Osteoporosis

Dr Elsa van Duuren

2012

Bone:

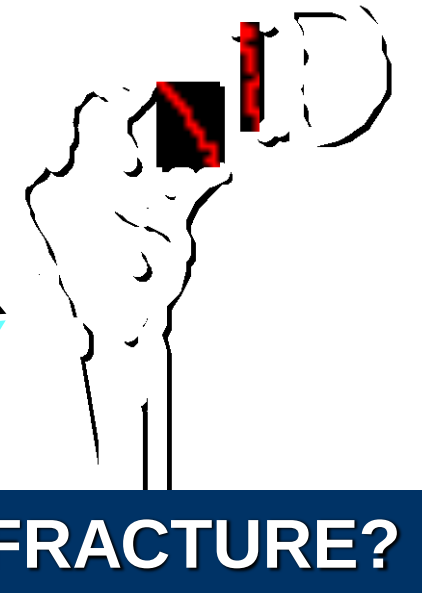
- Bone is a metabolically active organ
- Continuous change

- Physiologic function
- Structural function

Why Do Bones Break?

When load exceeds strength

Loads applied to the bone



Bone Strength

Applied Load

Bone Strength

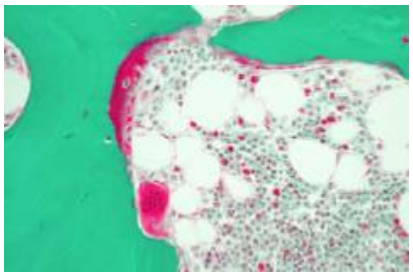
FRACTURE

Bouxsein, 2001

Main Determinants of Bone Strength

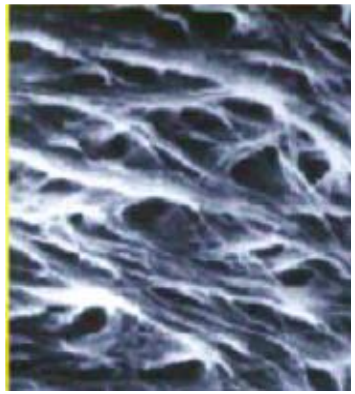
Bone Mass → **Bone Strength**

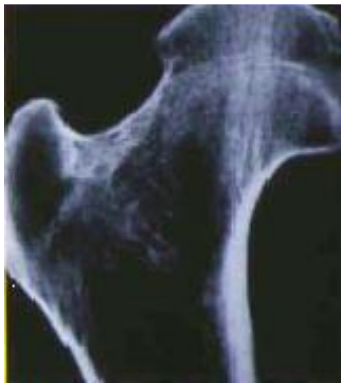
Bone remodeling

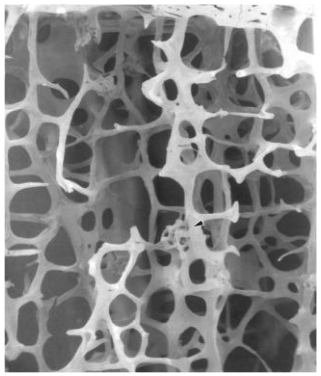


Bone Quality

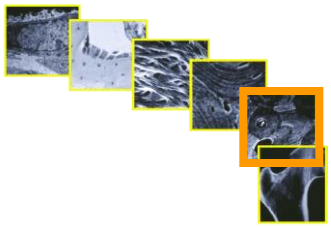
Bone matrix properties | **Macroarchitecture** | **Microarchitecture**

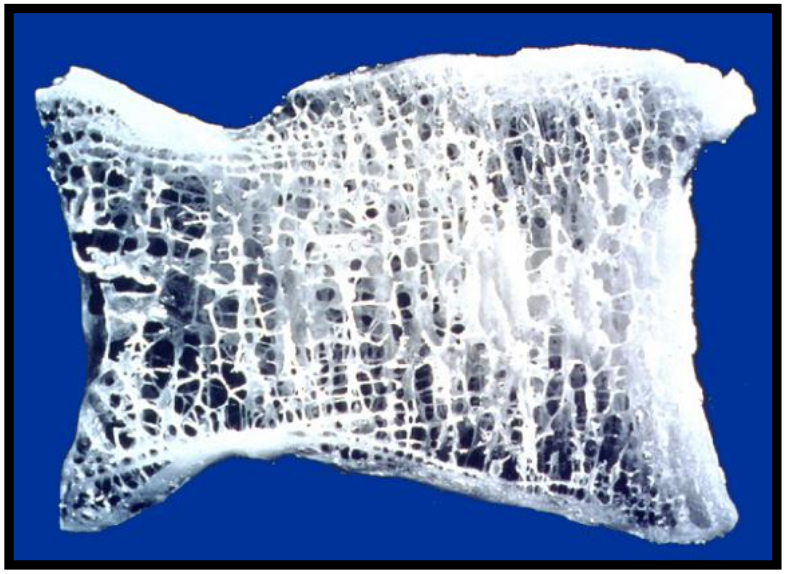






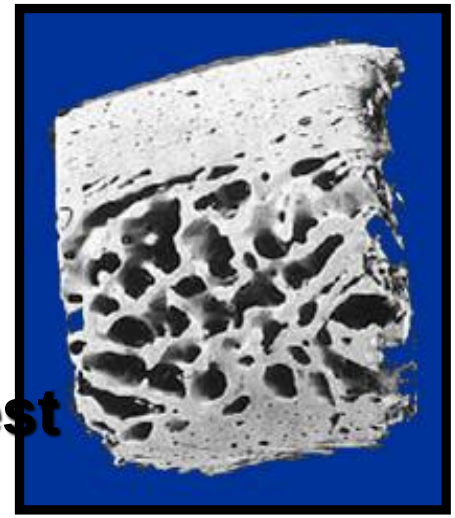
Cancellous and Cortical Bone





Cancellous

- Trabecular Number
- Trabecular Thickness
- Trabecular Separation
- Trabecular Connectivity



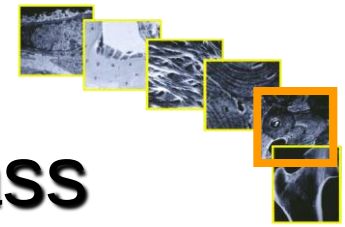
Iliac crest biopsy

Cortical

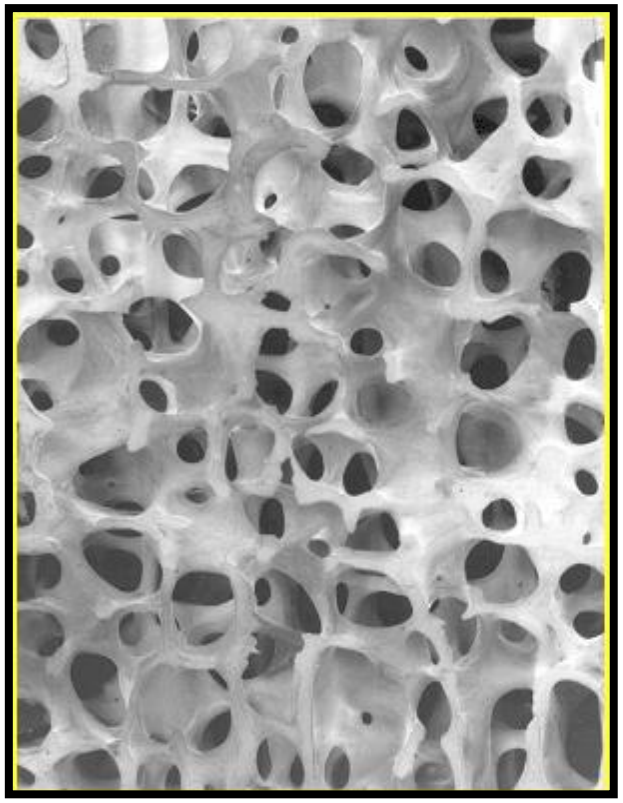
- Thickness
- Porosity

Lower photo courtesy D. Dempster

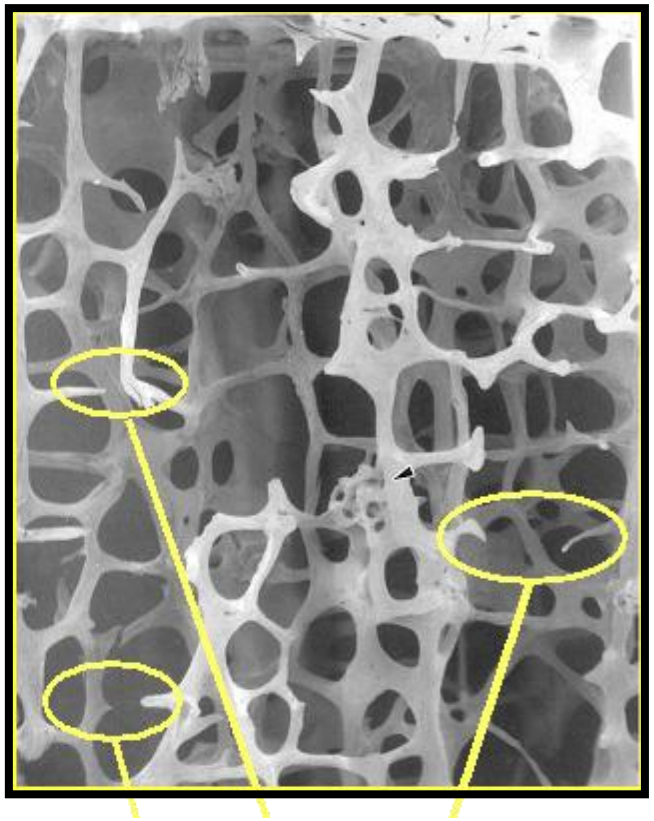
Osteoporosis Results in Changes in Cancellous Bone Mass and Architecture



Normal



Osteoporotic



Horizontal Disconnections

Courtesy of D. Dempster

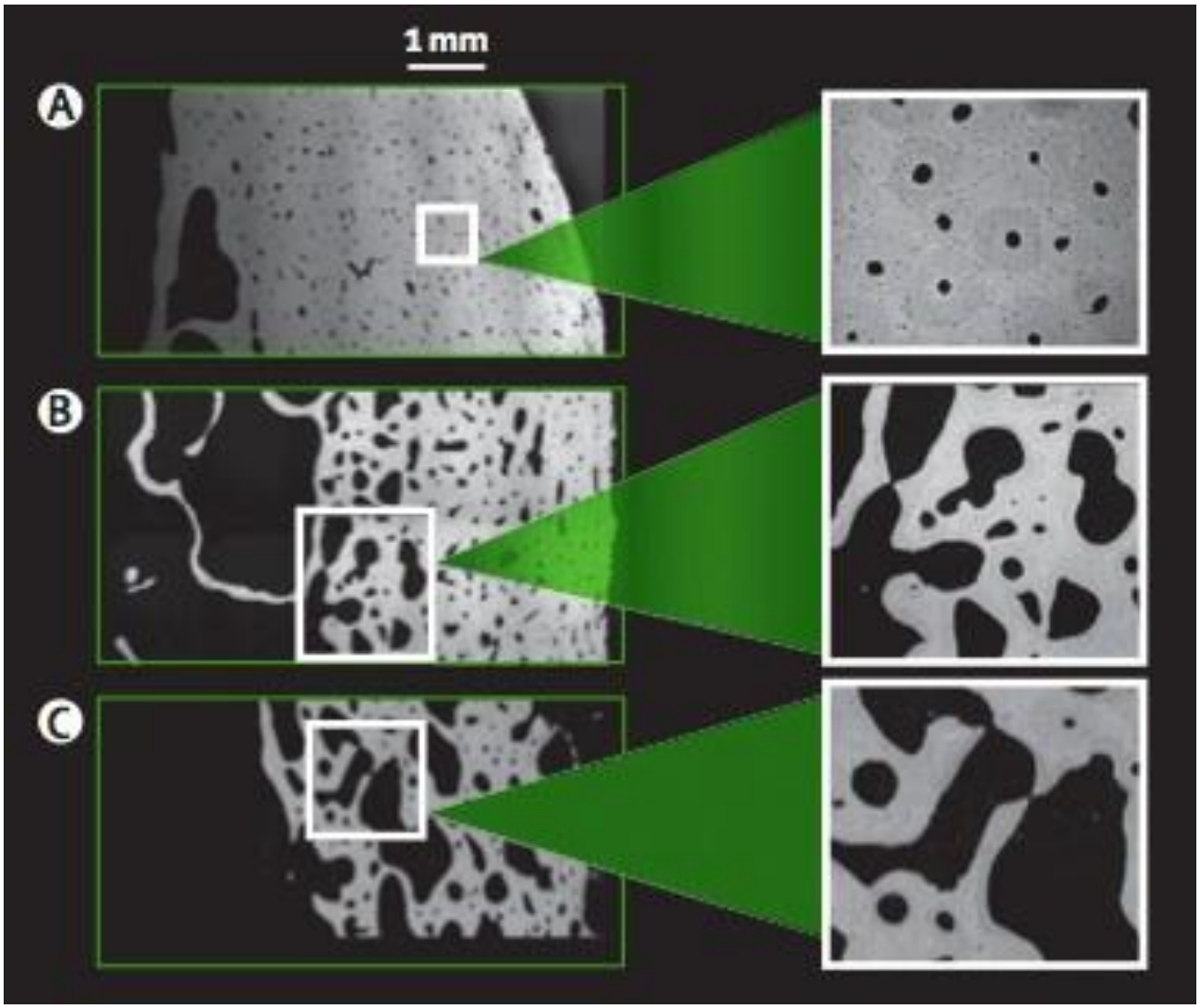
Cortical Porosity and Age

Age (Yrs)

