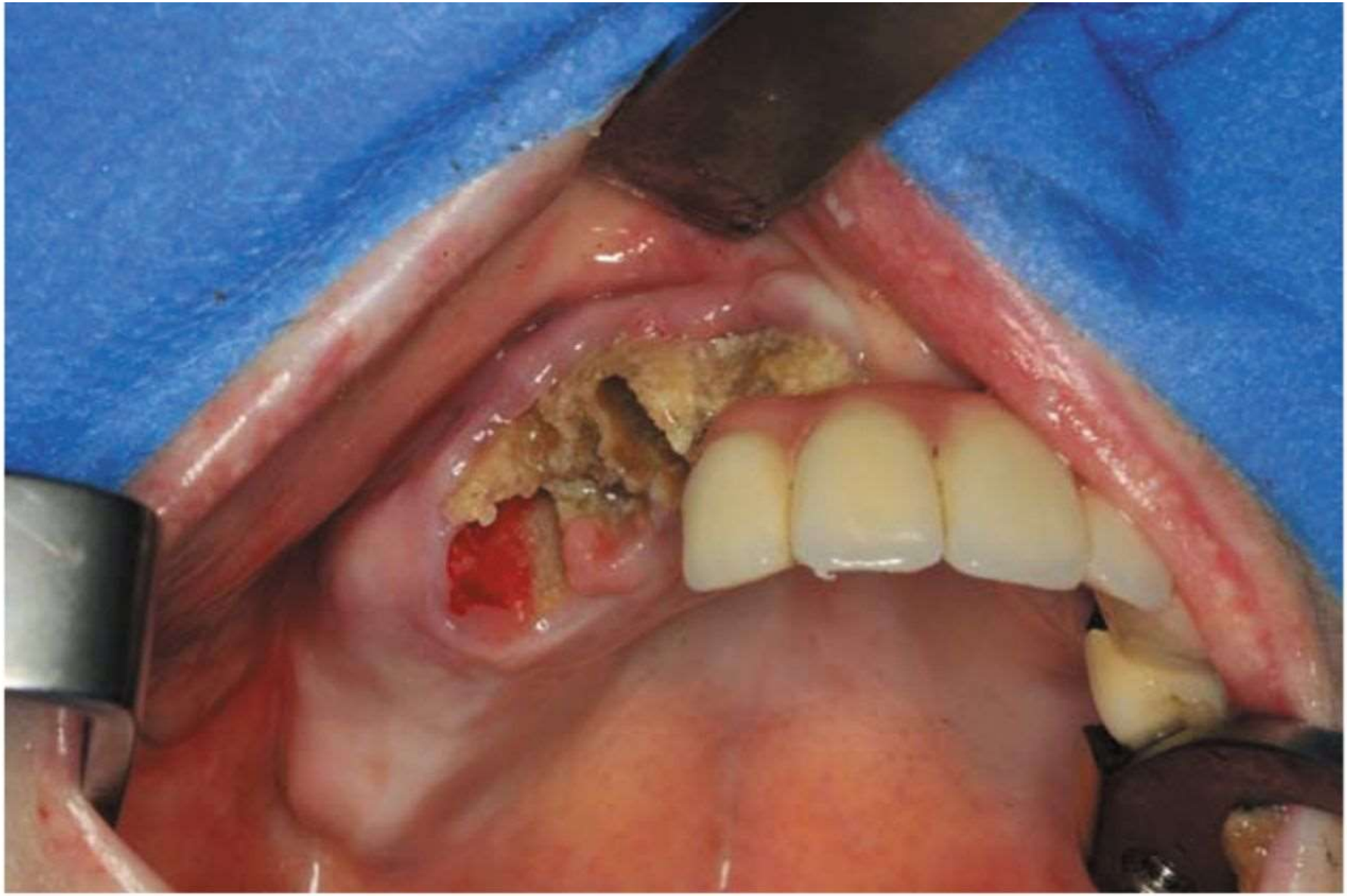
Pharmacokinetics of bisphosphonates

- **Weak oral absorption (1-10%, on empty stomach, Ca further inhibits absorbtion)**
- **No metabolism**
- **Elimination via kidney**
- **Those molecules which bind to the bone are eliminated parallel with the bone turnover. Half life is 5-10 years**
- **Effects persist for 1-2 years if discontinues the treatment**

Adverse effects of bisphosphonates

• Irritation of the oesophagus - stomach – to avoid take ½ - 1 hours before meal, in upright position

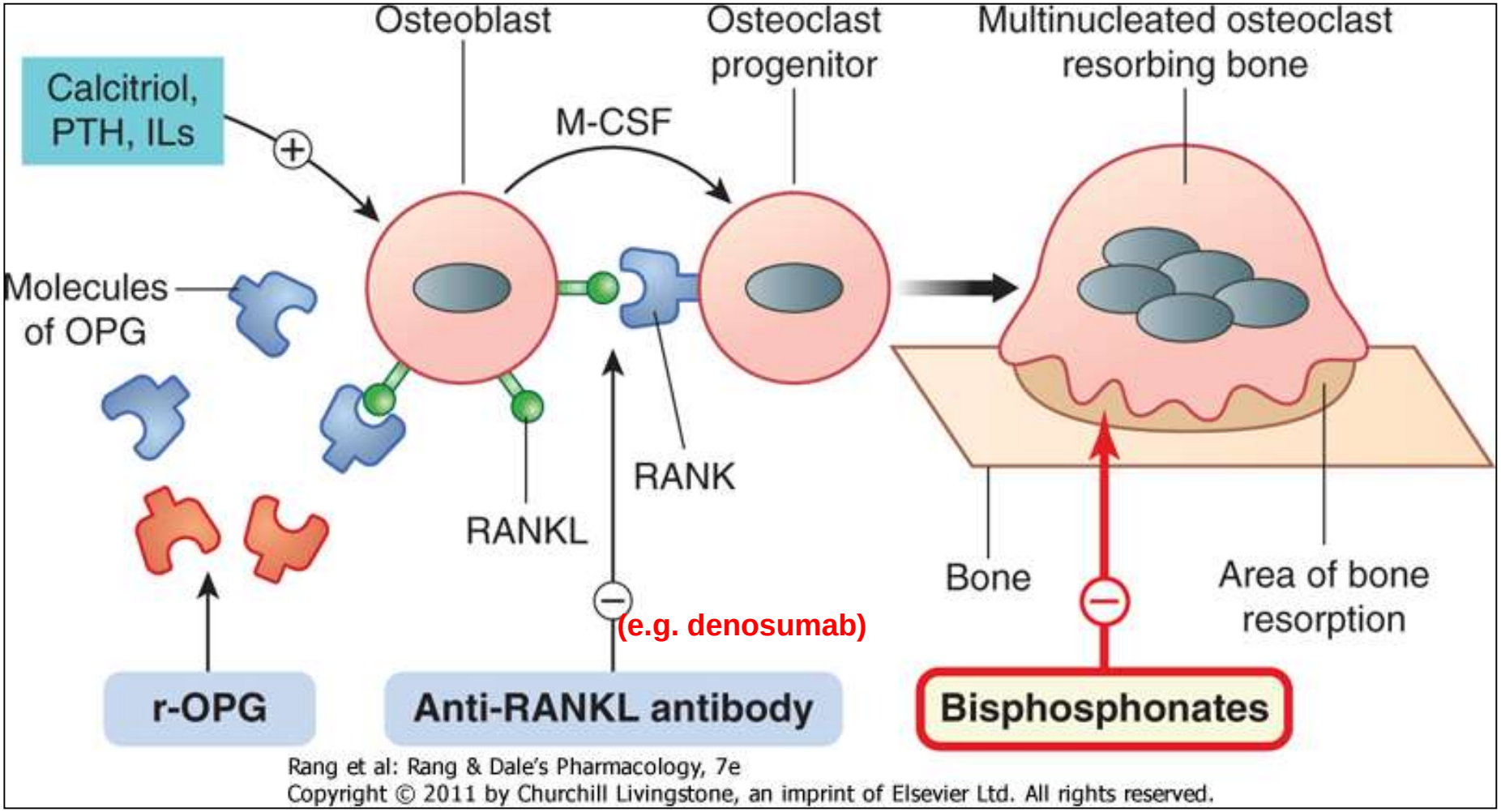
• Osteonecrosis, given intravenously, some bisphosphonates (in particular zoledronate)



Bisphosphonate-related Osteonecrosis

***Anticancer Research,* 09.2013 vol. 33 no. 9, 3917-3924**

2. Denosumab



Anti-RANKL antibodies, denosumab, bind RANKL and prevent the RANK-RANKL interaction (it would cause osteoclast differentiation, increased activity and survival).

- Denosumab decreases osteoclast action and subsequently less bone resorption will occur.

