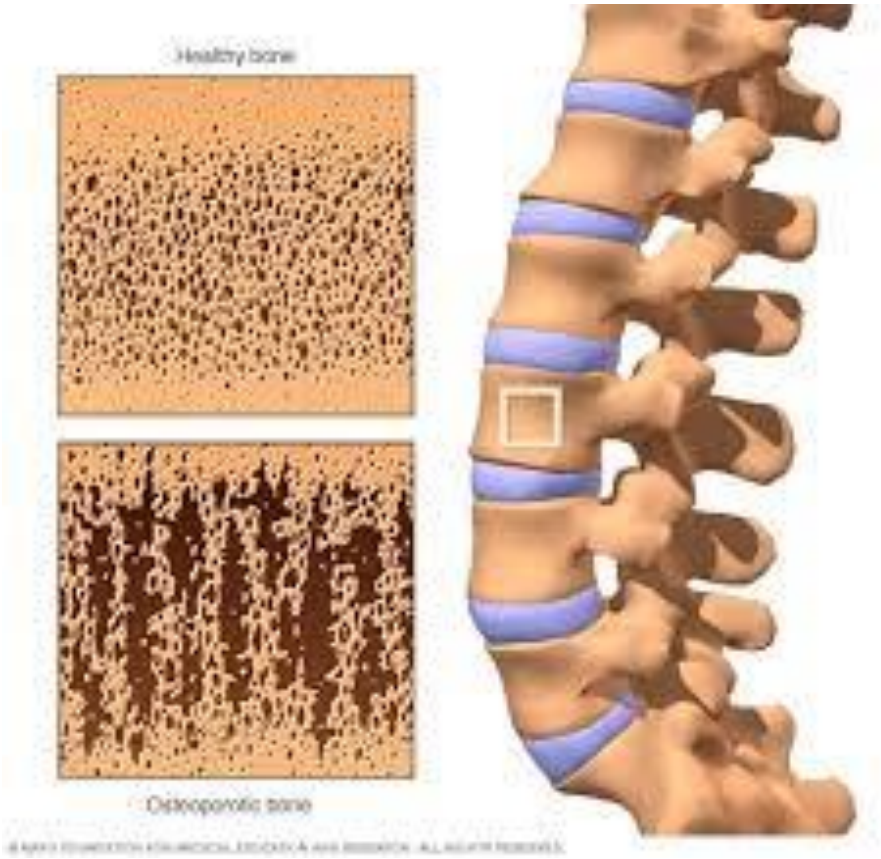
Osteoporosis treatment



Onset and progression of osteoporosis

Multiple Genetic factors (80%)

Multiple Environmental factors (20%)

Interactions Between

Diet

- Calcium
- Milk
- Vitamin D
- Protein
- Vitamin A
- Coffee
- Tea
- Alcohol
- Micro-elements

Calcium

- 1000 mg — Men, Women before Menopause
- 1200 mg — Elderly men ,Women after Menopause
- Source
- Dairy Products — Milk, Yoghourt, Cheese
- Vegetables — Broccoli
- Tablets — Calcium Carbonate(40% elemental), Citrate(24% elemental)

- Dosing Regimens
  - Split dosing → Better Reduction PTH *Reginster et al, 2002*

Breast feeding

- **Decrease Childhood Risk of Fracture**
- **Increase adulthood BMD when taken in childhood**
- **No effect in black**

The British journal of nutrition 2016

Vitamin-D

- Need
  - 50 to 70 years (400 units)
  - > 70 (600 units)
  - Therapeutic (800 units)
    - Reduction of Fracture risk

Supraphysiologic dose of Vit-D

- **Increase osteoclast activity**

  (↑M-CSF, ↑ RANKL)

Protein

- **Need 0.8g/kg daily** **Adequate**
- **High Protein Diet > 1.5g/kg daily** **Bone Loss**

  Increased Fracture Risk

- **High Protein + Ca + Vit D -Higher BMD**

Sport medicine 2024

Vitamin-A

- **Need** **700 µg/daily**
- **High Dose** **2000 or higher**

  Doubles Fracture Risk

- **Beta Carotene** **high BMD**

NOF-2023

Coffee

- **Coffee more than 2 cups/Day Increase Fracture**

  Risk

N Engl J Med 332:767–773, 1995

Tea

- **Black Tea Increases BMD**

European journal of clinical nutrition 2021

Alcohol

- **Alcohol**

- **Alcohol increases the risk of 7 types of cancer breast (in women), colorectal, esophagus, liver, mouth (oral cavity), throat (pharynx), and voice box (larynx).**

- **Alcohol inhibits osteoblast proliferation and bone matrix synthesis and increases the risk of fracture.**

Smoking

- **Decreases BMD**

Bone 2018

Physical activity

- Increase BMD
- Reduce Fracture Risk
  - Aerobic, Tennis, Weight bearing physical exercises, jogging >> Walking, Reduction in Hip and Vertebral Fracture