29

67

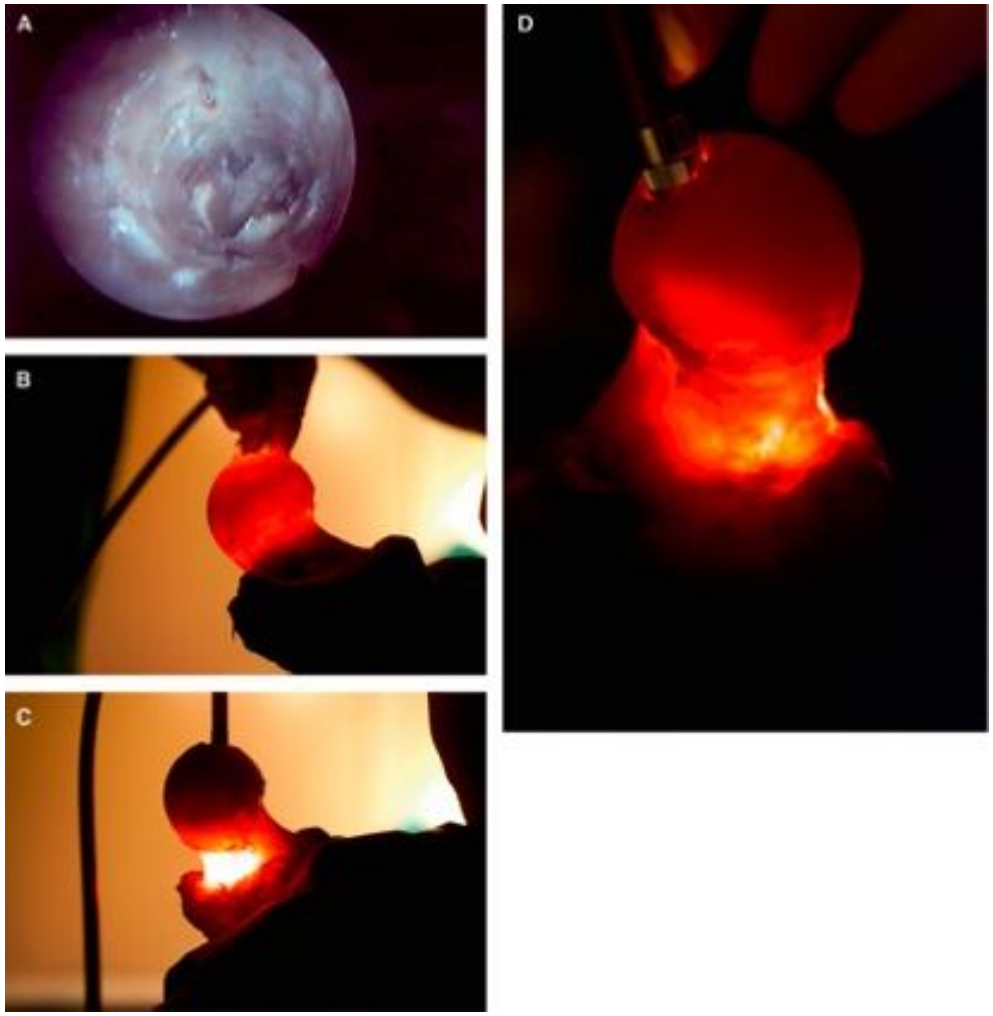
90



Strength:

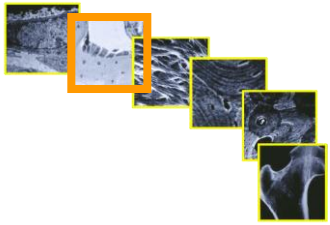
- 7 %

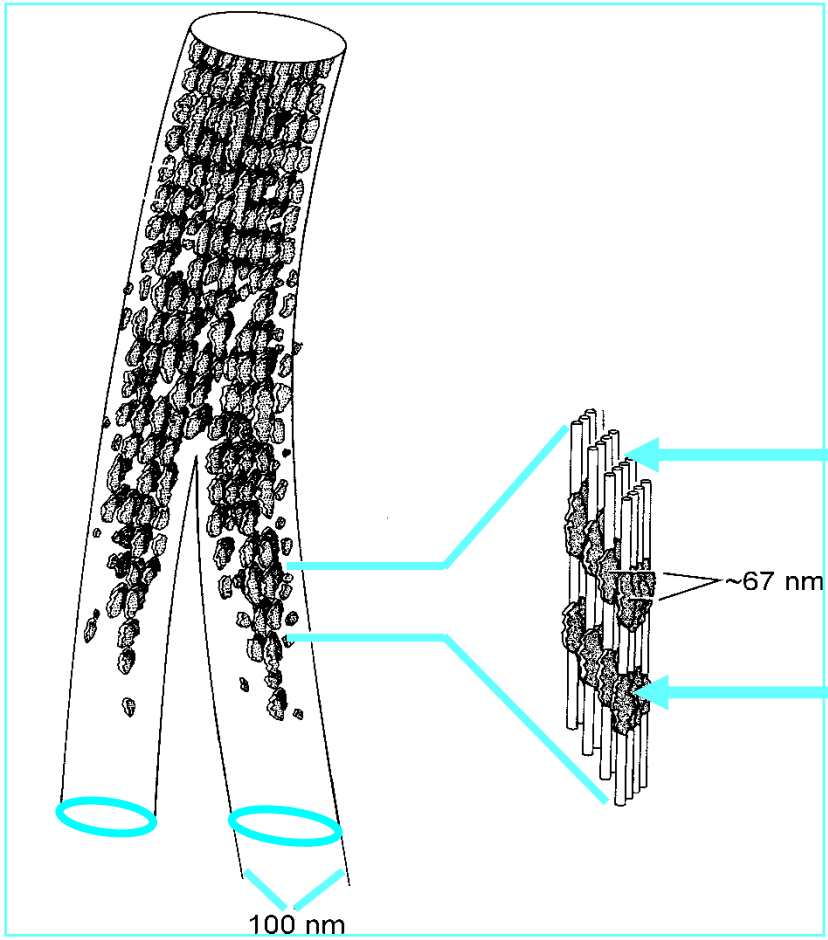
if Cancellous Bone was Removed from Femoral Neck