(60 mg sc/6 month)

Nonhormonal agents affecting bone mineral homeostasis

3. Calcimimetics - Cinacalcet

- activate calcium sensing receptor (CaSR)

- in the parathyroid gland by activating CaSRs will inhibit PTH secretion
- clinical use: secondary hyperparathyroidism (in chr. kidney disease), parathyroid carcinoma

- CaSR antagonists might be used to stimulate intermittent PTH secretion in osteoporosis

4. Thiazid diuretics

- may increase PTH mediated Ca reabsorbtion

- reduce hypercalciuria, so the incidence of urinary stones

Nonhormonal agents affecting bone mineral homeostasis

5. Fluoride

- accumulates in bones and teeth, it may stabilize the hydroxyapatite crystal

- promotes new bone growth

- with calcium supplementation *improved Ca balance* but in clinical studies failed to reduce bone fractures

6. Strontium ranelate

- in bone tissue cultures enhances the osteoblast activity

- promotes osteoclast apoptosis, decreases the bone resorption

- balance is shifted into the direction of bone formation

- approved in Europe (not USA) for the treatment of osteoporosis

Definition of osteoporosis

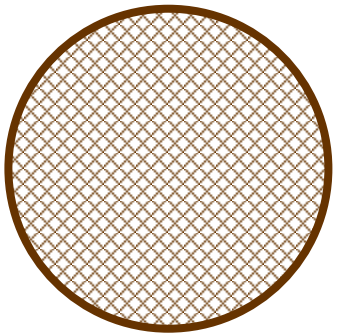
A systemic scheletal disease characterized by low bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fracture

Evaluation of osteoporosis

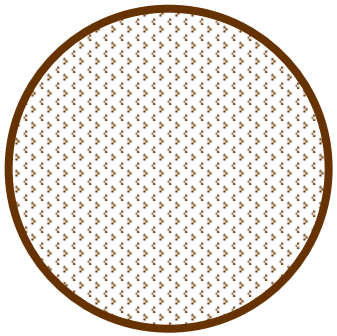
Osteoporosis

Low bone mass and microarchitectural deterioration

Normal bone



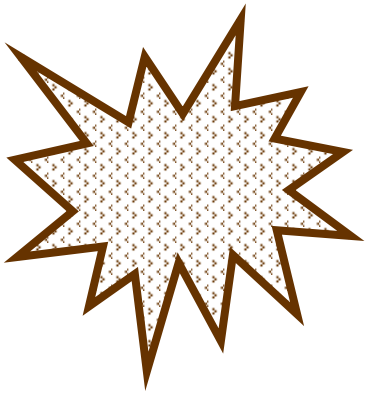
Osteoporosis



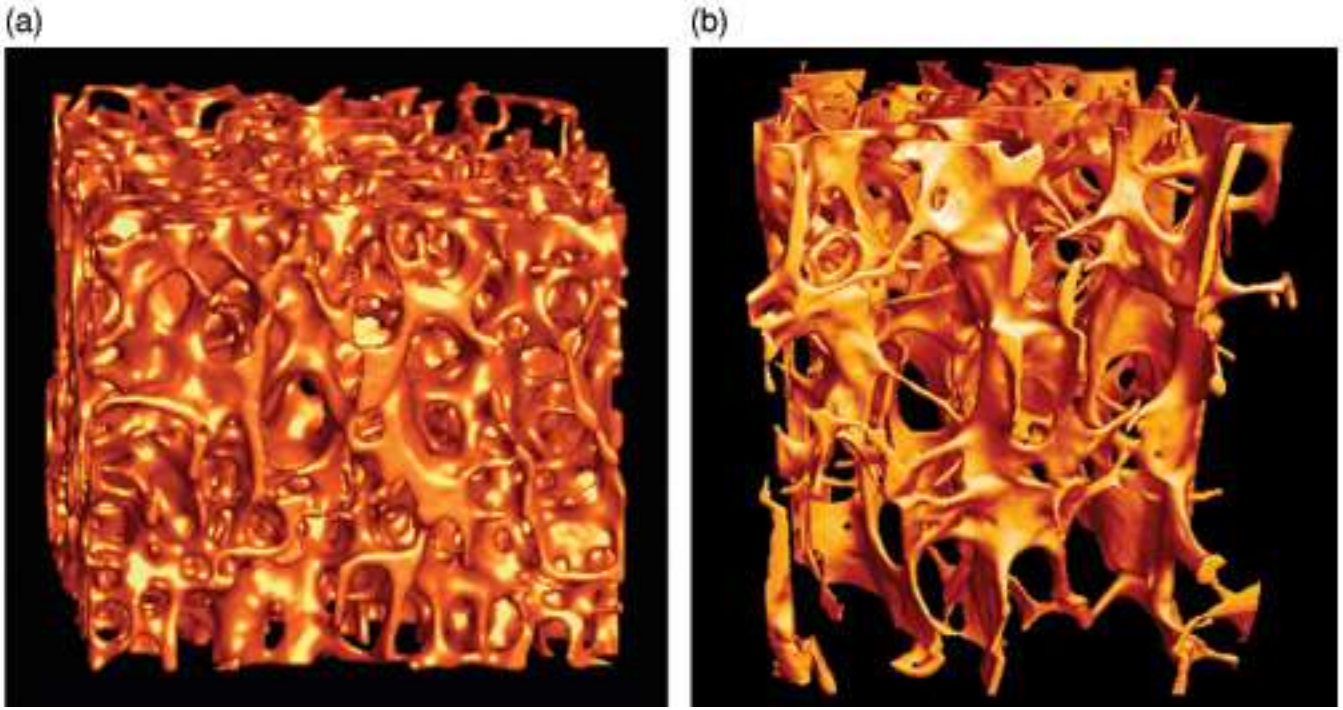
Surrogate endpoint:

Decrease of Bone Mineral Density (BMD)

Bone fracture



Outcome: bone fracture



a) 30-year-old female shows bone of normal density and architecture.

b) a similar image of a 63-year-old male shows a markedly different bone architecture, with fewer trabeculae and platelike structures.

Source: Lawrence Livermore National Laboratory Website.

The evaluation of the treatment of osteoporosis WHO

WHO disease categories based on BMD, T score (is designated by the number of standard deviations (SD) from the young normal mean)