Treatment with drugs

- Before starting the treatment, calcium and vitamin D should be normal,
- Secondary causes and hypercalciuria should be ruled out.
- More than 50% of osteoporosis in men is secondary
- Most fractures occur in osteopenic patients

Laboratory tests before treatment

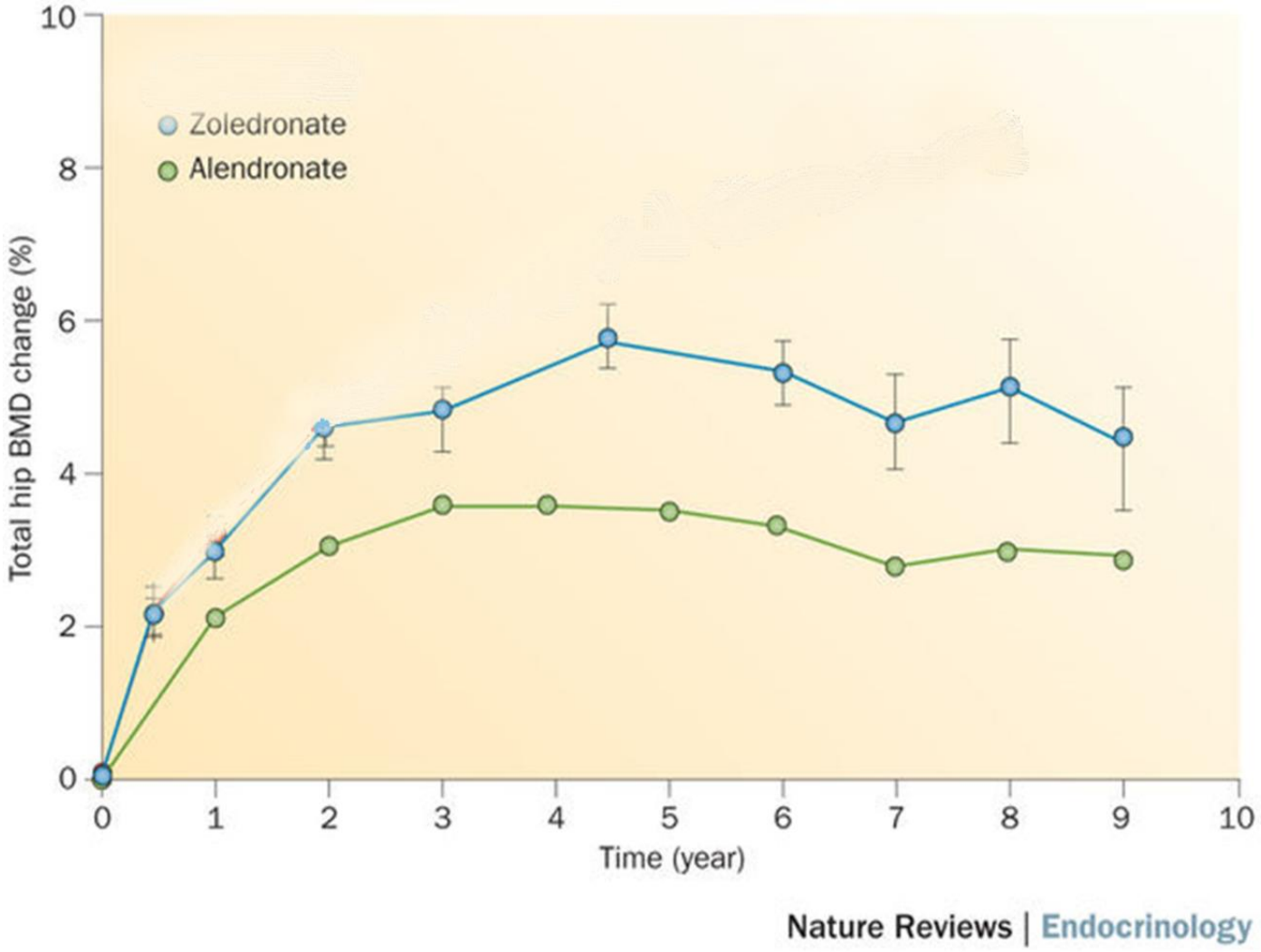
- For all patients: CBC, PTH, Ca, P, Alb, ALP, VIT-D, and protein electrophoresis
- For selected patients: TSH and other endocrine tests, GI and neoplastic tests if needed, bone biopsy

Bisphosphonate treatment (Anti-resorptive Agents)

- They inhibit the cholesterol synthesis pathway in osteoclasts, causing early apoptosis and inhibiting osteoclast migration and attachment