Holzer et al. *JBMR* 2009;24(3):468-474

Bone Structure:
Intimate Relationship Between Mineral and Collagen



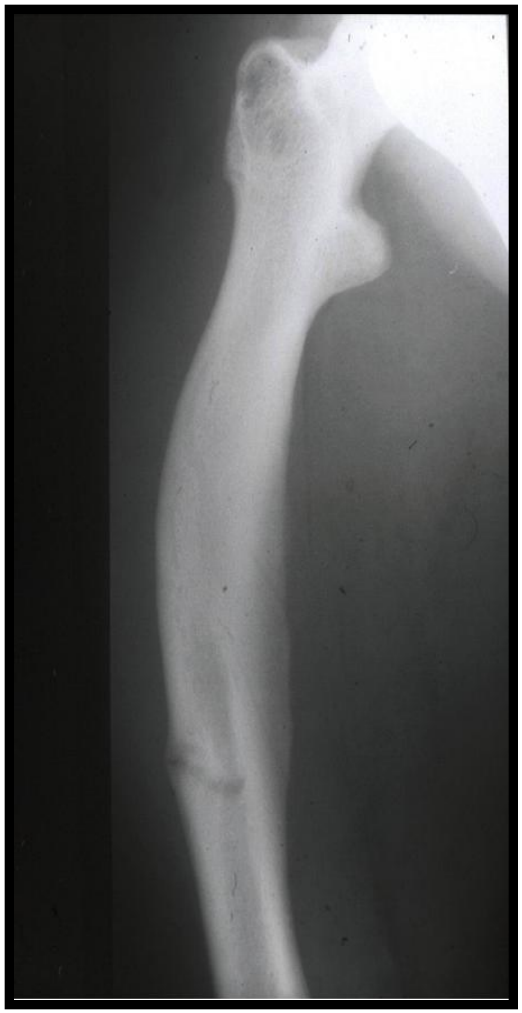


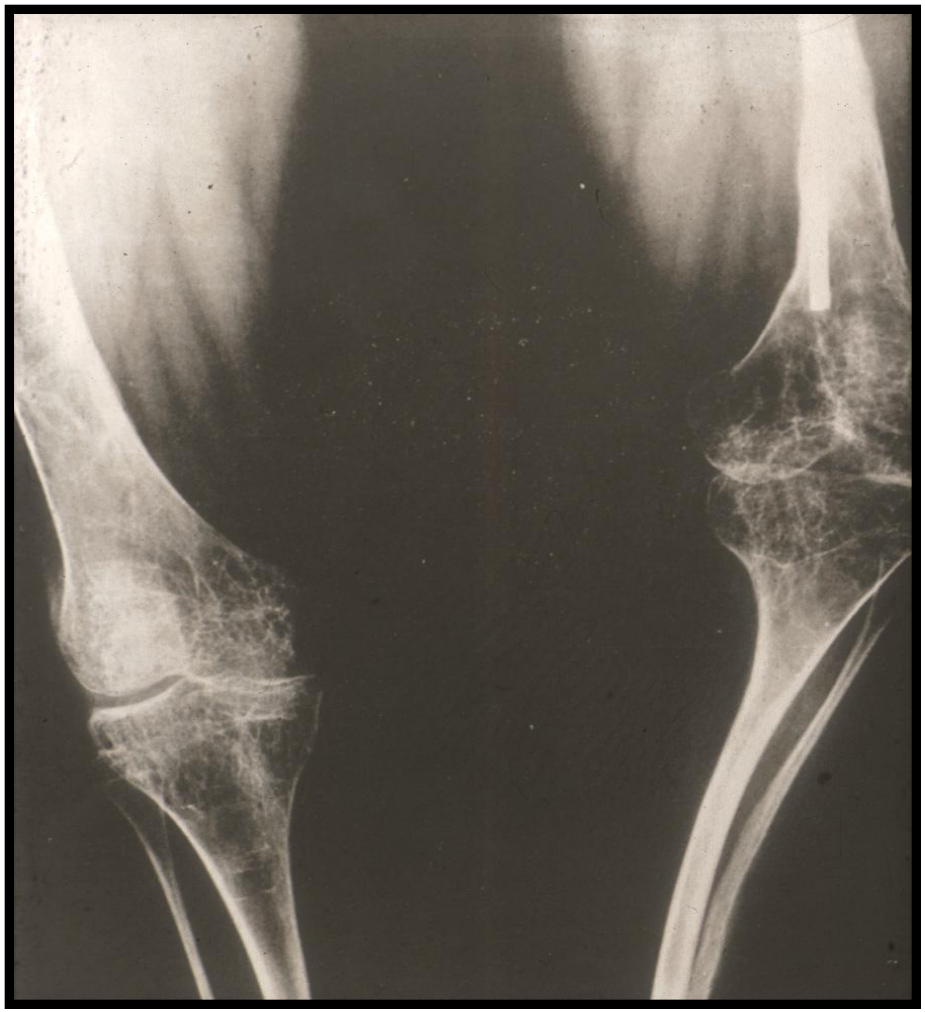
Collagen

Mineral

Landis et al, 1996

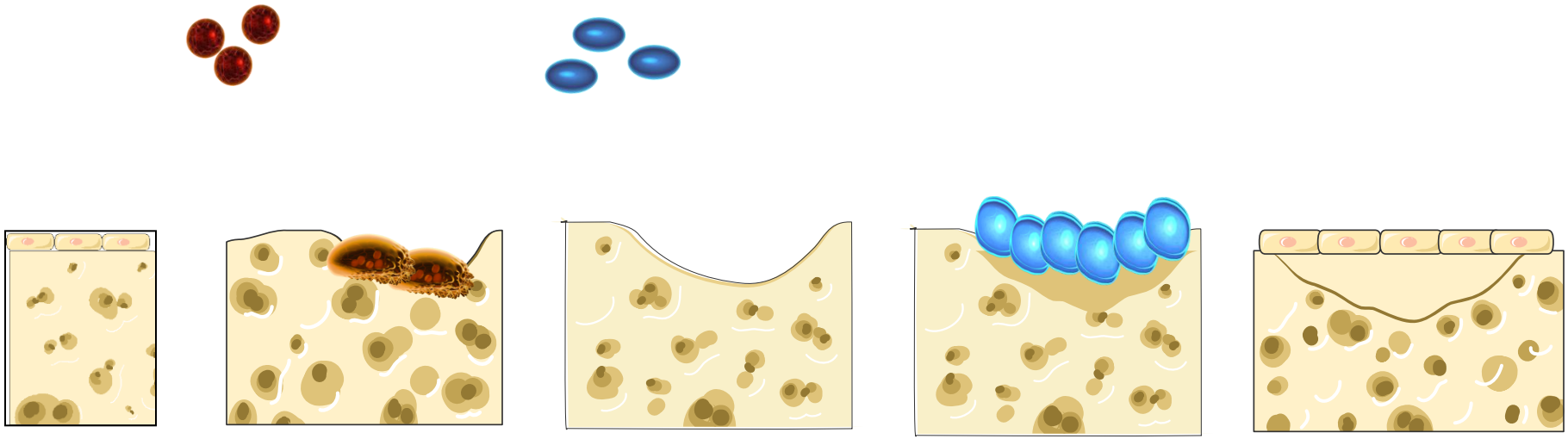
Mineral and Collagen Deficiencies



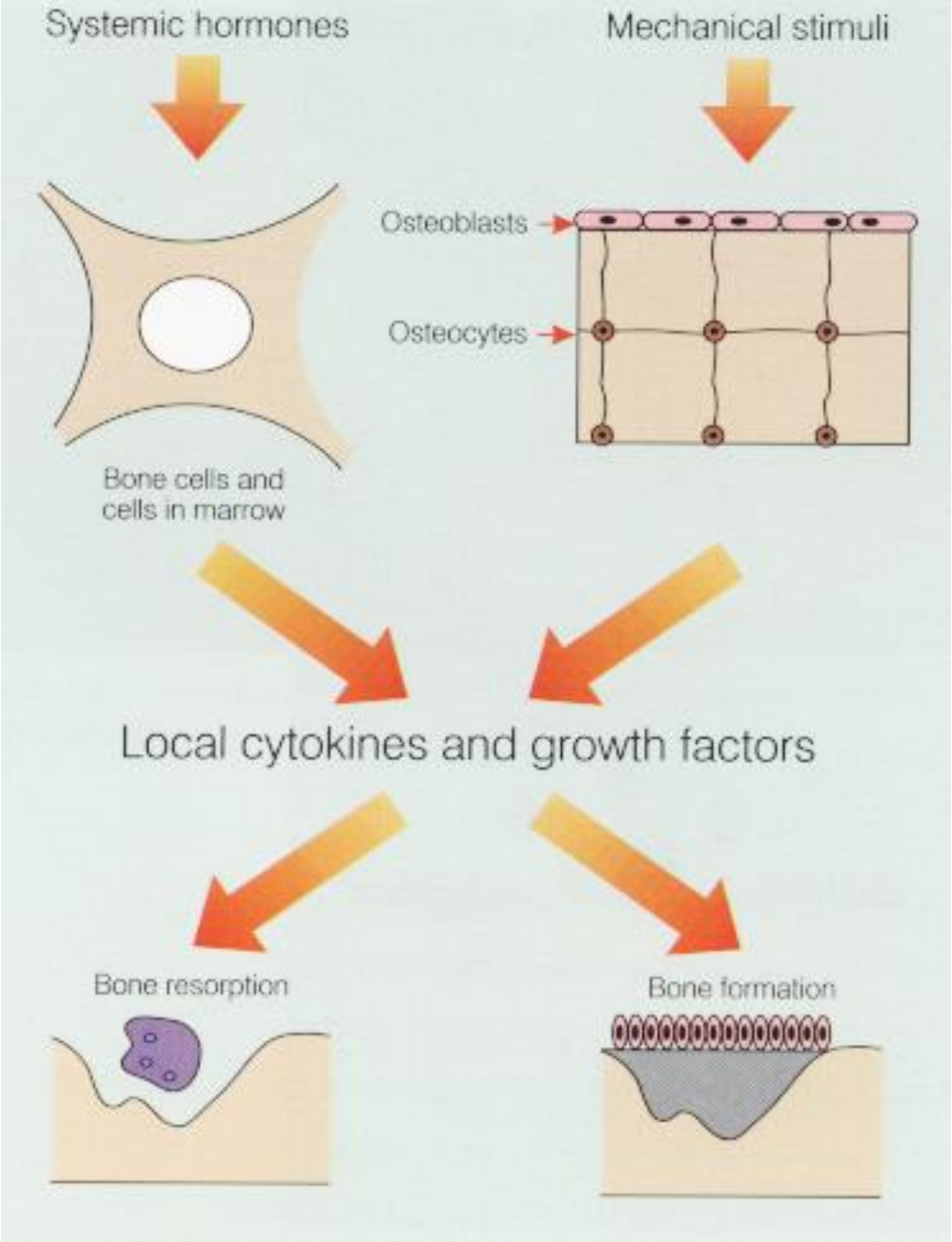


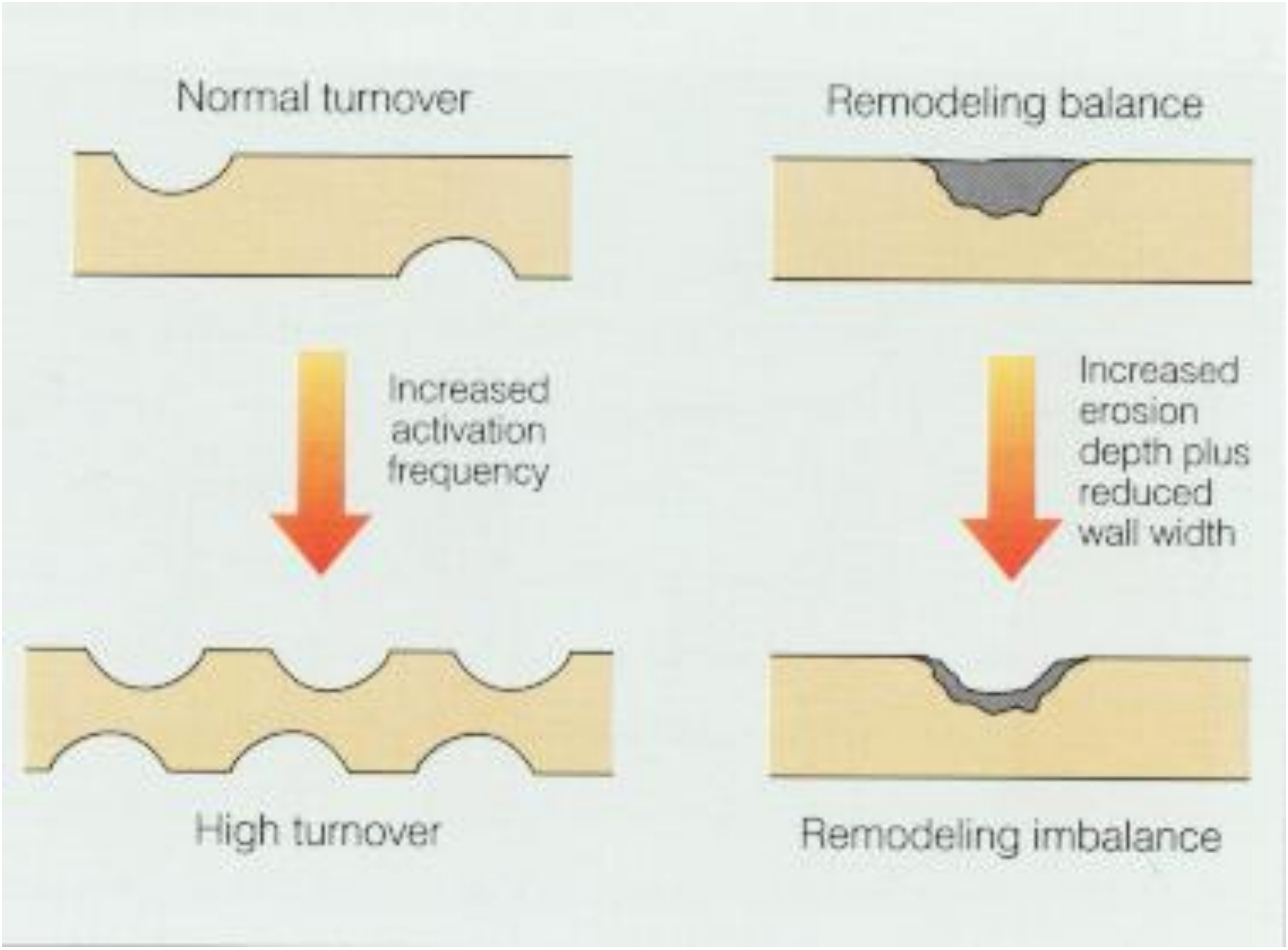
Courtesy of Dr. Papapoulos

BONE REMODELING IN ADULTHOOD

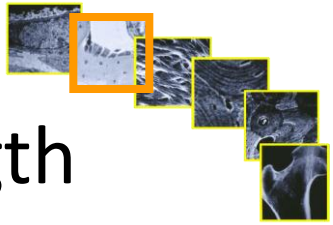


From Riggs BL et al. *J Bone Miner Res.* 2005;20:177-184.