Normal: ± 1 SD

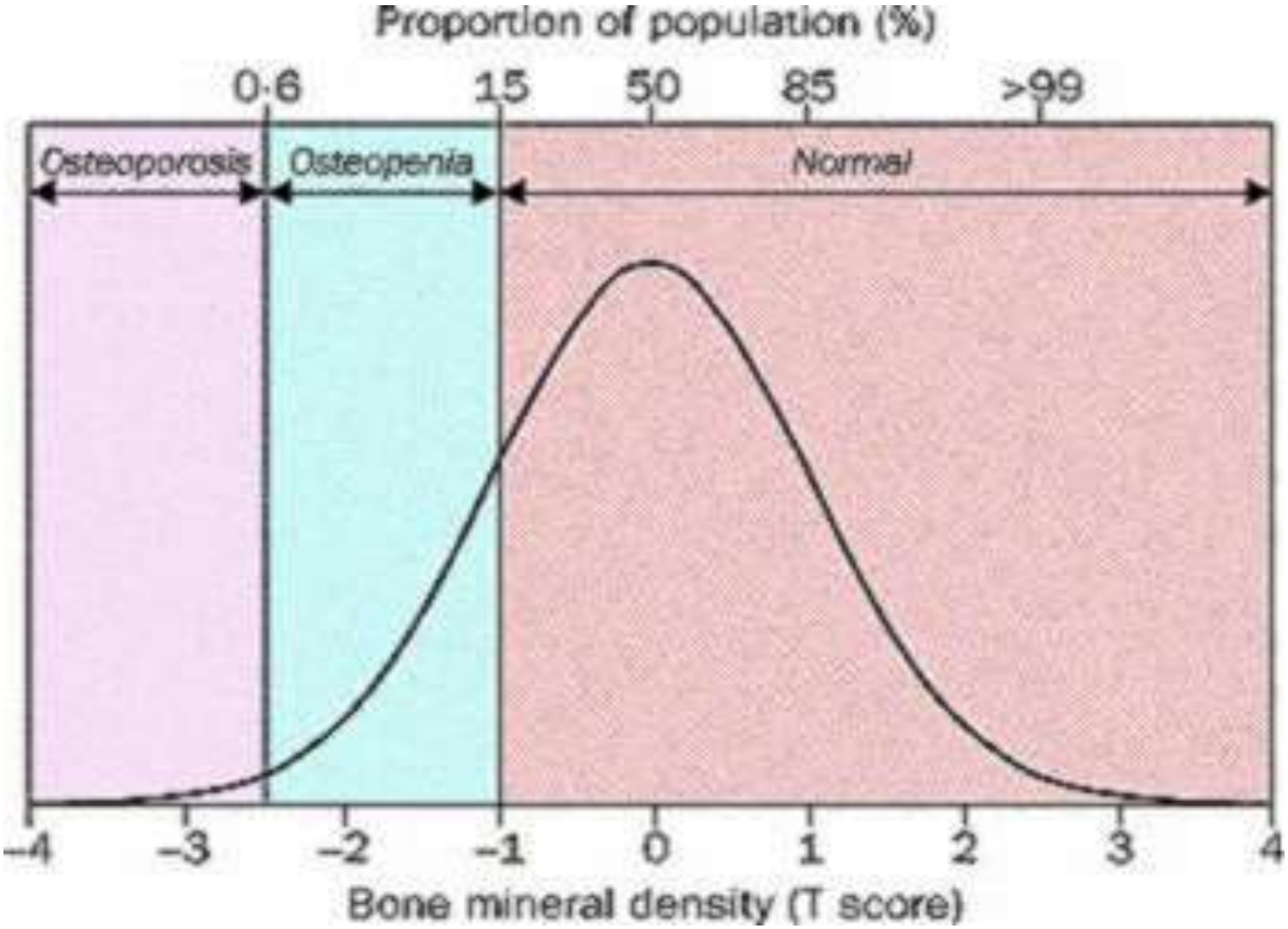
Osteopenia: - 1-2,5 SD

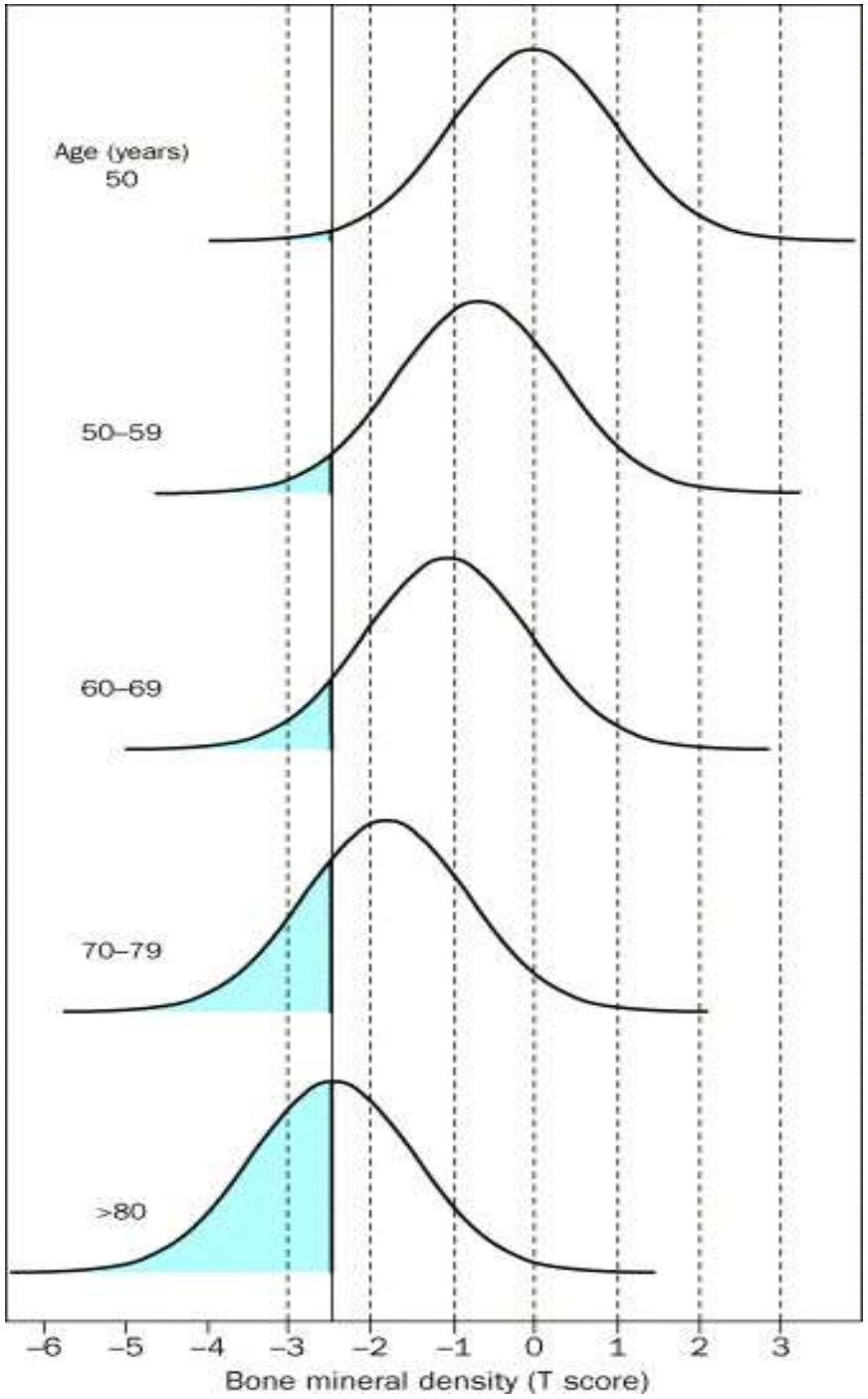
Osteoporosis: below - 2,5 SD

Severe osteoporosis: below - 2,5 SD + at least one vertebral fracture

Distribution of Bone Mineral Density (BMD) in healthy women aged 30-40 years

Kanis JA, Lancet, 359:1929, 2002





Distribution of BMD in women of different ages

Kanis JA, Lancet, 359:1929, 2002

- Area marked in blue denote the prevalence of osteoporosis
- The prevalence of osteoporosis increases approximately exponentially by age
- The number of bone fractures follows the prevalence of osteoporosis

Risk factors for osteoporosis

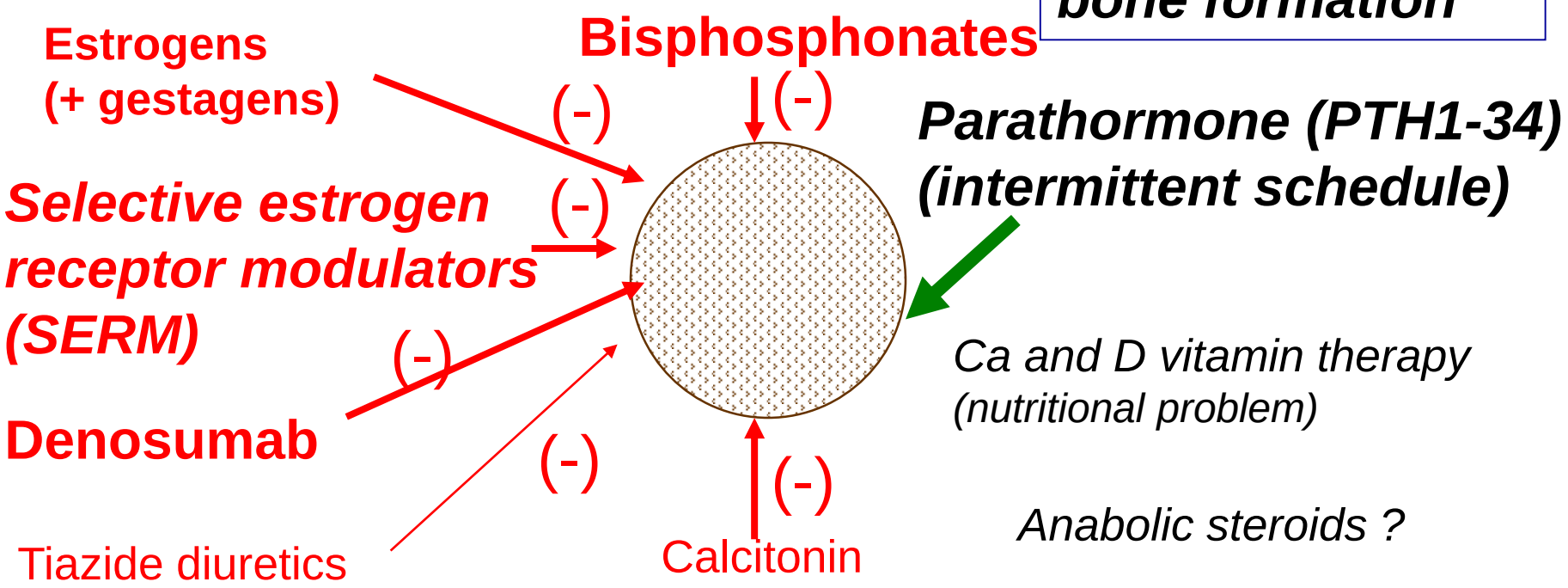
Eastell R, NEJM, 338:736

- **Genetic factors**
- **Environmental factors:** ***smoking***, alcohol, physical inactivity, ***thin habitus, low body weight, < 58 kg)*****,** low Ca intake and little exposure to sunlight
- **Menstrual status:** menopause < 45yr, previous amenorrhea
- **Drug therapy:** glucocorticoids, antiepileptic drugs (phenytoin), excessive substitution therapy with thyroxine, hydrocortisone, anticoagulants, heparin, dicoumarin derivatives
- Endocrine (hyperparathyroidism, thyreotoxicosis), gastrointestinal (malabsorbtion), rheumatologic, hematologic diseases