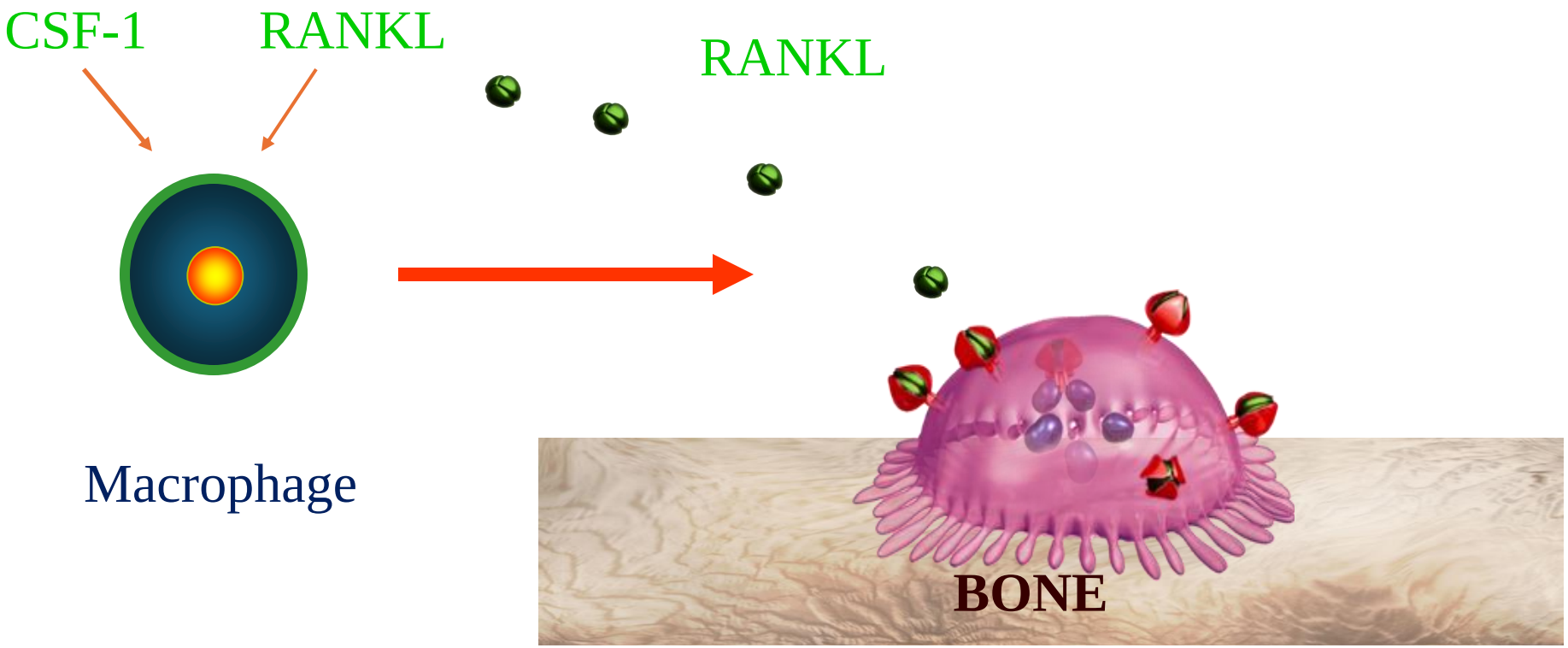
- **Risedronate tab 5mg/daily, 35mg/weekly**
- **Alendronate tab 10mg/daily, 70mg weekly**
- **Ibandronate tab 150mg/monthly, 3mg/every 3 mo IV**
- **Zoledronic acid vial 5 mg/per year for osteoporosis and every 2 years for osteopenia and Paget disease**
- **By Ibandronate no reductions in non-vertebral or hip fractured occurred**