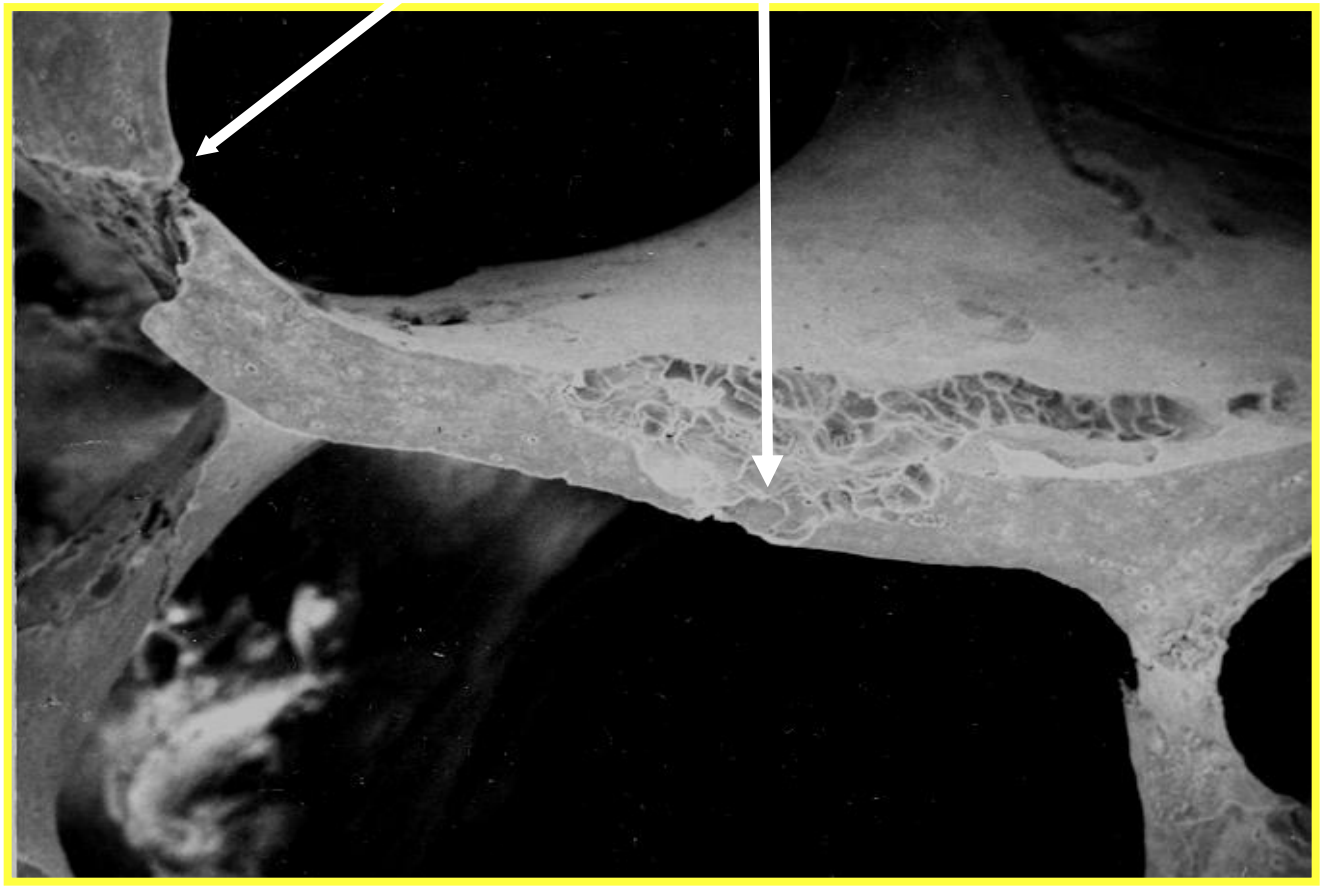

Systemic hormones
Mechanical stimuli
Osteoblasts
Osteocytes
Bone cells and
cells in marrow
Local cytokines and growth factors
Bone resorption
Bone formation


Normal turnover
Remodeling balance
Increased activation frequency
Increased erosion depth plus reduced wall width
High turnover
Remodeling imbalance