Pharmacologic treatment strategy of postmenopausal osteoporosis

Inhibitors of resorption

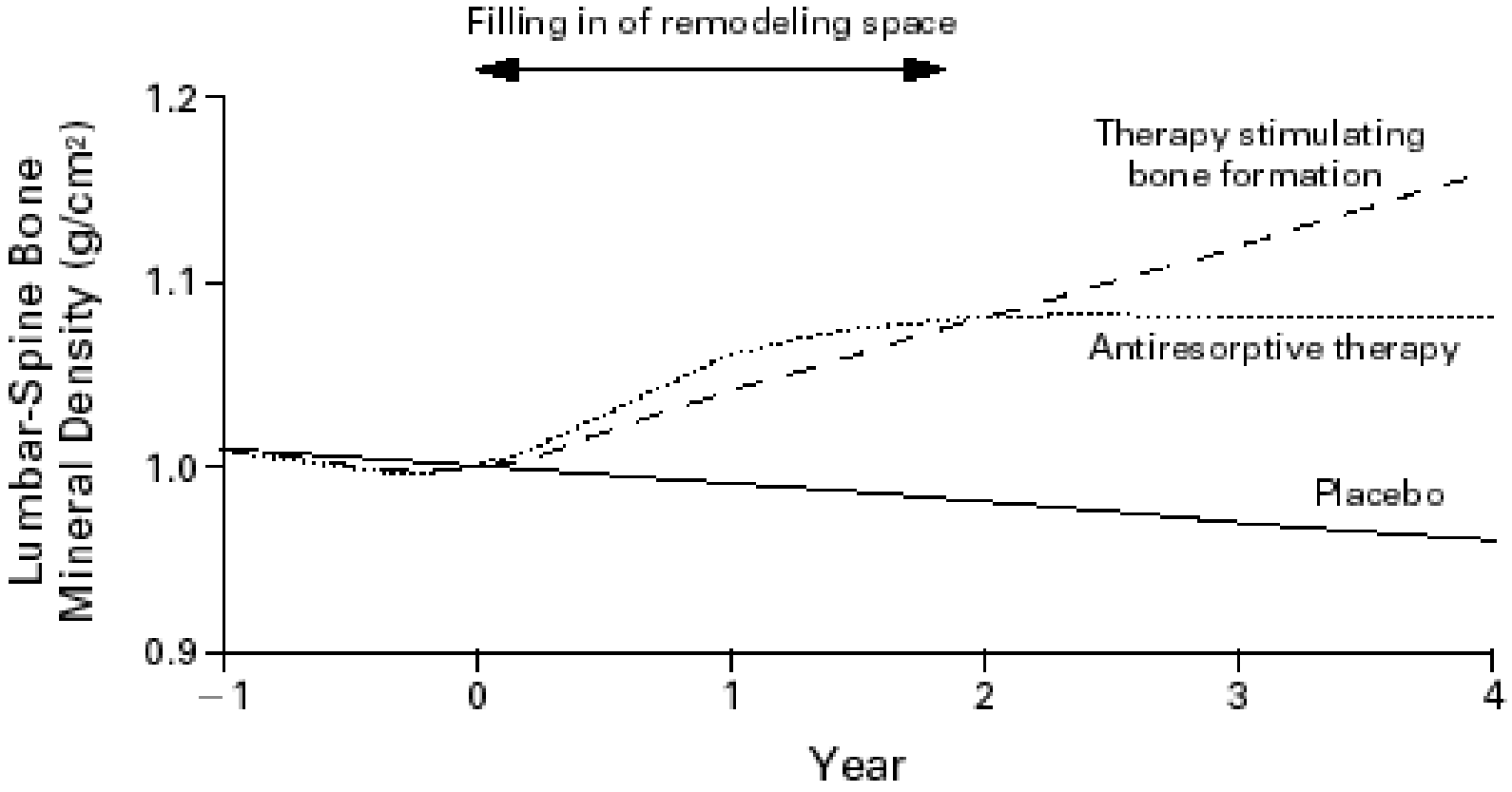
Stimulators of bone formation



The main direction of therapy is the inhibition of the increased osteoclast activity **(-)**

Treatment of postmenopausal osteoporosis

Eastell R, NEJM, 338:736,1998



The results of antiresorptive therapy increases BMD during the first 1-2 years, thereafter a plateau is formed.

1. Hormone substitution therapy

- The menopause induces accelerated bone loss within the first 4-5 years which is followed by a linear decrease, above 75 years of age bone loss becomes accelerated again

- Hormone replacement therapy (HRT) increases BMD, decreases bone turnover and the number of bone fractures. It is effective until administered.

- ***Estrogen (combined with progestin if the uterus is intact) increases risk of breast cancer, may enhance the risk of cardiovascular diseases***

- ***Prolonged HRT is not recommended anymore***

2. Selective Estrogen Receptor Modulators (SERM) Raloxifene, Bazedoxifene

- Act on the estrogen receptors
  - in some organs they act as agonists, while in others as antagonists

- In the treatment of osteoporosis those SERMs have clinical importance which are
  - **Agonists**: in the bones
  - **Antagonists**: in the breast and the uterus

- SERMs do not increase the overall cardiovascular risk but increase significantly the risk of thromboembolism

Raloxifene in postmenopausal osteoporosis

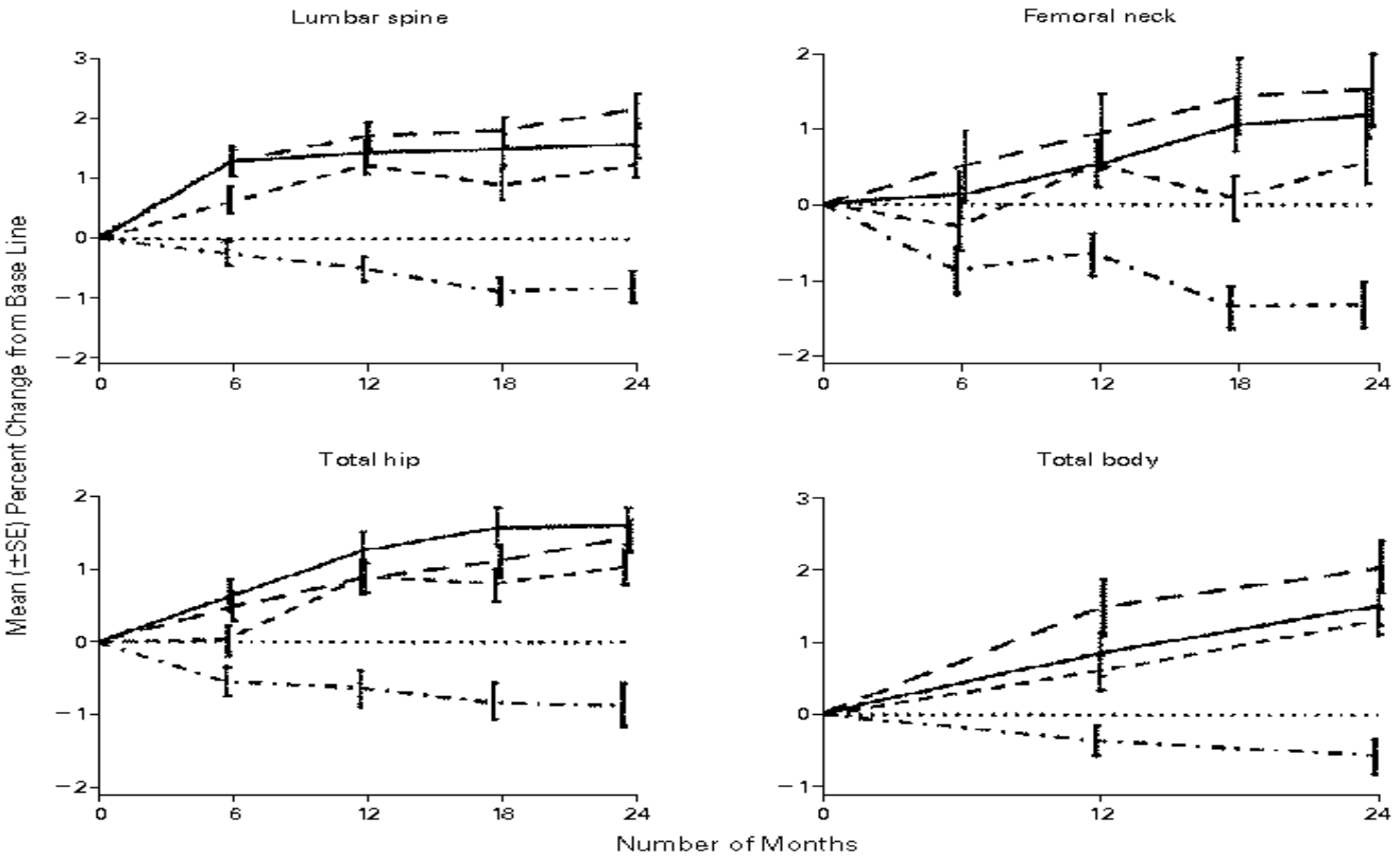
Delmas et al. NEJM, 337:1641, 1997.

Placebo

30 mg R

60 mg R

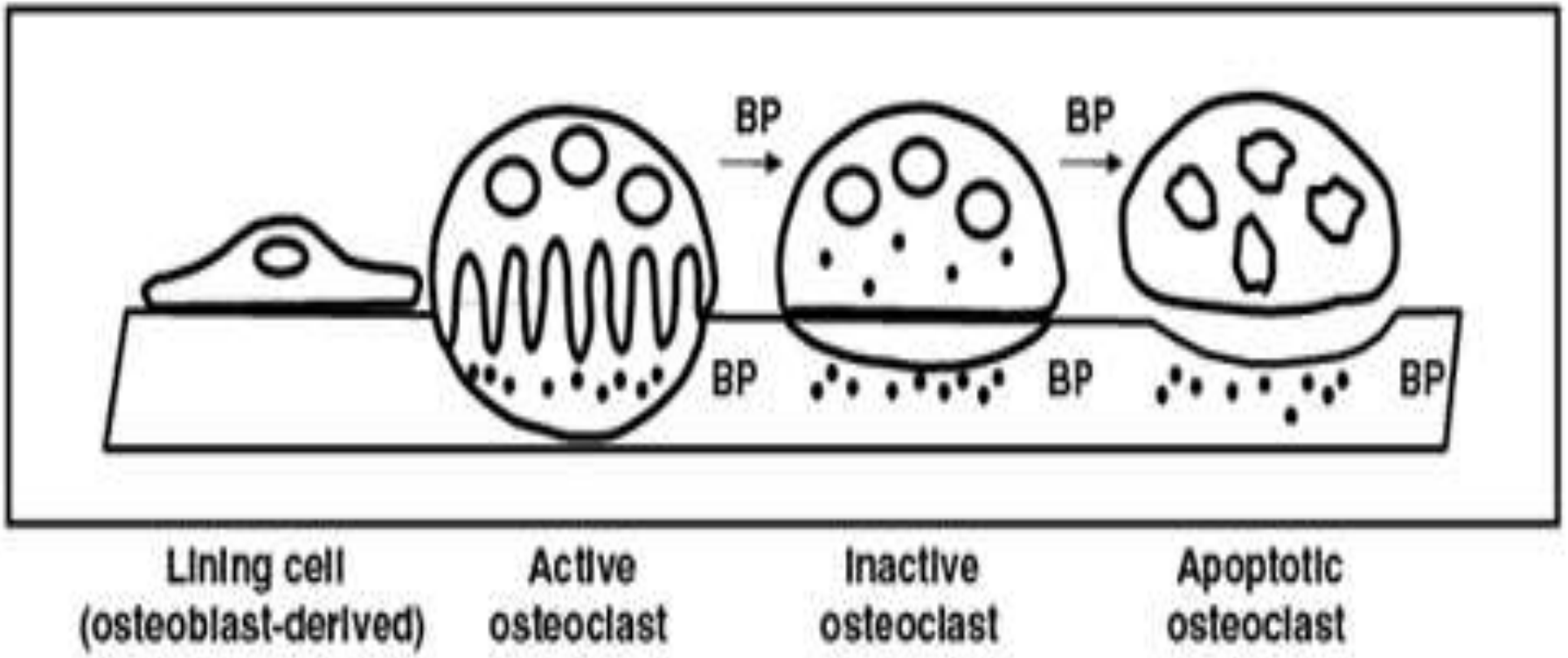
150 mg R



Raloxifene in postmenopausal osteoporosis

- Efficacy on the bones is equal to that of estrogen
- The thickness of endometrium , breast pain, vaginal bleeding, hot flushes did not increase compared with placebo
- **Imposes the same increased risk of venous thromboembolism as estrogen**
- Protects against spine fractures but not hip fractures (unlike *bisphosphonates*, *denosumab* and *teriparatide* protect against both)