How much(6%) and how long (4-years) bisphosphonate increase BMD in hip

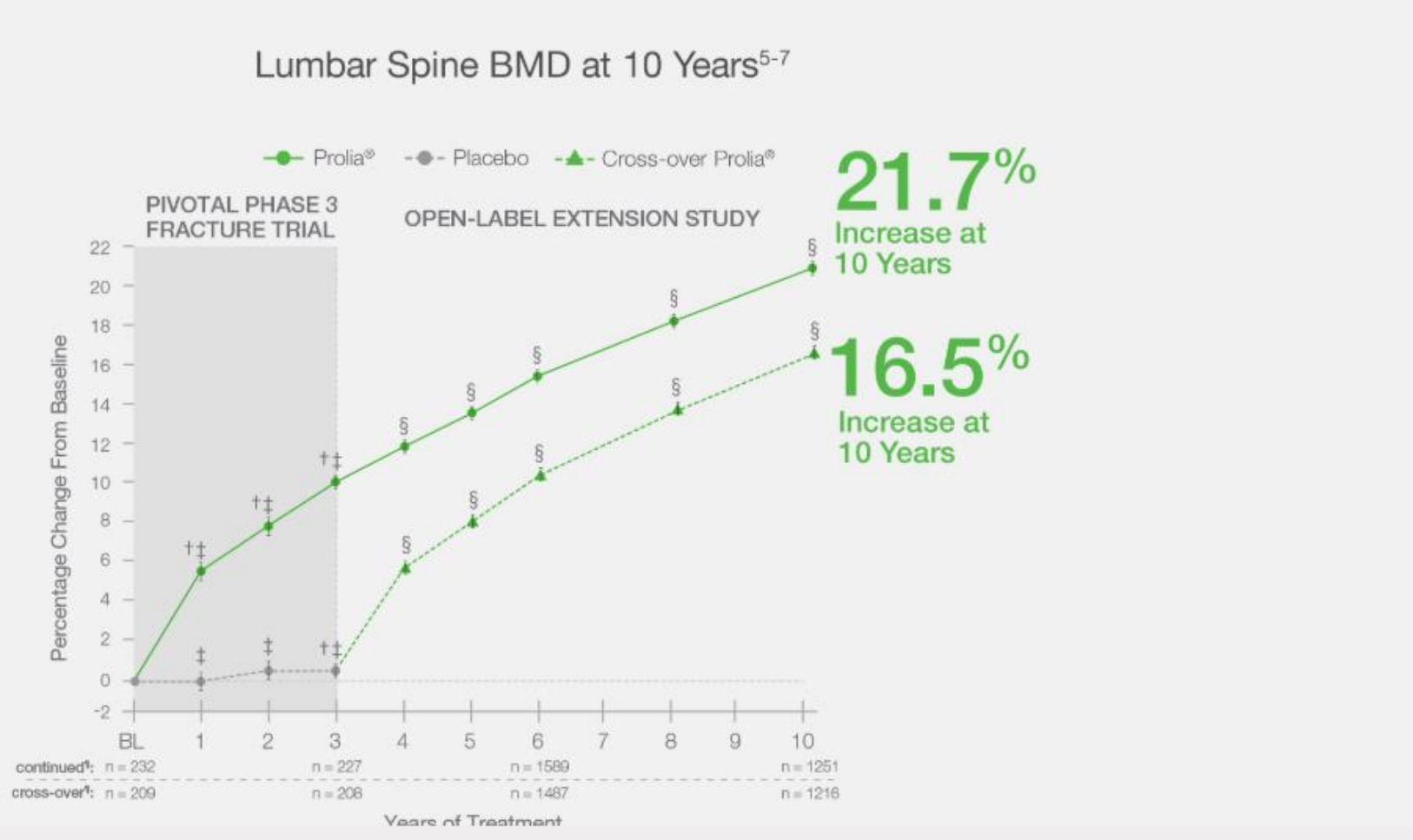


Anti-rankl (anti-receptor activator of nuclear factor kappa-B ligand) [Anti-resorptive Agents]