Trabecular Perforation: May Decrease Cancellous Bone Strength

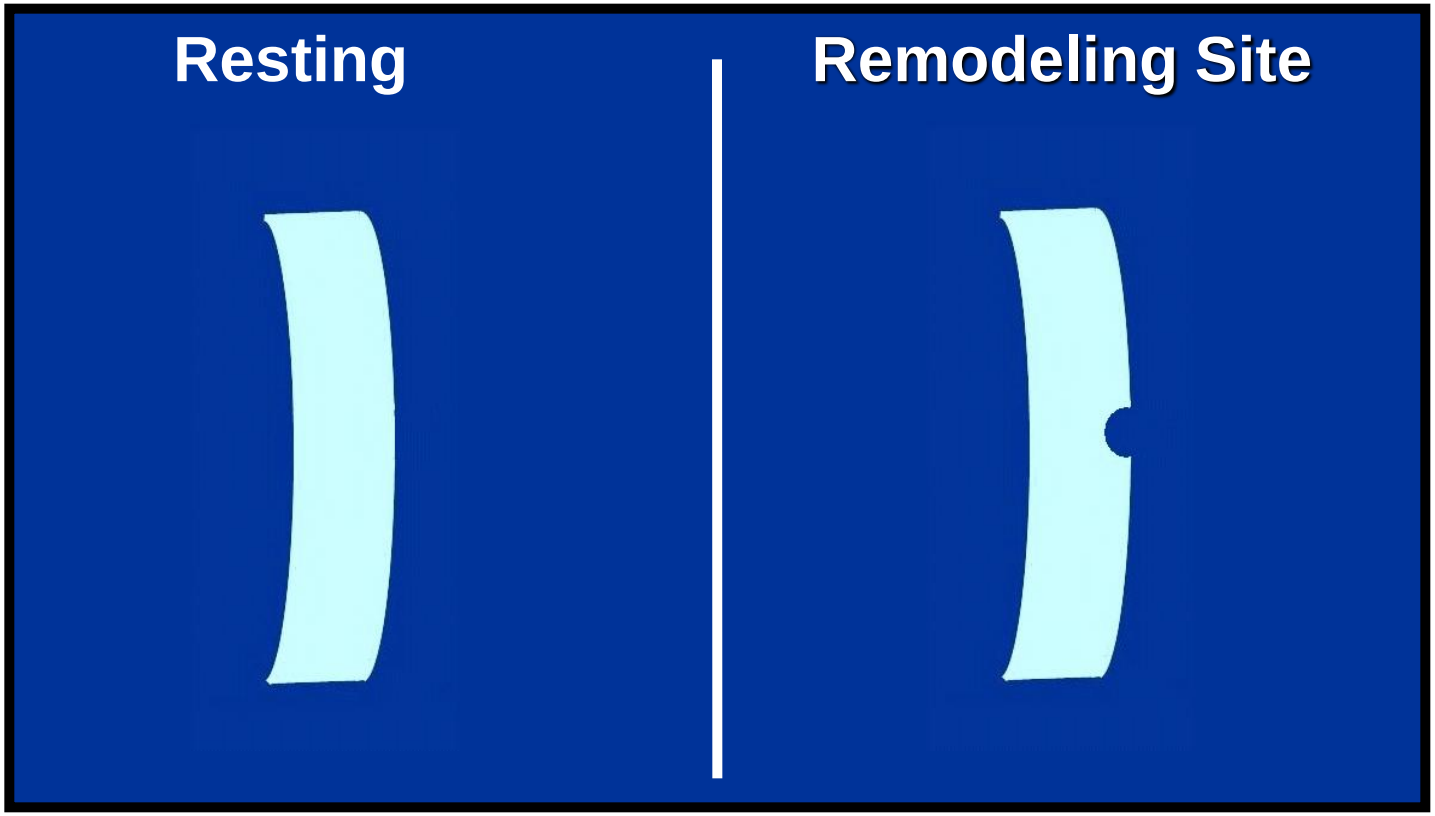


Trabecular perforations



Dempster and Lindsay ,1993

How Increased Remodeling Can Predispose to Bone Fragility



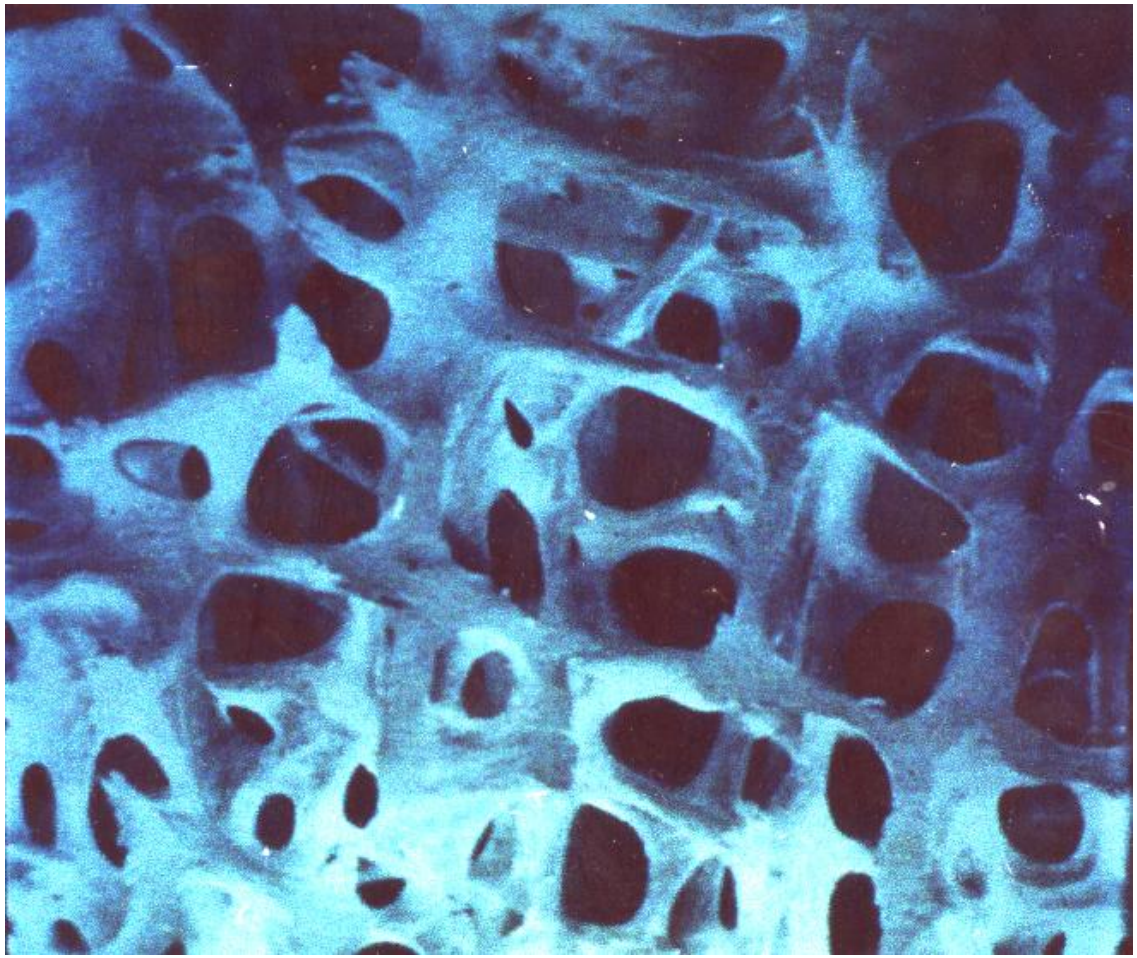
Parfitt AM, 1991

Definition: Osteoporosis

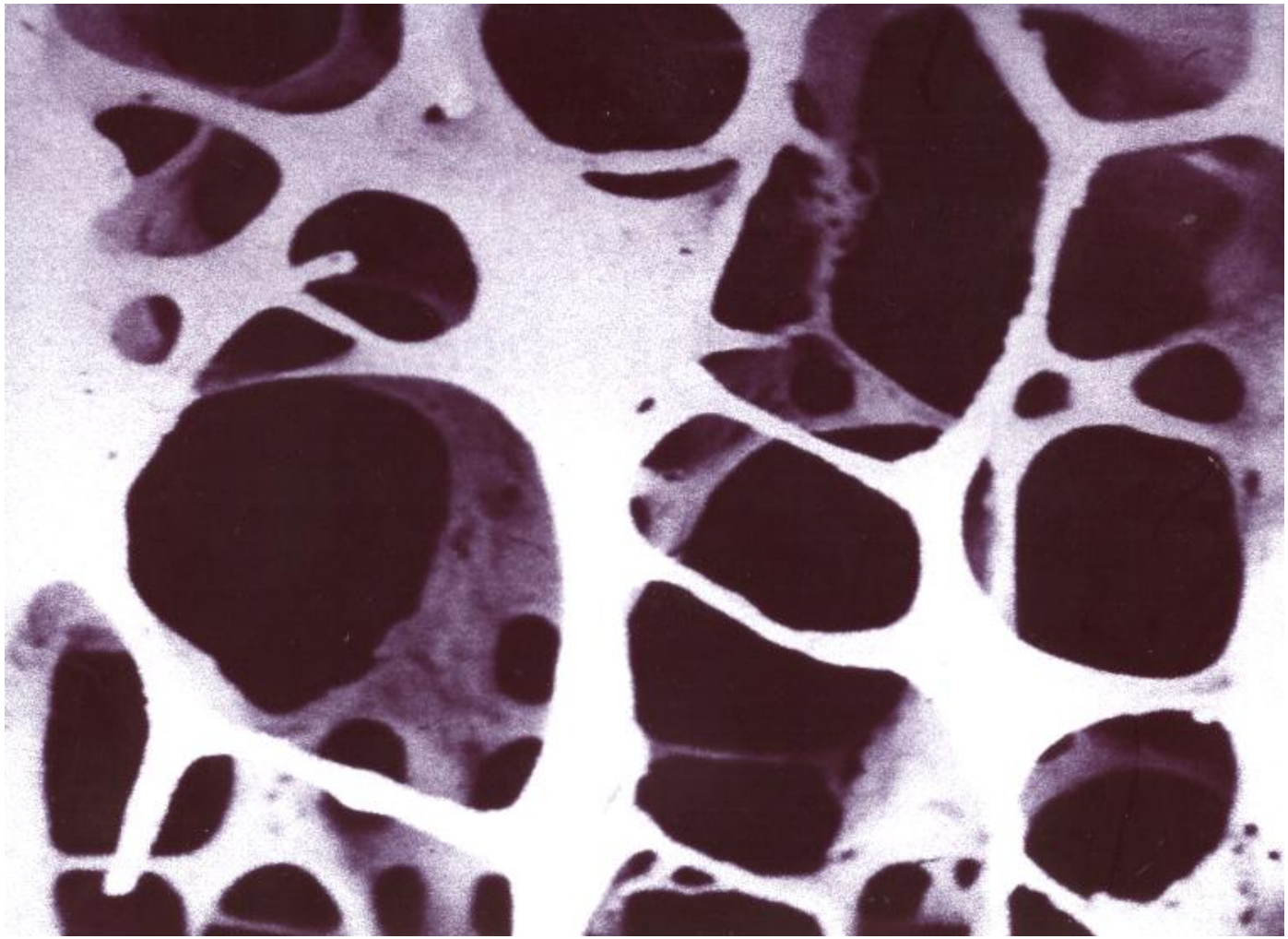
A systemic skeletal disease characterised by:

- Low bone mass
- Micro architectural deterioration of bone tissue
- Increased bone fragility
- Susceptibility to fracture

Normal bone



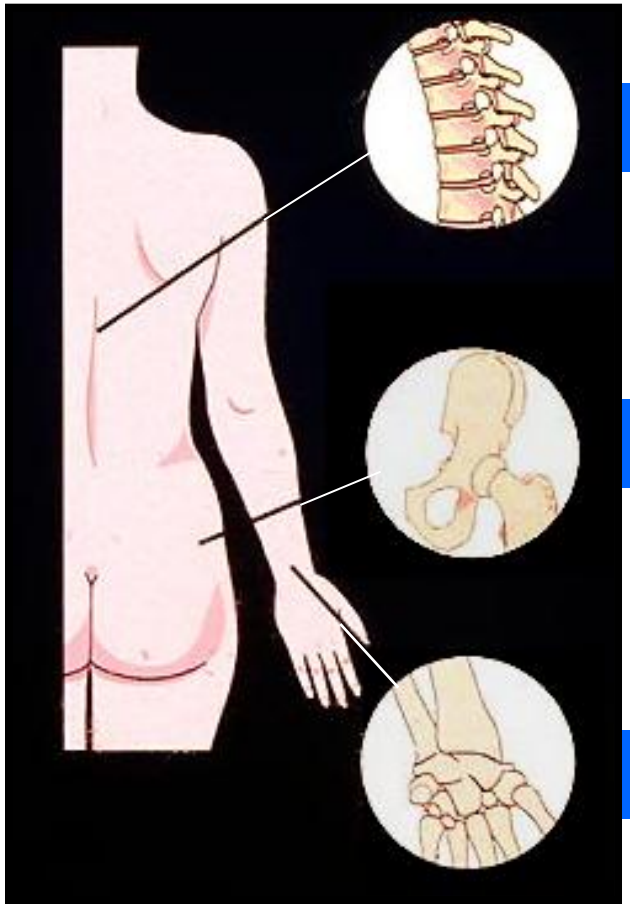
Osteoporotic bone



Clinical picture of osteopososis

- Asymptomatic
- Low trauma fractures
- Stress fracture
- Wrist fracture
- Vertebral fracture
- Hip fracture

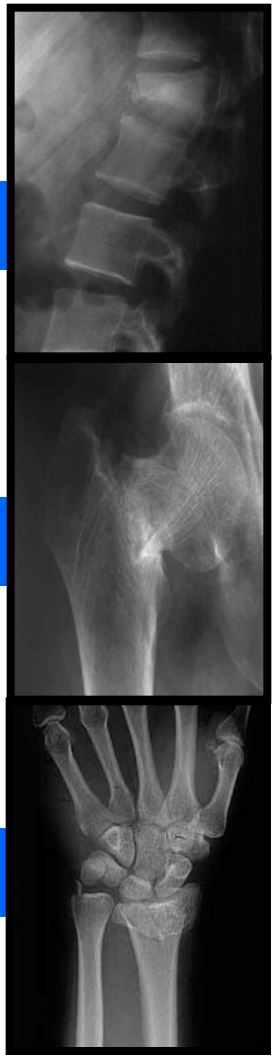
Osteoporosis:
Common Fracture Sites



Spine

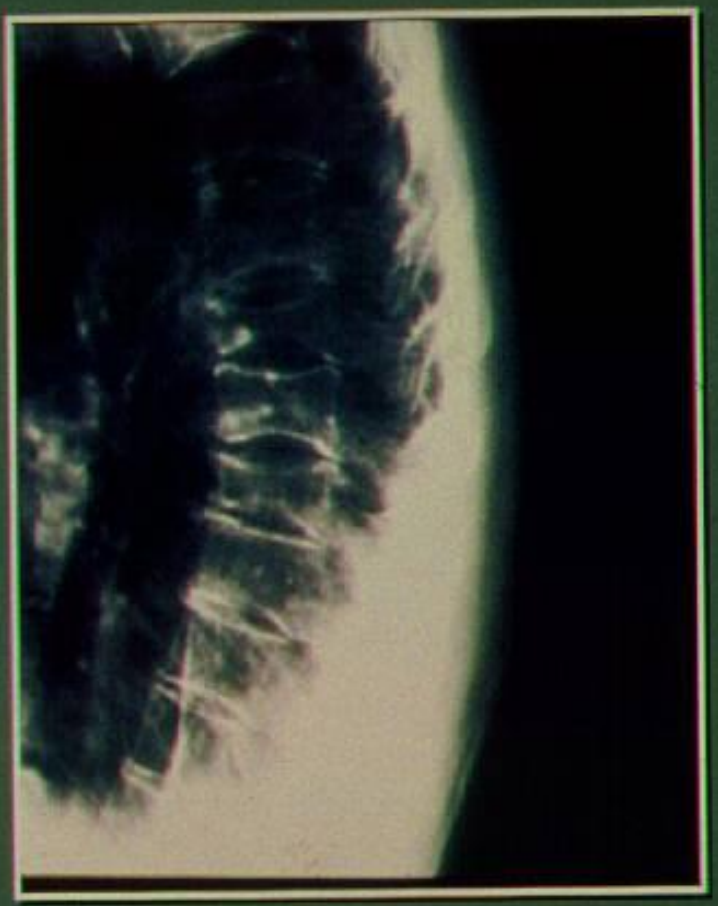
Hip

Wrist



Courtesy of J A Kanis

Osteoporosis – Clinical view



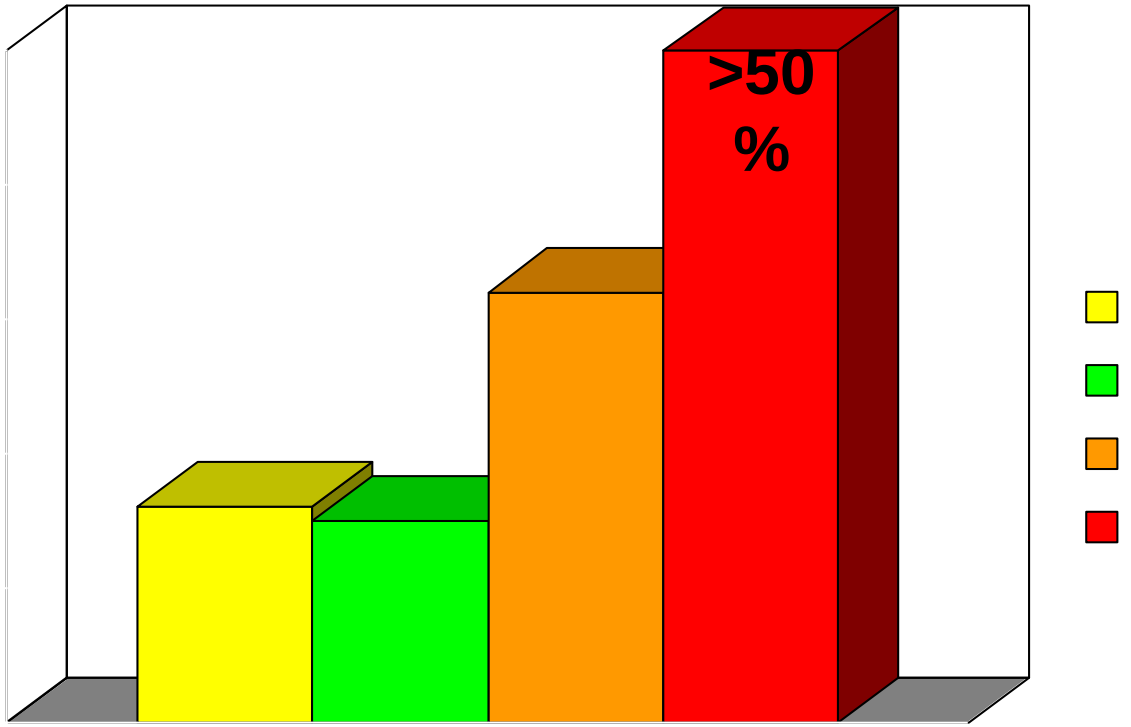
Estimated lifetime fracture risk (at 50 years-old)

	Women	Men
Hip	17.5 (16.8-18.2)	6.0 (5.6-6.5)
Vertebra	15.6 (14.8-16.3)	5.0 (4.6-5.4)
Forearm	16.0 (15.7-16.7)	2.5 (2.2-3.1)
Any of the above	39.7 (38.7-40.6)	13.1 (12.4-13.7)

(breast cancer: 9%
cardiovascular disease: 40%)