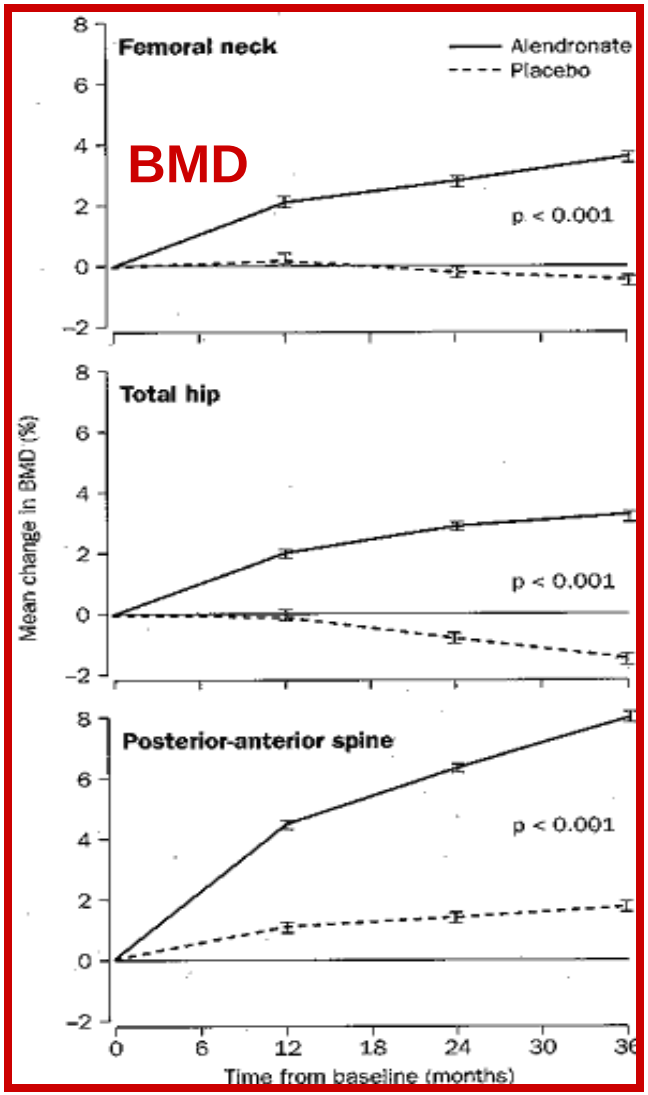
3. Bisphosphonates

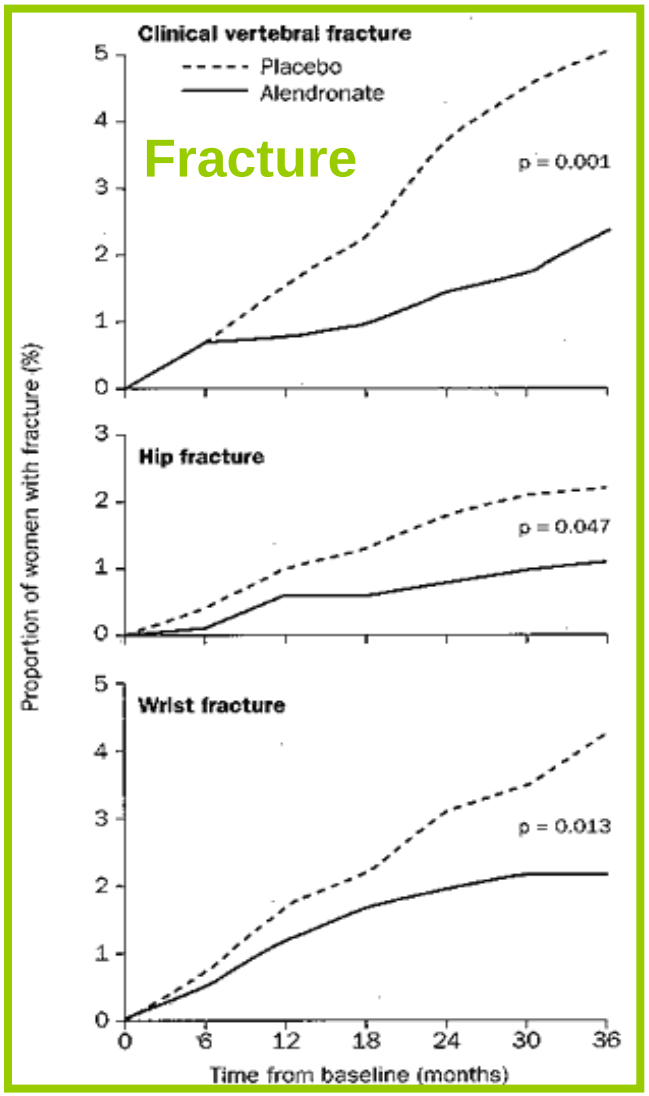


- **Bisphosphonates bind to the mineral substance of the bones**
- **They are taken up together with bone break down products into the osteoclast, they cause apoptosis**

Fracture intervention trial with alendronate in postmenopausal osteoporosis

Black et al., Lancet, 348:1535, 1996





- 2027 pts, 55-81 yr, postmenopausal females
- Femoral BMD, T score: - 2,1 SD
- At least 1 vertebral fracture
- 5-10 mg alendronate/day
- Primary endpoint: vertebral fracture

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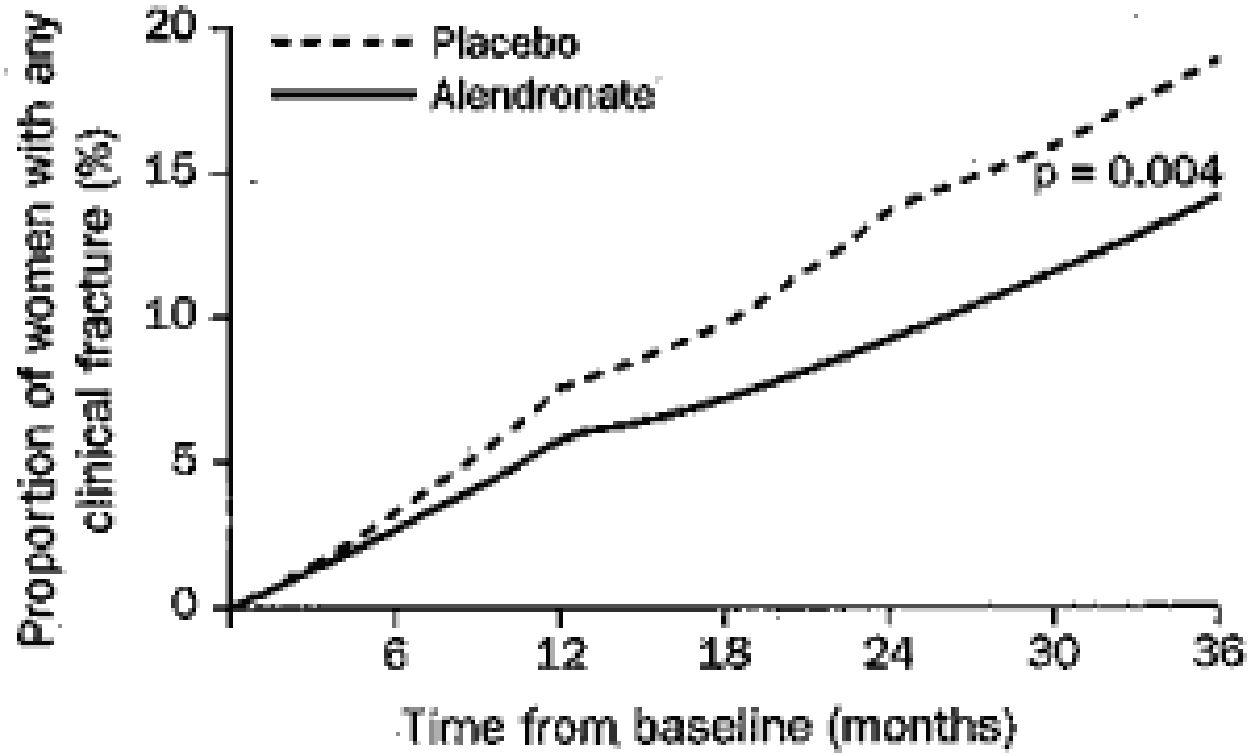
Black et al., Lancet, 348:1535, 1996