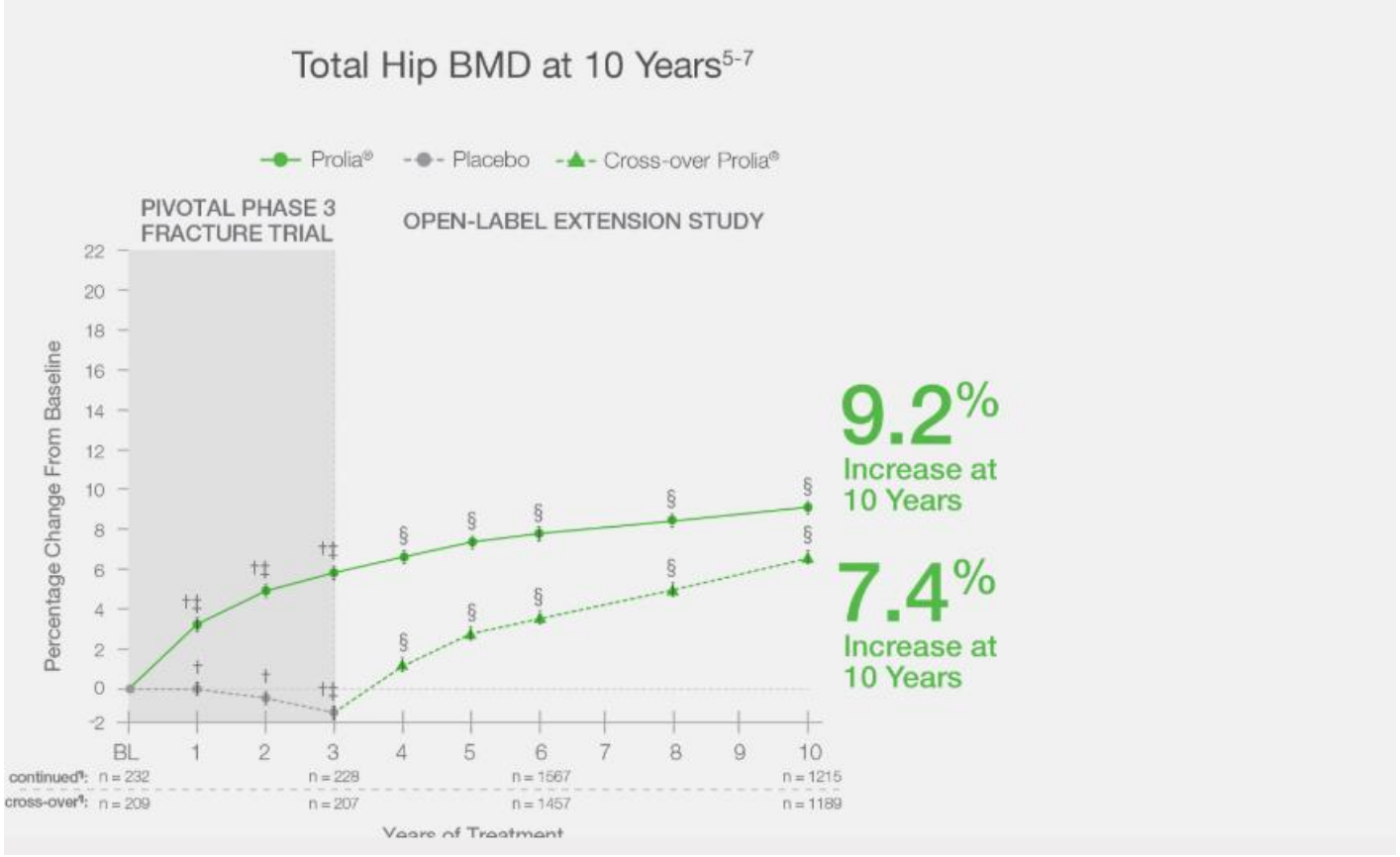
OSTEOCLAST



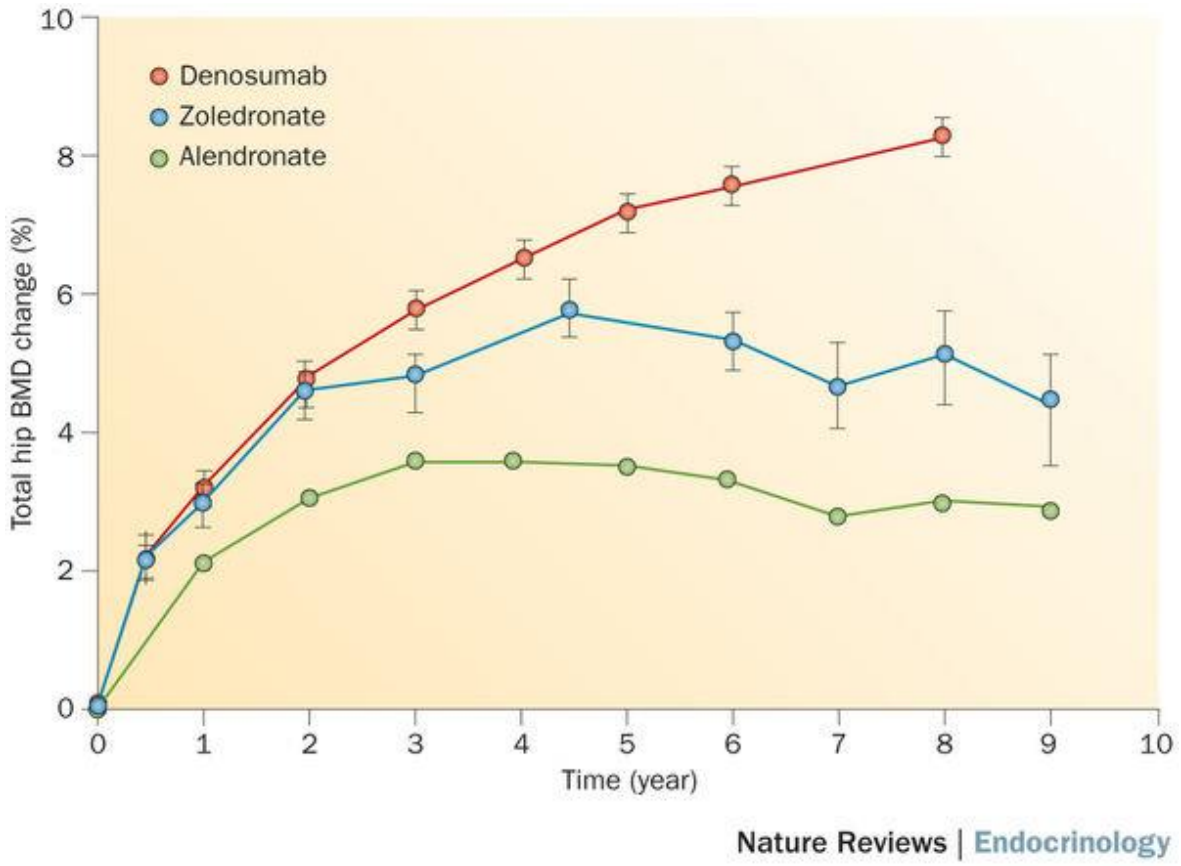
Anti-rankl effects on lumbar spine



Anti-rankl effects on total hip



Comparison of bisphosphonates with Anti-rankl on hip

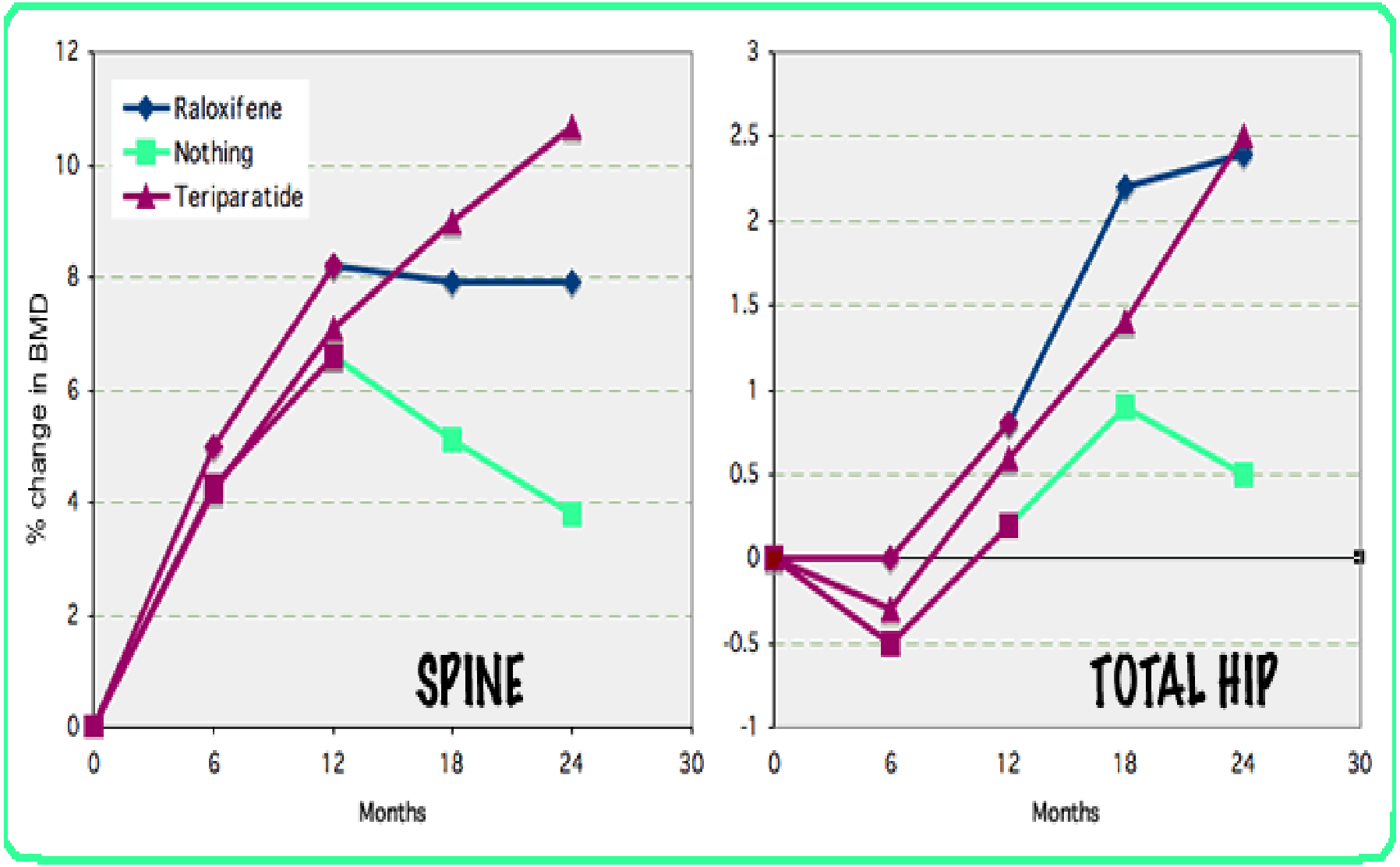


Post-denosumab rebound phenomenon (PDRP)

- **Effects are rapidly reversible and when discontinued, bone turnover rates increase to levels above the pretreatment baseline**
- **Post-denosumab “rebound” phenomenon has been linked to an increased incidence of multiple vertebral fractures**
- **PDRP occurred 8 to 16 months after the last dose, raising concerns about a rebound in fracture risk when denosumab wears off**

Teriparatide (PTH) [Anabolic Agents]