Melton 1991

Lifetime Fracture Risk: a 50 Year Old White Woman

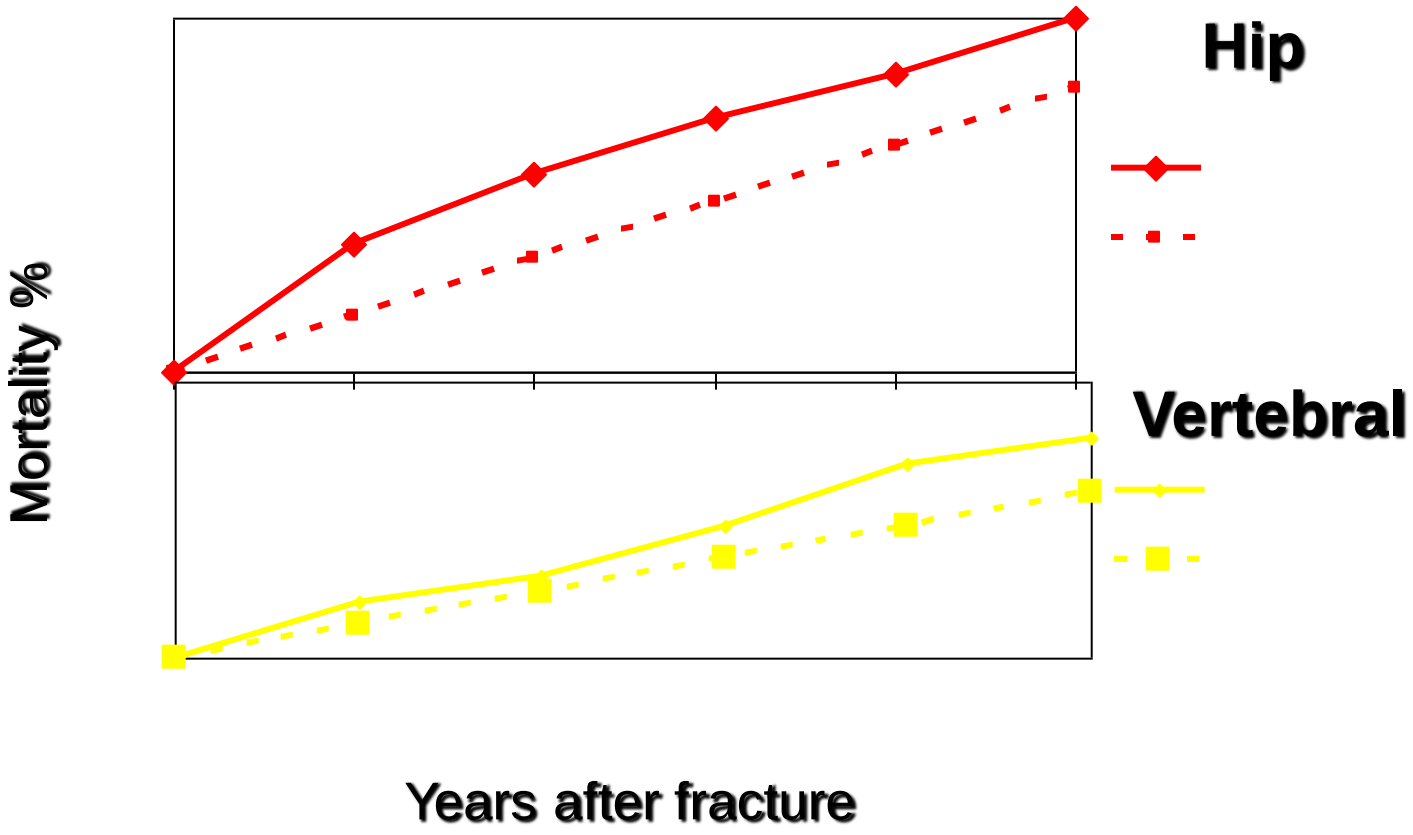


Consequences of Osteoporosis

- Increased morbidity
  - acute pain and temporary disability
  - deformity, permanent disability, lower quality of life
- Increased mortality
  - Following hip and vertebral fracture

*Cooper 1997. Am J Med 103(2A):12S-19S

Mortality Following Hip and Vertebral Fractures



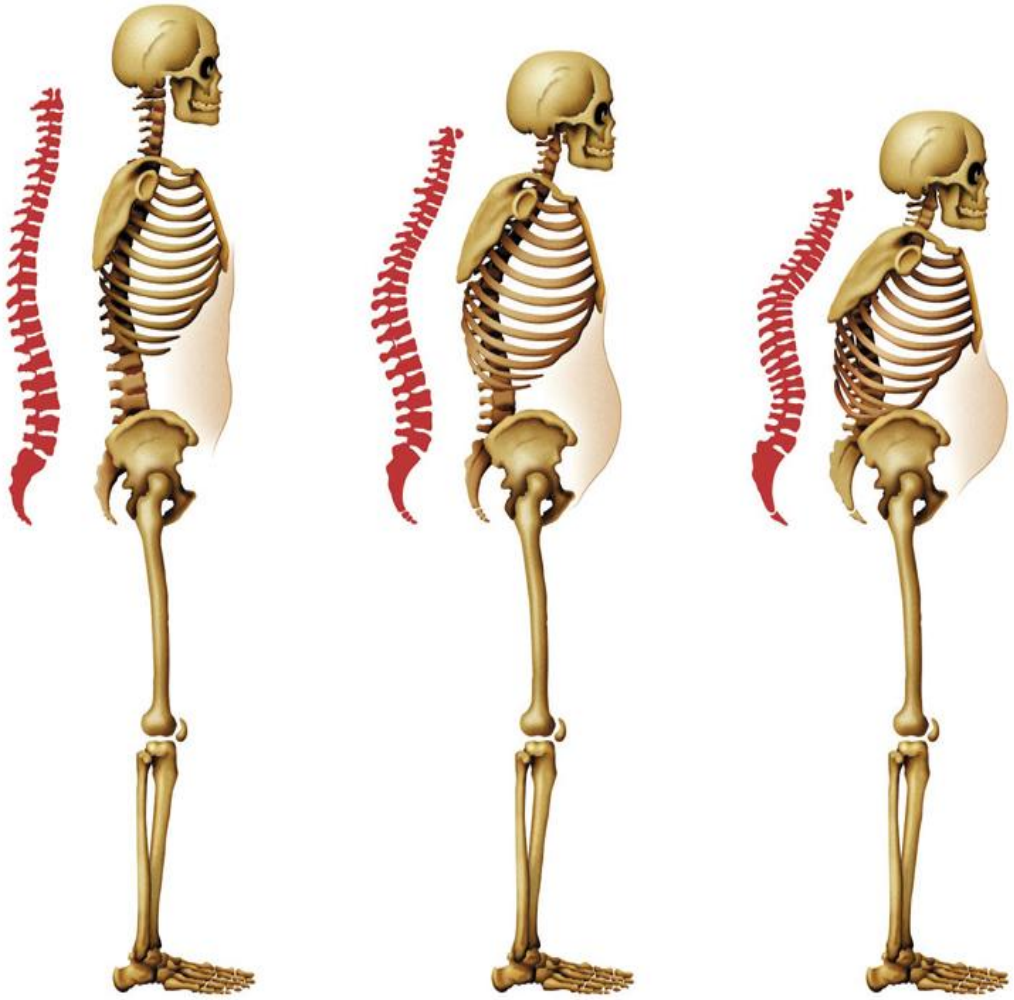
Source: Cooper 1997. Am J Med 103(2A):12S-19S

Hip Fracture Outcomes

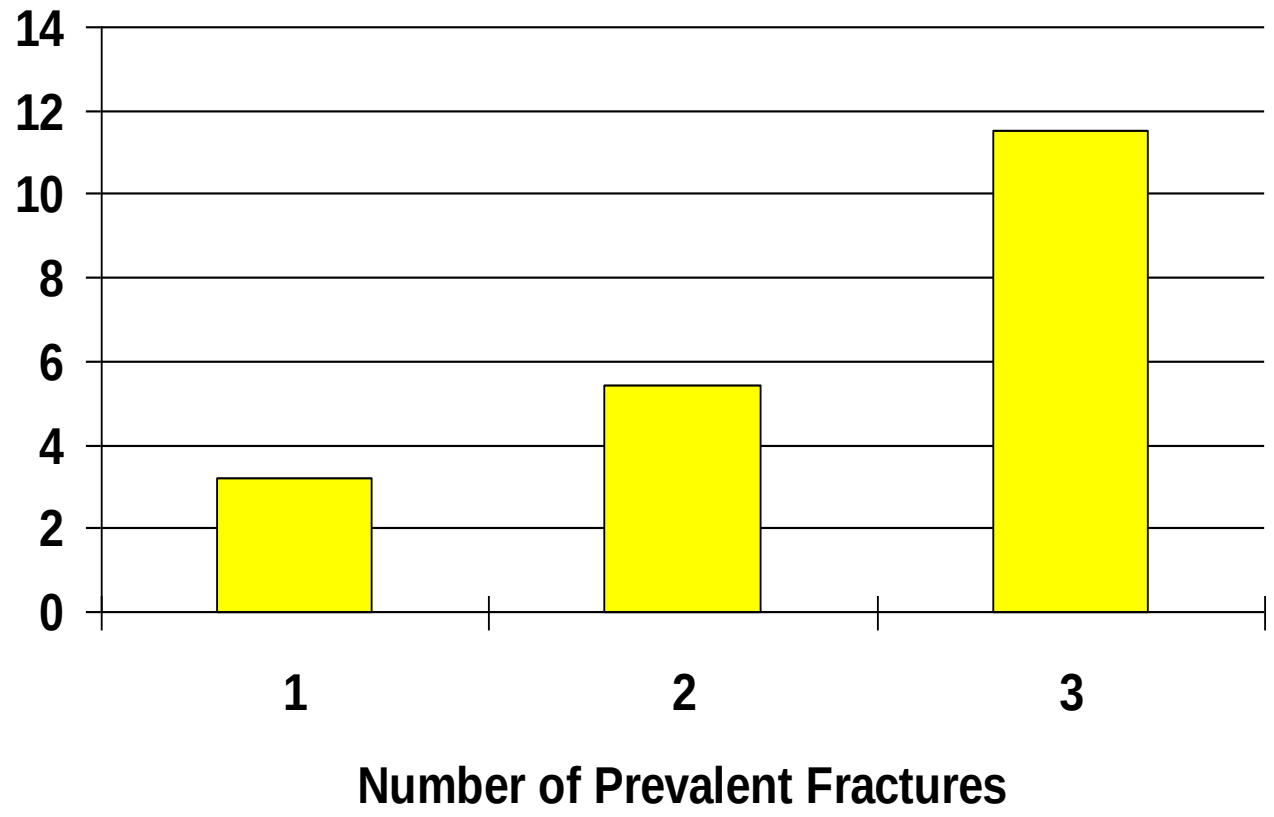
- **24% mortality rate within first year***
- **30% mortality rate in men after first year**
- **50% of patients are unable to walk without assistance†**
- **~ 33% are totally dependent‡**
- **Up to 95% of women with recent hip or wrist fracture were not being treated with anti-osteoporotic regimens§**

Ray NF et al. *J Bone Miner Res*. 1997;12:24-1235.
†Riggs BL, Melton LJ III. *Bone.* 1995;17(5 suppl):505S-511S.
‡Kannus P et al. *Bone.* 1996;18(1 suppl):57S-63S.
§Torgerson D, Dolan P. *Ann Rheum Dis.* 1998;57:378–379.