Long-term bisphosphonate use leads to abnormal bone formation

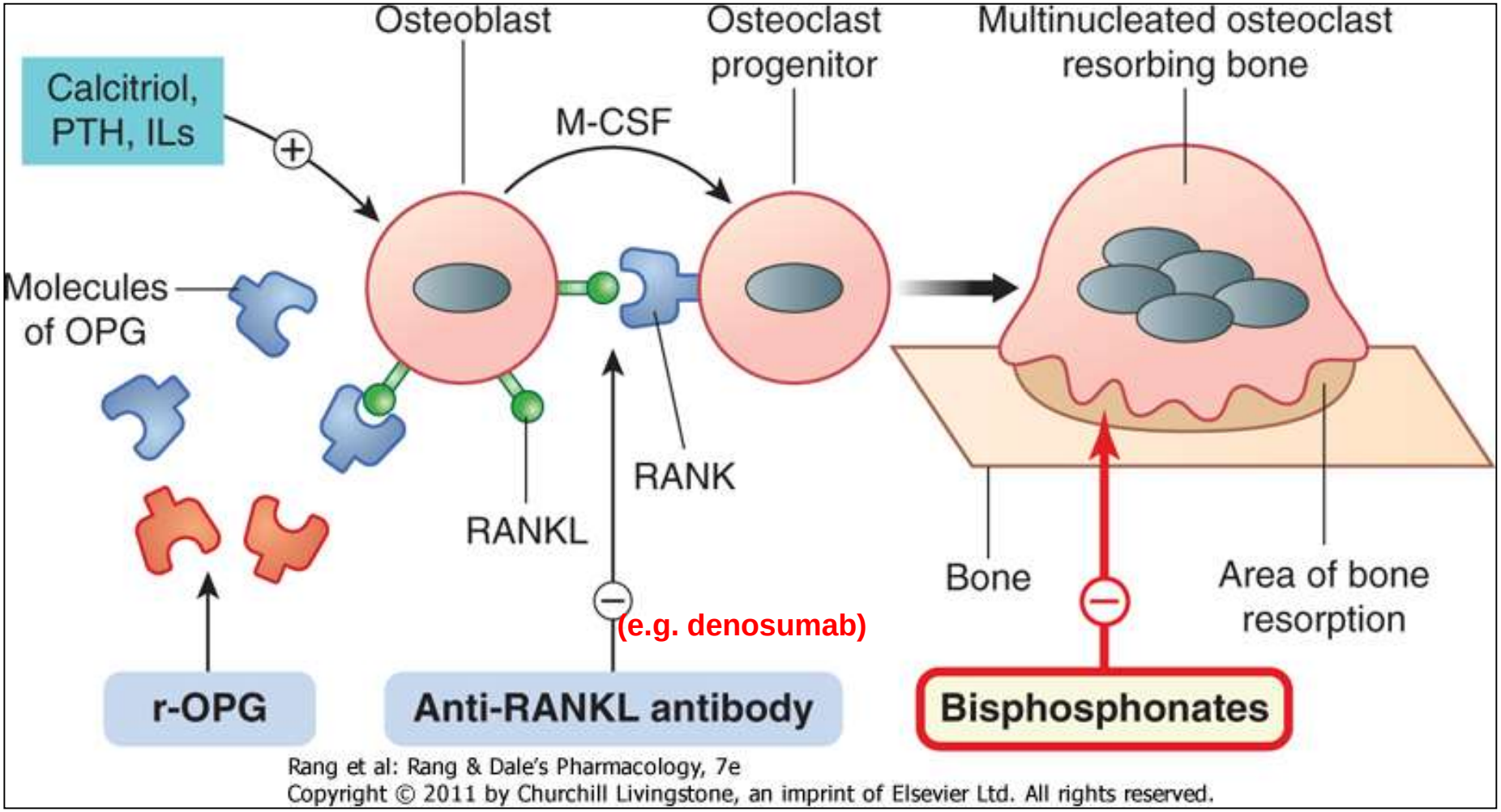
American Association of Orthopaedic Surgeons 2010 Annual Meeting

- "The biopsies of women treated over 5 years show that the bone become very, very old,". "This suggests to us that suppression of bone turnover, which is what bisphosphonates do over the long term, results in a loss of heterogeneity of the tissue properties, and this may be a contributing factor to the risk of *atypical fractures*" (Lane J)

- Bisphosphonate use improved structural integrity early in the course of treatment, but that these gains were diminished as treatment extended beyond 4 years.

- Women who are being treated with bisphosphonates should take a drug holiday if they have been on them for 5 years

4. Denosumab



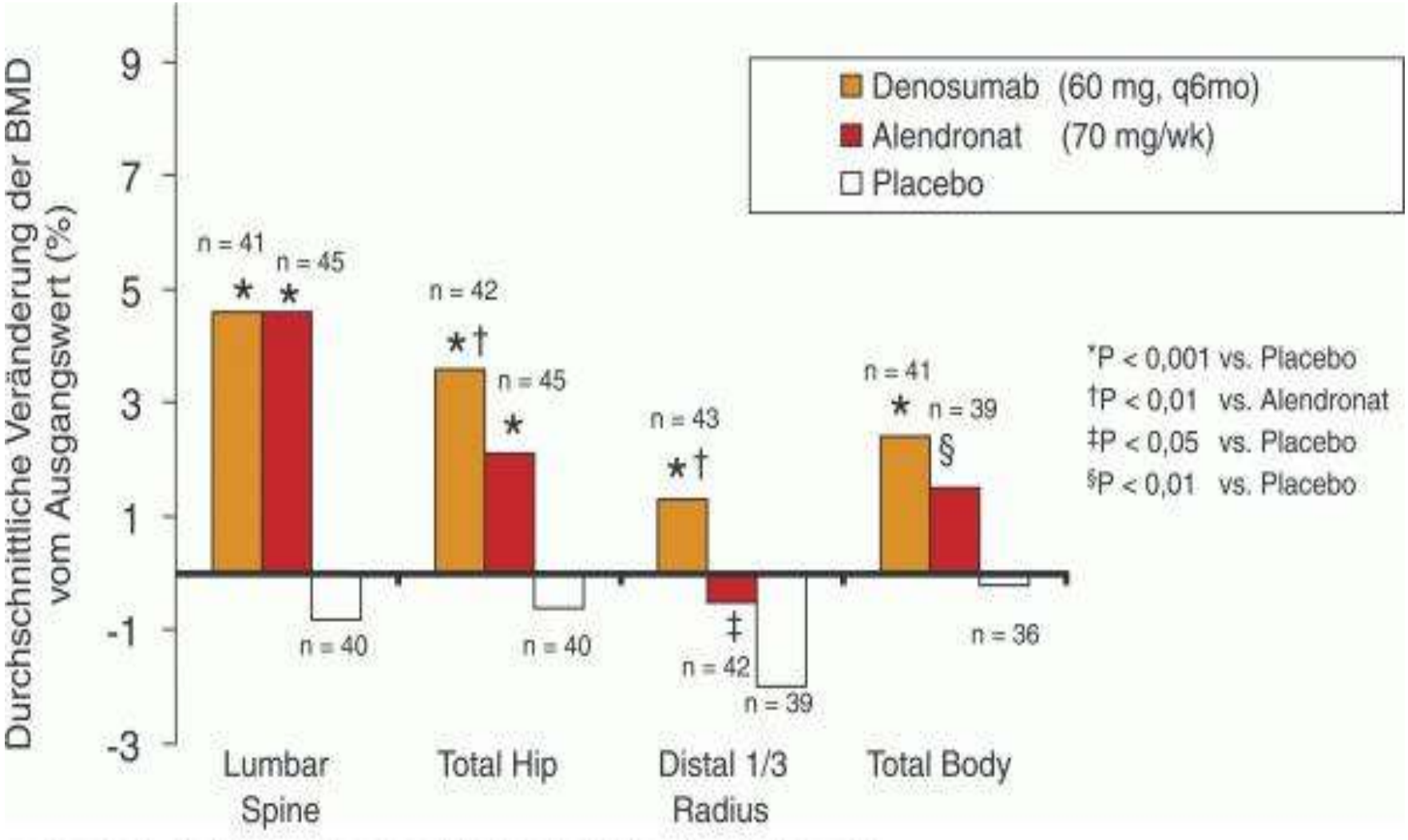
Anti-RANKL antibodies, denosumab, bind RANKL and prevent the RANK-RANKL interaction (it would cause osteoclast differentiation, increased activity and survival).

- Denosumab decreases osteoclast action and subsequently less bone resorption will occur.

(60 mg sc/6 month)

Denosumab vs alendronat

Preisinger E. J für Mineralstoffwechsel, 14:144-145, 2007



Denosumab

Advantages over bisphosphonates:

• It lowers markers of bone turnover more quickly than oral bisphosphonate therapy;

• It does not accumulate in bone, perhaps resulting in decreased risk for adynamic bone disease

•The combination of denosumab with intermittent PTH therapy may have additive benefits that are not seen with PTH and bisphosphonate therapy.