Post teriparatide drop BMD



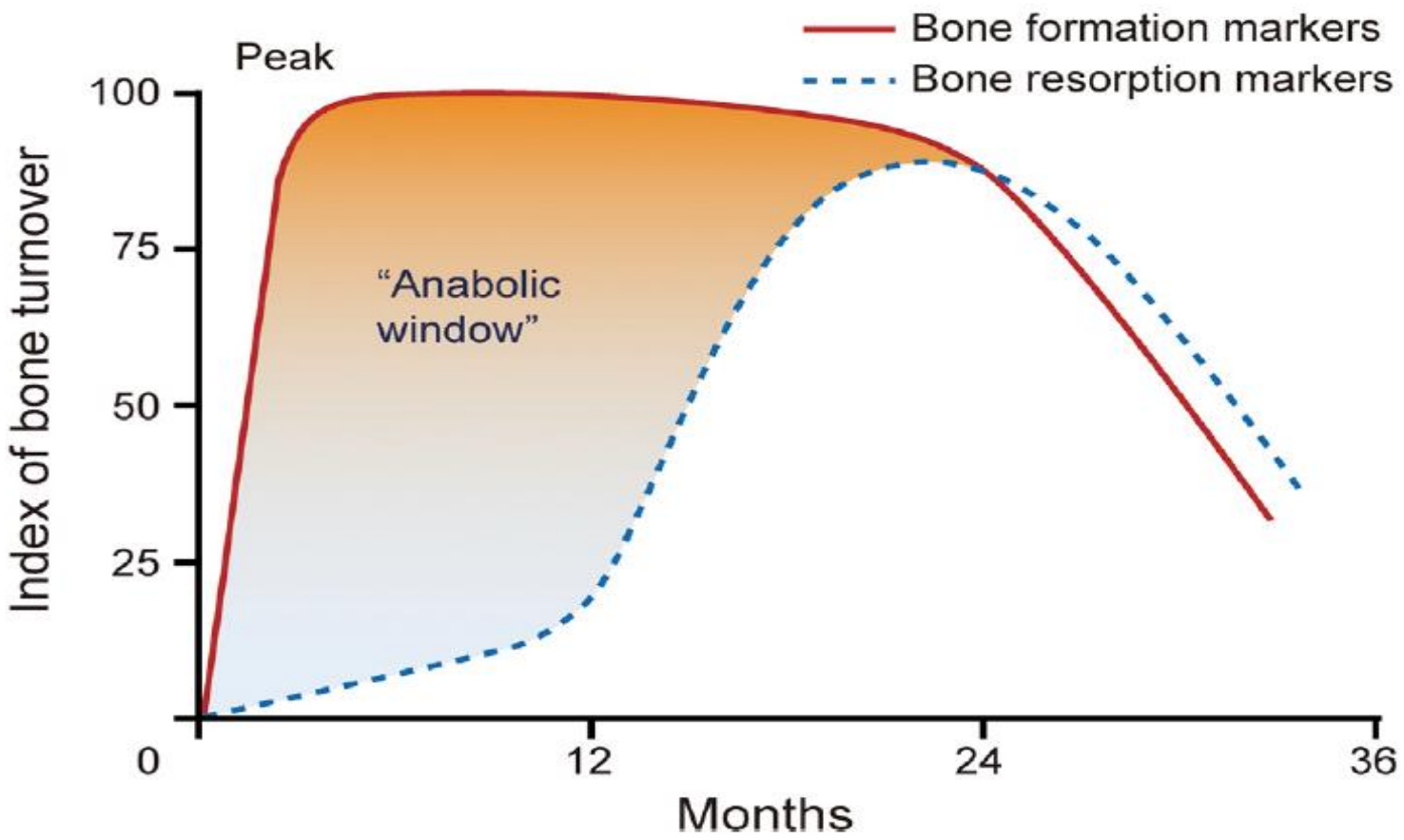
Antiresorptive Agents After Anabolic Agents

- **Oral alendronate** is clearly effective not only in preventing post-teriparatide and post-PTH bone loss but also in further **increasing hip and spine BMD**

- **Denosumab** when given after 2 years of teriparatide increased **spine BMD** by an additional **9.4%** and increased **total hip BMD** by an additional **4.8%**

- So if patient that treated with **teriparatide** is high risk to subsequent Fx it is better to use **denosumab** for sequential therapy

The figure shows the concept that bone formation is first stimulated by PTH followed by a later increase in bone resorption



Combination therapy

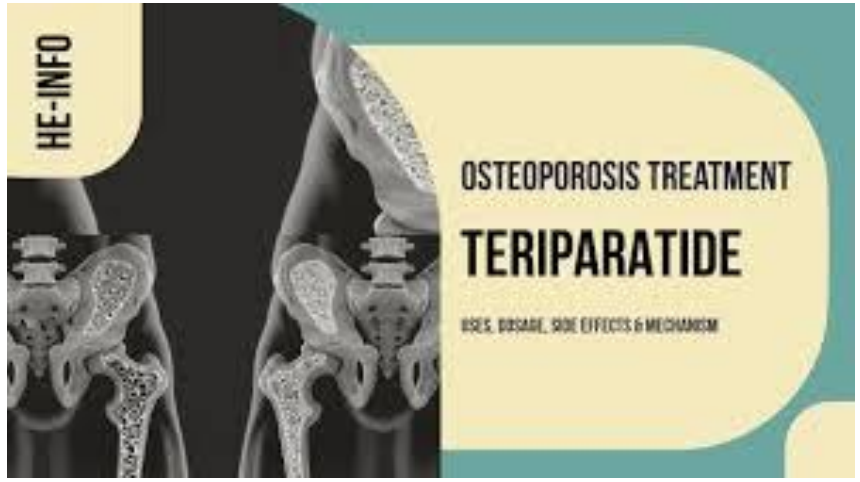
- **The simultaneous use of PTH with alendronate in women and men has a lower effect in increasing density than, using PTH alone**
- **On the contrary, the simultaneous use of PTH with Prolia increased the density of the hip and spine, than using either alone**