Vertebral Fractures:
Can Result in Physiological Changes



Prevalent Fractures and Future Fracture Risk



Black et. al, 1999

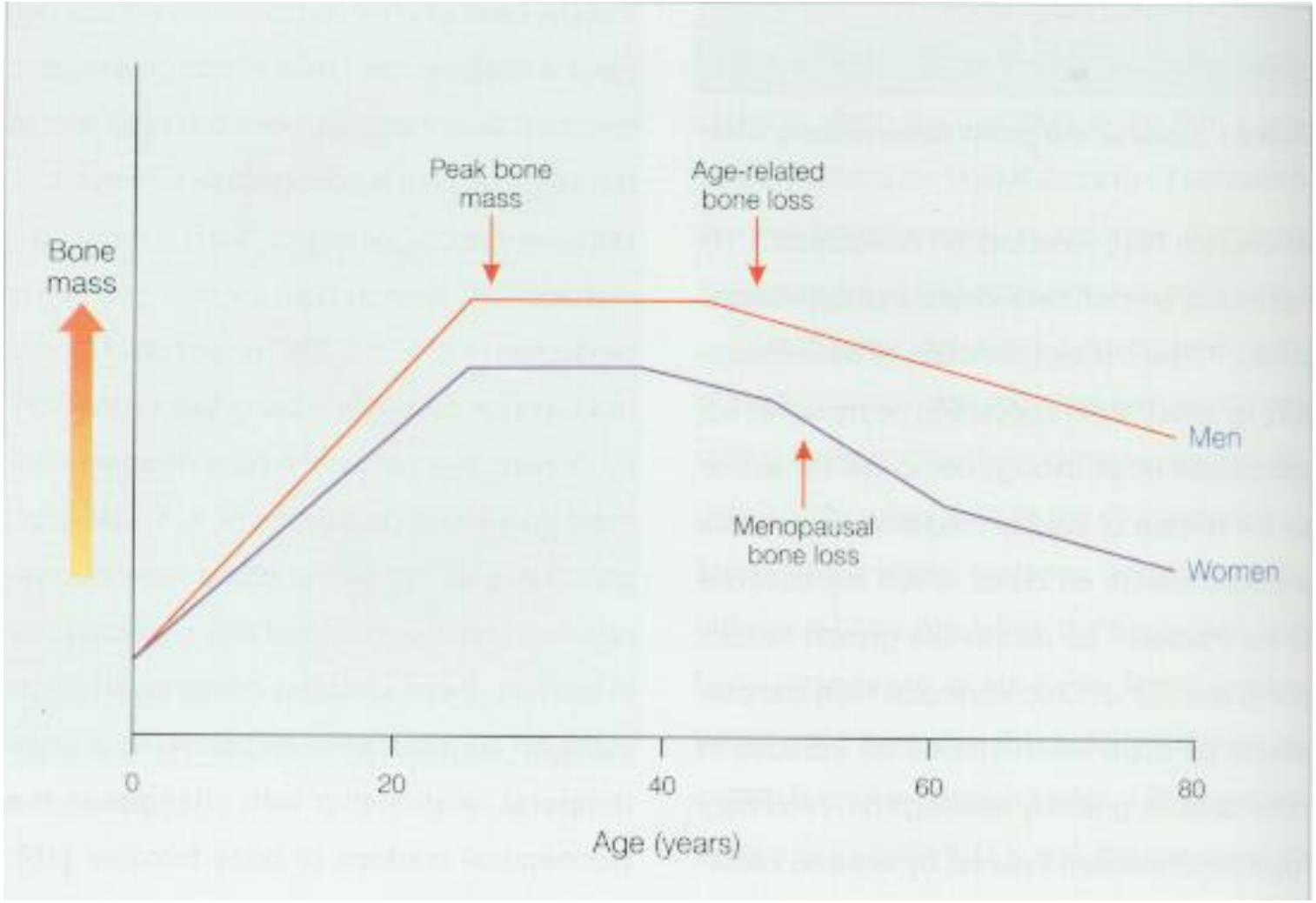
Public Health Issues - Osteoporosis in US

- In 1995, osteoporosis caused:
  - 3 million fractures
  - 100,000 deaths
  - 432,000 hospitalizations
  - 2.5 million outpatient visits
  - 180,000 nursing home admissions
  - $13.8 billion in direct healthcare expenditures
    - approximately 40% of cost due to non-hip fractures

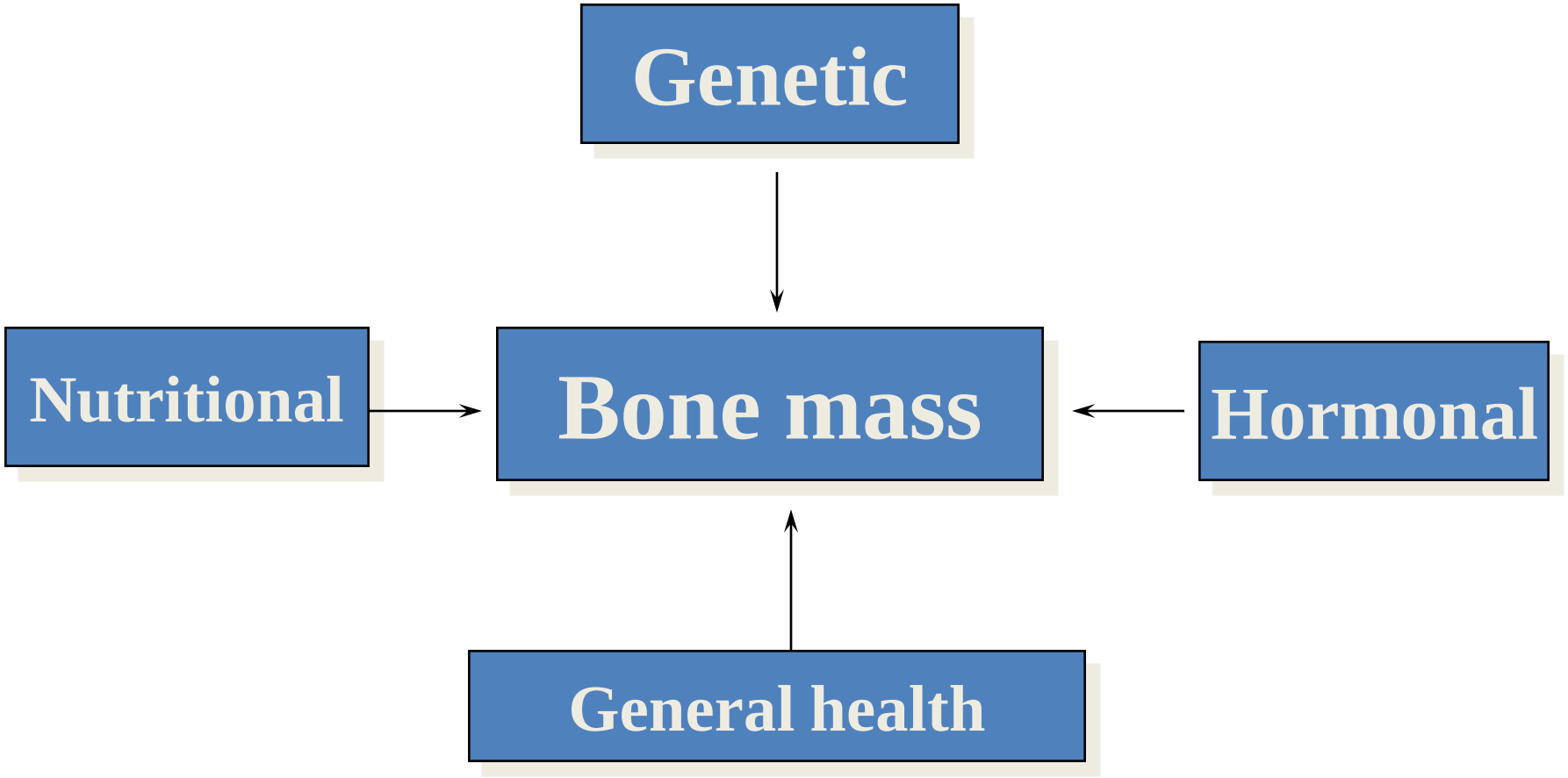
Ray, NF et al., JBMR 1997

Why do we get osteoporosis:

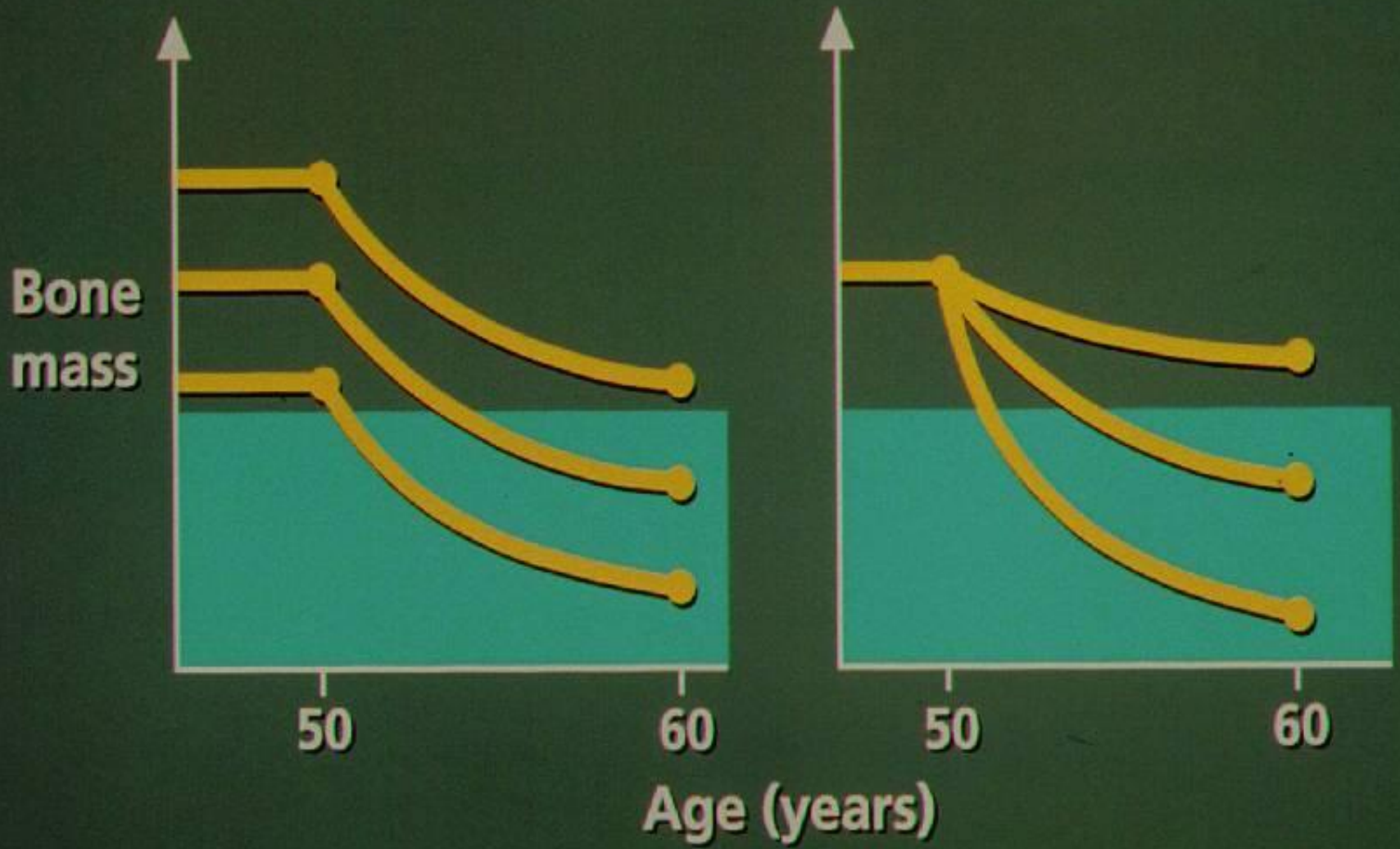
Lifetime changes in bone mass



Factors affecting peak bone mass



Development of osteoporosis: Peak bone mass vs. rate of bone loss



Risk factors for osteoporosis

- Age
- Caucasian or Asian
- Previous fragility fracture
- Positive family history
- Early/surgical menopause/Estrogen deficiency/ hypogonadism in men
- Low body mass index (<19 kg/m^2)

Lifestyle factors

- Diet:
  - Low calcium
  - High protein
  - Chronic high sodium
- Caffeine
- Phosphate beverages
- Smoking
- Alcohol
- Physical activity

Secondary causes of osteoporosis

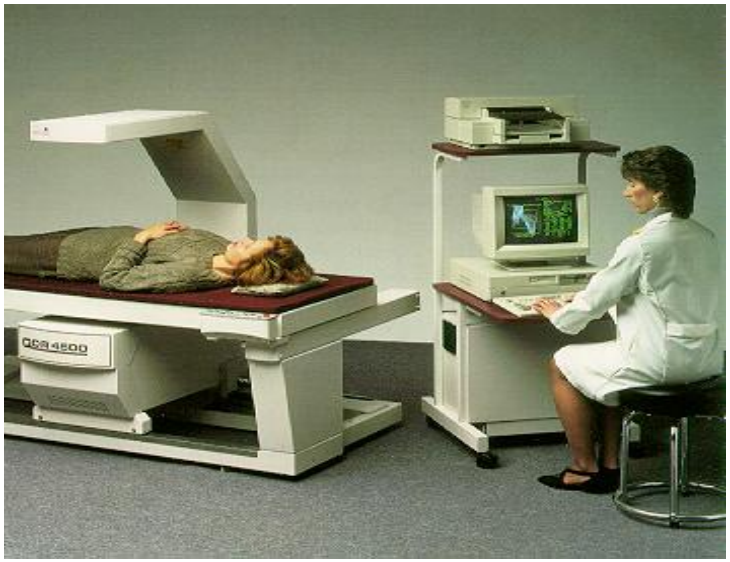
- Drugs
  - Corticosteroids, Thyroxine
- Endocrine diseases
- Gastric surgery
- Multiple myeloma
- Hypopituatirism
- Inflammatory diseases
- Hypogonadism

Evaluation of osteoporosis:

- It’s all about risk

Osteoporosis: Diagnosis

- **Bone density is the most important predictor of fracture risk**
- **Central dual-energy x-ray absorptiometry (DEXA) is the gold standard for diagnosis**



Bone Mineral Density

Category	T - score
Normal	> -1.0
Osteopenia	-1 to -2.5
Osteoporosis	≤-2.5
Severe/established osteoporosis	≤-2.5 and prescence of one or more fractures

Role of BMD in Fracture Prevention:

- **60%–80% of bone strength is related to BMD**
- **Decreases in bone density correspond to increases in fracture risk**
- **Increases in bone density correspond to fracture risk reduction**

Who do we send for BMD testing?