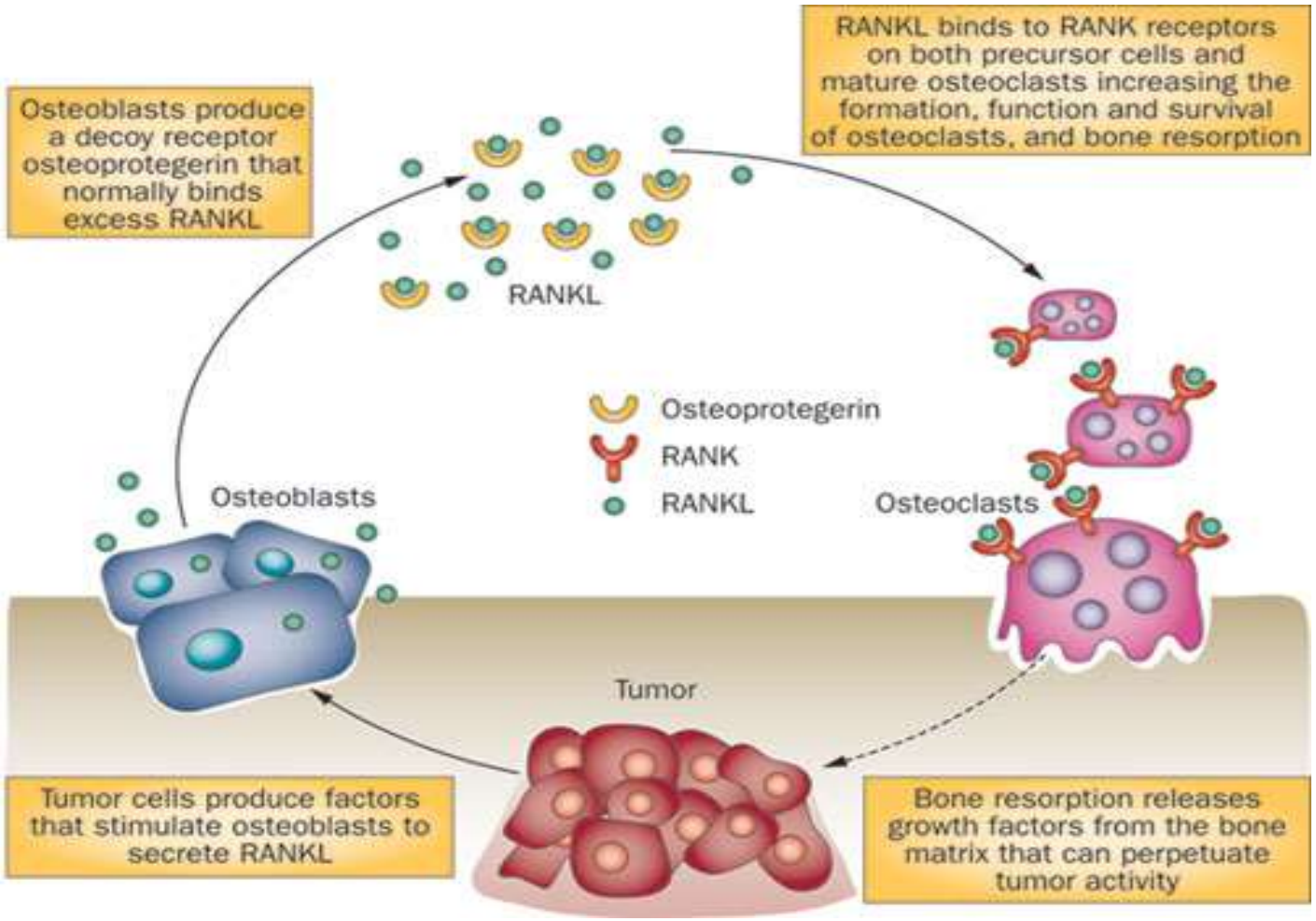
Disadvantages:

• risk of hypocalcaemia in chronic kidney disease or malabsorbtion

• if is discontinued its effect is reversed

RANK ligand (RANKL) in the vicious cycle of bone metastases.

Brown JE & RE. Coleman RE *Nature Reviews Clinical Oncology* 9, 110-118 2012



RANKL is essential for the formation, function and survival of osteoclasts.

Stimulation of osteoblasts by tumor-secreted factors increases the expression of RANKL in bone metastasis. **Denosumab** interrupts this cycle, prevents the formation and function of osteoclasts

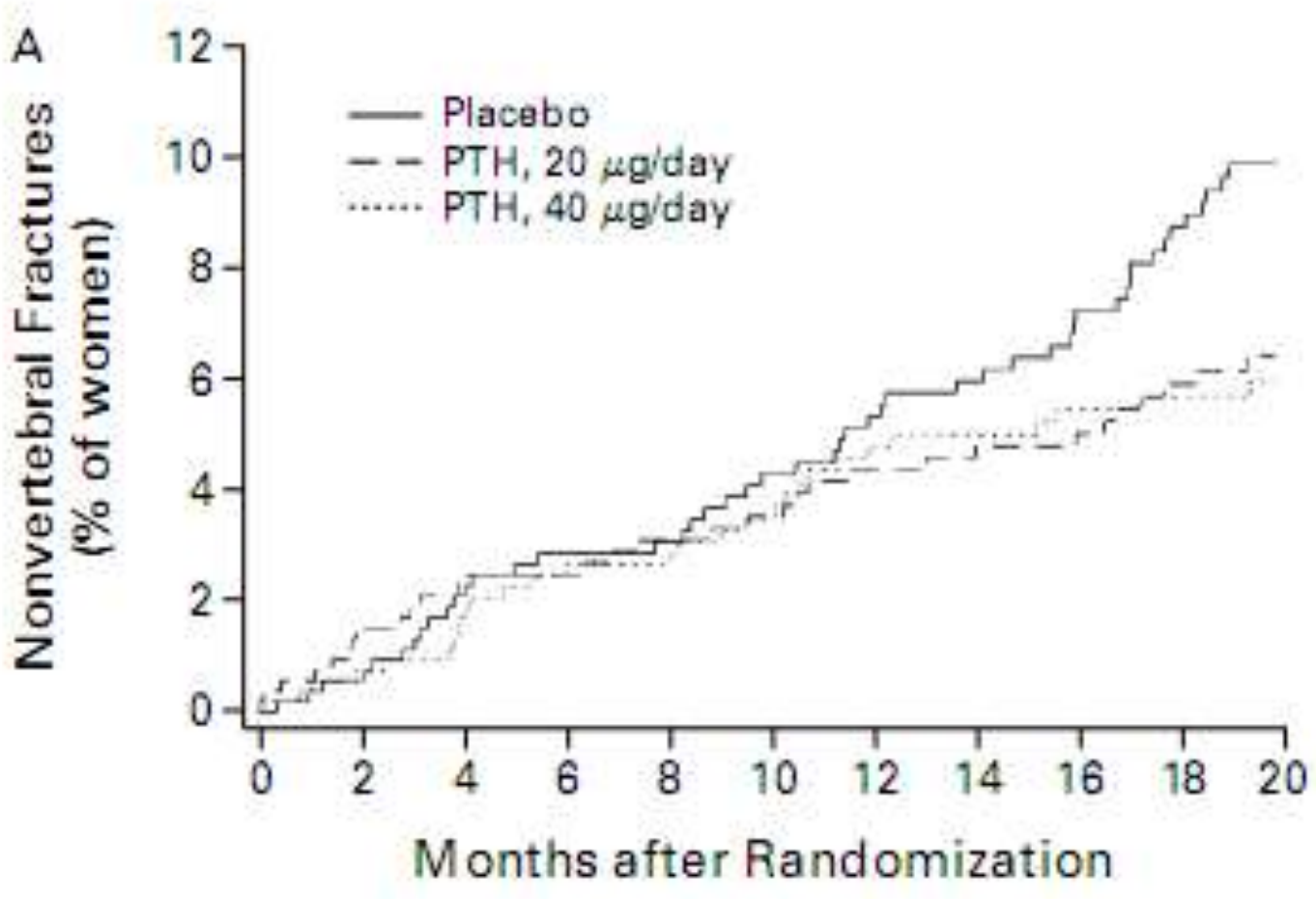
Parathyroide hormone (PTH 1-34) Teriparatide, Abaloparatide

- Teriparatide is the 1-34 amino acid sequence of the PTH. Abaloparatide is a PTH related protein
- PTH stimulates both bone resoprtion and bone formation
- Continuous and intermittent treatment stimulates bone formation equally, however,
  - continuous treatment leads to persistent increase of PTH level and relatively larger bone resorption
  - **daily** small doses lead to minimal bone resorption and **substantial bone formation**

Indicated for max. 24 months as osteosarcoma developed in rats at life long treatment

Parathyroide hormone (PTH 1-34) (Teriparatide)

Neer et al., NEJM, 344: 1434, 2001



PTH (1-34): daily 20 or 40 µg vs placebo. (p<0.05)

Vitamin D intake

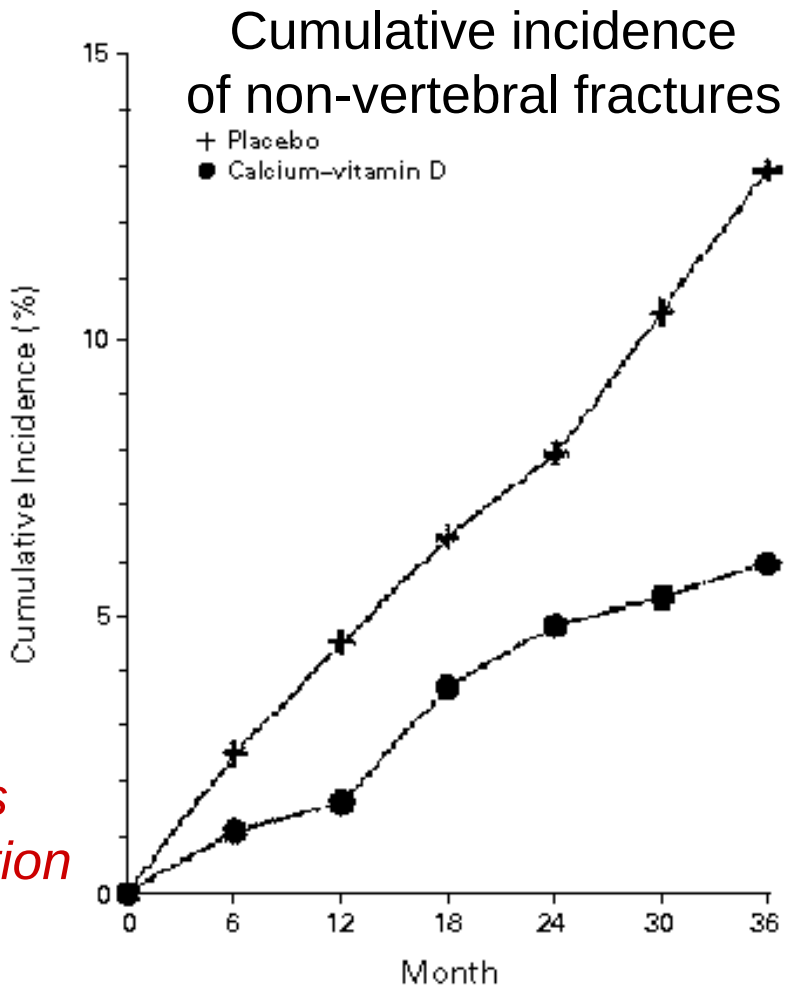
- Vitamin D3 (cholecalciferol) or
- Vitamin D2 (ergocalciferol)
- Active forms of vitamin D
  - 1α-hydroxyvitamin D3 (1α-hydroxycalciferol)
  - 1,25-dihydroxyvitamin D3 (1,25-dihydroxycholecalciferol)