N N Engl J Med 349:1207–1215, 2003

Daily teriparatide versus weekly

- **Daily teriparatide (20 μg) had a strong effect on trabecular bone of vertebra**
- **Daily teriparatide did not increase cortical BMD of proximal femur**
- **Weekly high-dose teriparatide (56.5 μg) had a moderate effect on trabecular bone of vertebra but increased cortical BMD of proximal femur**

bone.2024



Patients at imminent risk of fracture:

- **Patients with a recent fracture are at very high risk of more fractures over the next 2 yr; this risk is largely independent of baseline T-score**
- **The treatment goal for these patients is to rapidly and maximally reduce fracture risk**
- **Greater BMD increases are associated with greater reduction in fracture risk**
- **patients who have had multiple prior fractures (even if not within the last 2 yr) are also at imminent risk**

HRT-Therapy (Anti-resorptive Agents)

- Increased breast cancer
- Increased heart disease, brain and pulmonary embolism events
- Formation of gallstones
- Colorectal cancer reduction
- Reduction of hip fractures

Result: It should be used in a woman who has unbearable vasomotor symptoms at the beginning of menopause, and it is better to be transdermal

SERMS (selective estrogen receptor modulators) [Anti-resorptive Agents]

- **Tomoxifen:** After 2 years of use in breast cancer, it caused a slight increase in bone density, a decrease in LDL and total cholesterol
- Its 5-year use in breast cancer prevention caused a 50% reduction in breast cancer, a 45% reduction in hip fractures, and a 29% reduction in vertebral fractures.
- It slightly increased the risk of endometrial cancer
- It had no effect on cardiac health

SERMS(selective estrogen receptor modulators)

- **Raloxifene:** acts as an estrogen agonist on bone and an estrogen antagonist on breast and endometrium
- After 2 years of use, the BMD of the spine and hip increases by 2.4% and the whole body by 2%
- It reduces the risk of vertebral fracture by 40%
- LDL was reduced by 12%, but it was not cardioprotective

Calcitonin(Anti-resorptive Agents)

- **Calcitonin is a 32-amino-acid peptide produced by the parafollicular cells of the thyroid gland**
- **The pivotal clinical treatment trial did not show significant changes in bone mineral density after 3 years**
- **However, the 200 IU dose of nasal calcitonin was associated with a 50% reduction in vertebral fractures**
- **No reduction in non-vertebral or hip fractures was found**
- **There is a possible association with prostat cancer**
- **Calcitonin may reduce pain following an acute vertebral compression fracture**

Romosozumab (Dual-Action Agents) [Anti-resorptive + Anabolic]

- The most powerful anti-osteoporosis drug with one year of use
- A monoclonal antibody against sclerostin and against RANK-L
- Monthly treatment of 210 mg /SC for one year caused a significant increase in spine density by 13.7% and femoral neck by 6.2%.
- Patients who have had major cardiovascular events in the last year should avoid prescribing this medicine

Osteoporosis treatment rules

- **Shorter treatment :why? for less complication in long term treatment and blunt effect of long treatment**
- **End of most osteoporosis treatment is Bisphosphonate (except HRT and SERM)**
- **In imminent risk of fracture or multiple fractures use anabolic agents**

Reducing the risk of fracture	Spine density Improvement %	Hip density improvement%	Drug name
50% hip, spine and forearm	8	4	Alendronate
40% hip, 50% spine, 40% nonvertebral	6-7	3	Risedronate
60% spine, othersites ineffective	6.5	3.4	Ibandronate
41% hip, 70% spine, 25% nonvertebral	6.9	6	Zolendronic acid
40% hip, 68% spine, 20% nonvertebral	9.2	6	Prolia
50% spine, ineffective on the hip and othersites	4	2.5	Raloxifen
34% spine and hip			Estrogen
65% spine, 53% nonvertebral	9.7	2.6	Triparatide
86% spine, 43% nonvertebral	9.8	3.4	Abaloparatide
38% hip, 73% spine	13.7	6.2	Romososumab

- **Among the mentioned drugs, calcitonin, denosumab, teriparatide, abaloparatide, and romosozumab are not used to prevent osteoporosis.**