Effect of calcium and vitamin D supplementation in men and women ≥65 year of age

Dawson-hughes et al., NEJM 348:670. 1997

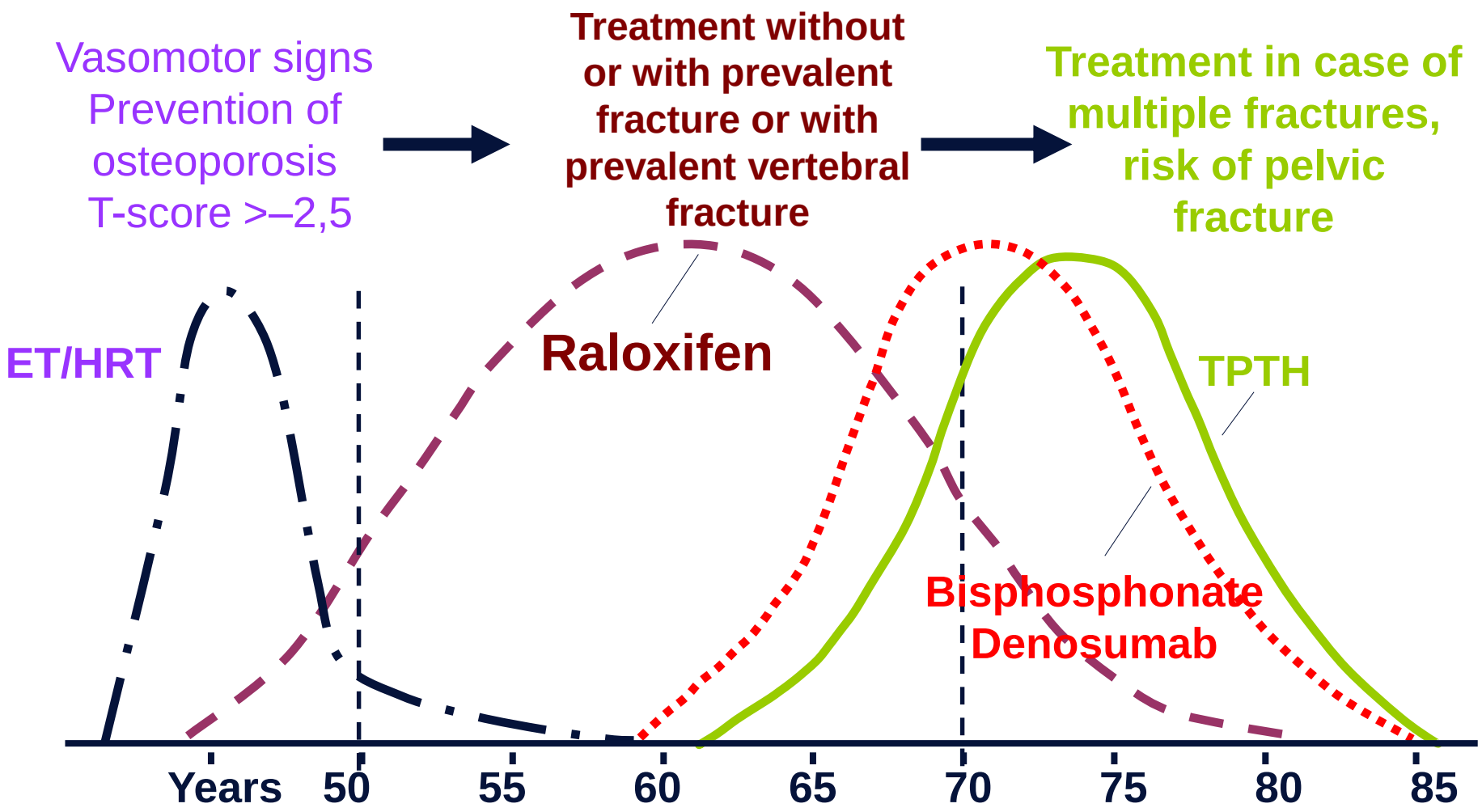
- 176 males and 213 females
- Endpoint: non-vertebral fracture
- 500 mg Ca + 700 IU vitamin D_3 (cholecalciferol)

Ca and vitamin D therapy is an important component of osteoporosis treatment given either alone or in combination with inhibitors of resorption.

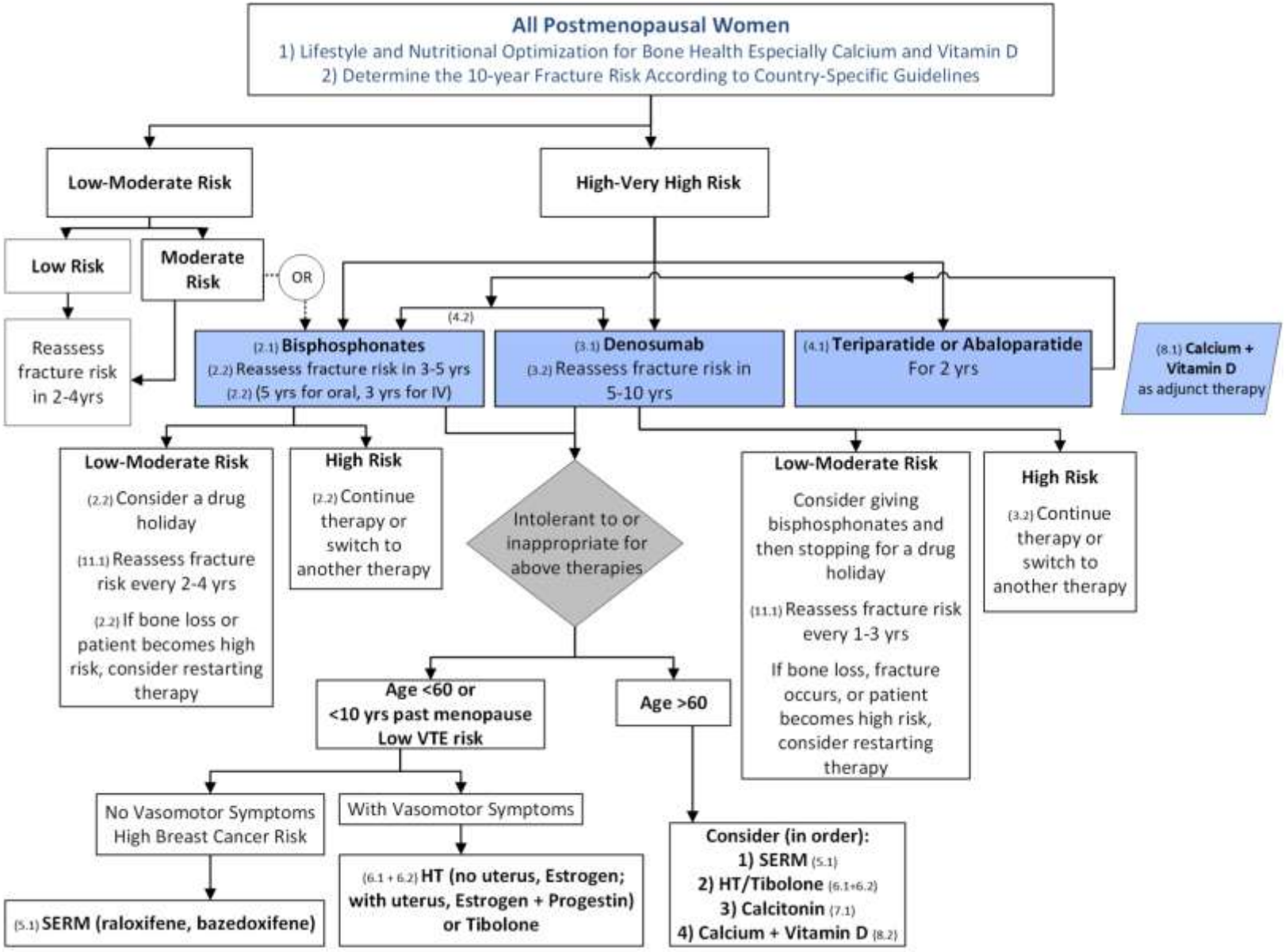


Treatment of postmenopausal osteoporosis

Following P Laktos



ET = estrogen monotherapy, HRT = combined hormone replacement therapy, TPTH = teriparatide



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