- Risk factors for osteoporosis
- Use of any drugs that can affect bone
- Any illness that affects bone
- Low trauma fracture
- Radiographic osteopaenia

Evaluation of Osteoporosis

- Evaluate risk factors
- Evaluate for secondary causes
  - Full blood count, ESR
  - Liver functions, protein electrophoresis
  - Ca, Phosphate, parathyroid hormone, 25(OH) Vitamin D
  - Urine for Ca
  - Thyroid functions
  - Gonadal hormones
  - Markers of bone turnover

Bone markers:

- Bone formation:
  - Bone Specific ALP
  - Osteocalcin
- Bone resorption products
  - Pyridium crosslinks: Deoxypiridinoline
  - NTX
  - CTX

How do we decide on whether to treat:

FRAX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File Edit View Document Comments Forms Tools Advanced Window Help
Create PDF Combine Files Export Start Meeting Secure Sign Forms Review & Comment
4 / 13 125% Find
significance for hip fracture probability, with a family fracture there was a fourfold increase in fracture probability.
FRAX™ WHO Fracture Risk Assessment Tool
HOME CALCULATION TOOL PAPER CHARTS FAQ REFERENCES
Select a Language
Calculation Tool
Please answer the questions below to calculate the ten year probability of fracture with BMD.
Country : UK
Name / ID :
About the risk factors
Questionnaire:
1. Age (between 40-90 years) or Date of birth
Age: 60
Date of birth: Y: M: D:
2. Sex Male Female
3. Weight (kg) 62
4. Height (cm) 168
5. Previous fracture No Yes
6. Parent fractured hip No Yes
7. Current smoking No Yes
8. Glucocorticoids No Yes
9. Rheumatoid arthritis No Yes
10. Secondary osteoporosis No Yes
11. Alcohol 3 more units per day No Yes
12. Femoral neck BMD
Select
Clear Calculate
BMI 21.9
The ten year probability of fracture (%)
without BMD
Major osteoporotic 14
Hip fracture 4.43
Weight Conversion:
pound:
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Height Conversion:
inch :
convert
Fig. 1 Input and output for the FRAX™ model
Springer
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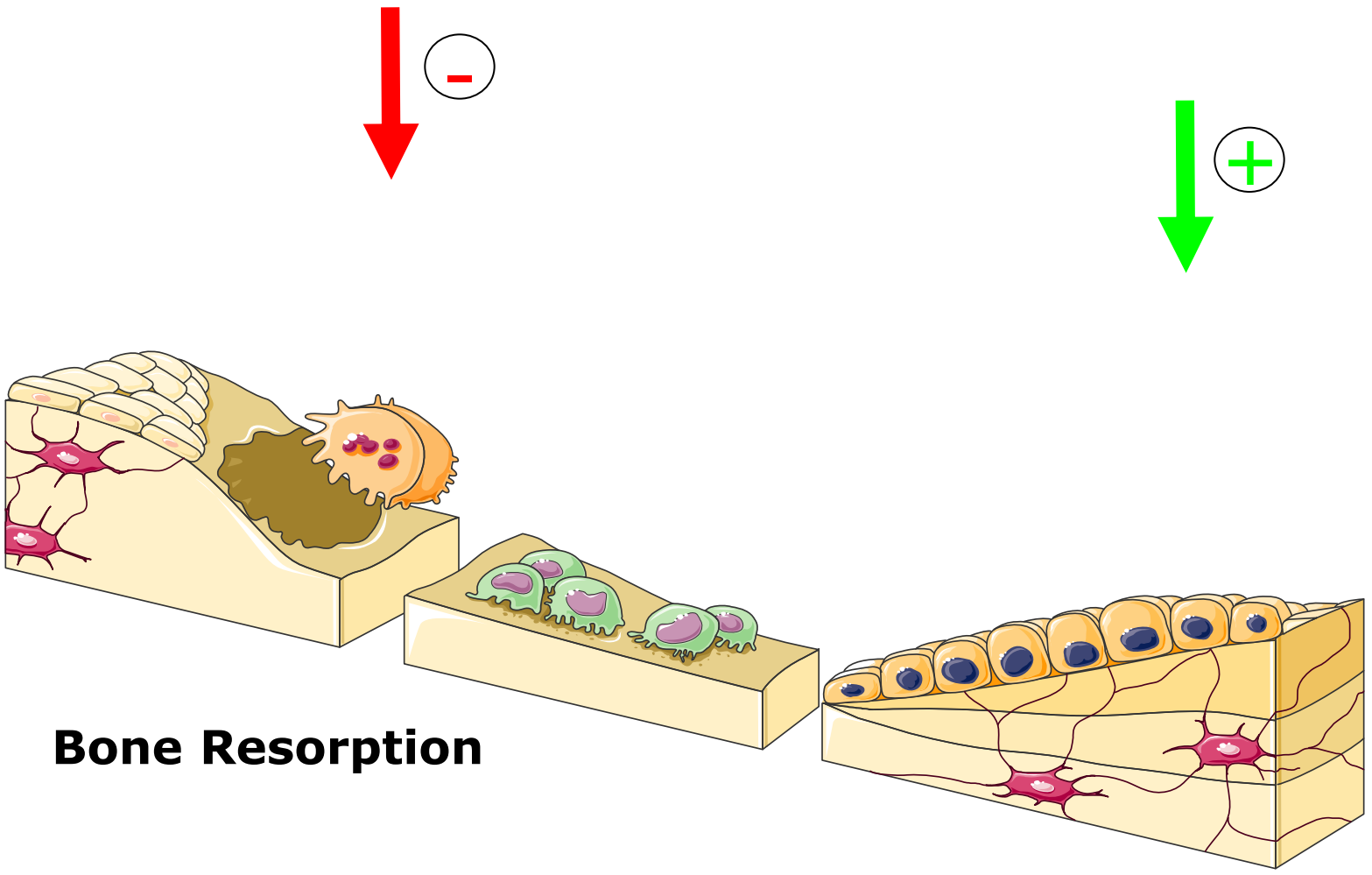
Treatment modalities

- Adequate nutrition
- Regular physical activity
- Avoid unhealthy lifestyle
- Pharmacologic treatment

Pharmocologic treatment

- Improving bone strength

Osteoporosis: Treatment targets



Treatment of osteoporosis

- Calcium and vitamin D
- Anti-resorptive
  - HRT
  - Raloxifene
  - Bisphosphonates
  - Strontium
- Anabolic agents
  - PTH
  - Strontium

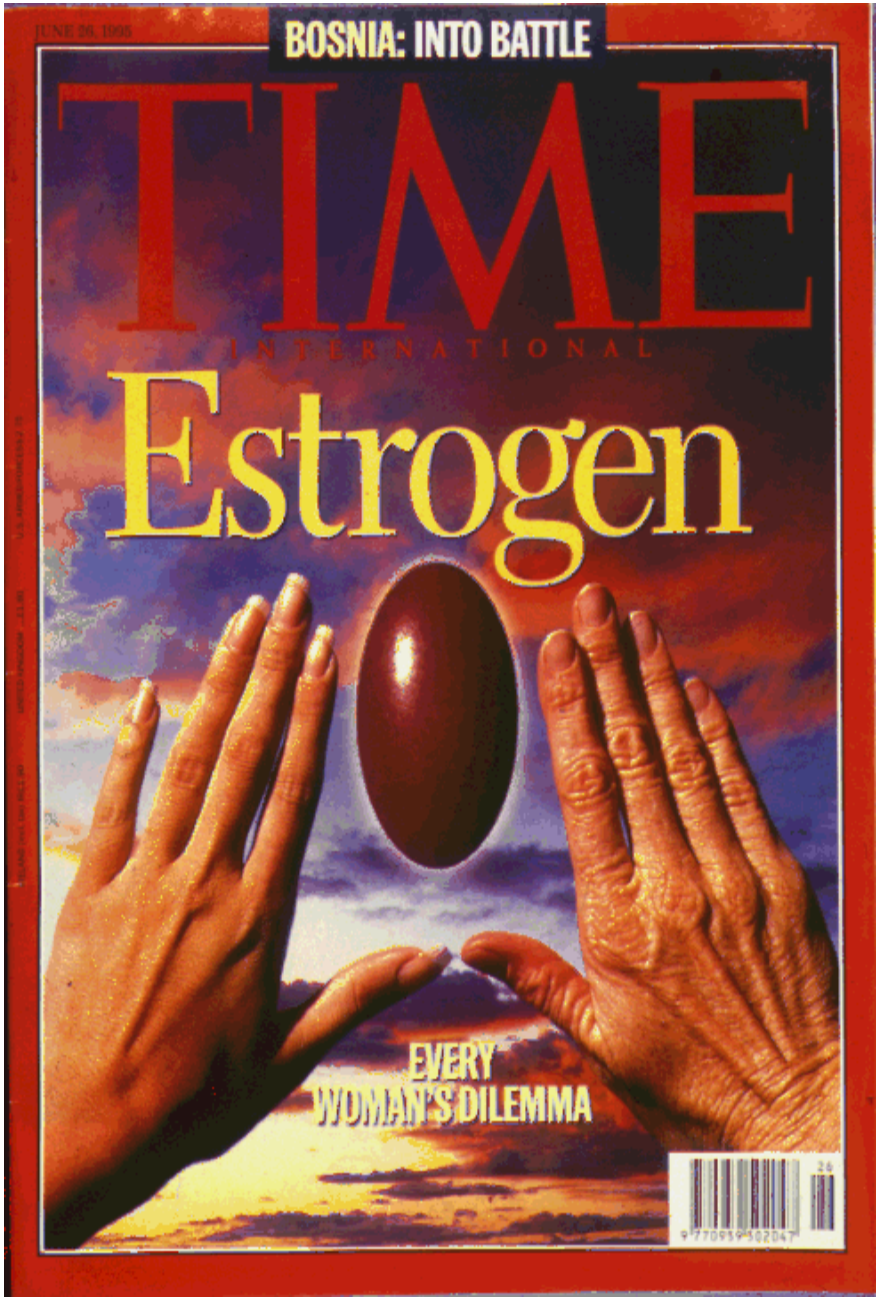
Calcium in osteoporosis

- Help achieve better peak bone mass
- To maintain bone mass
- Prevent age related bone mass loss

Vitamin D

Vitamin D supplementation

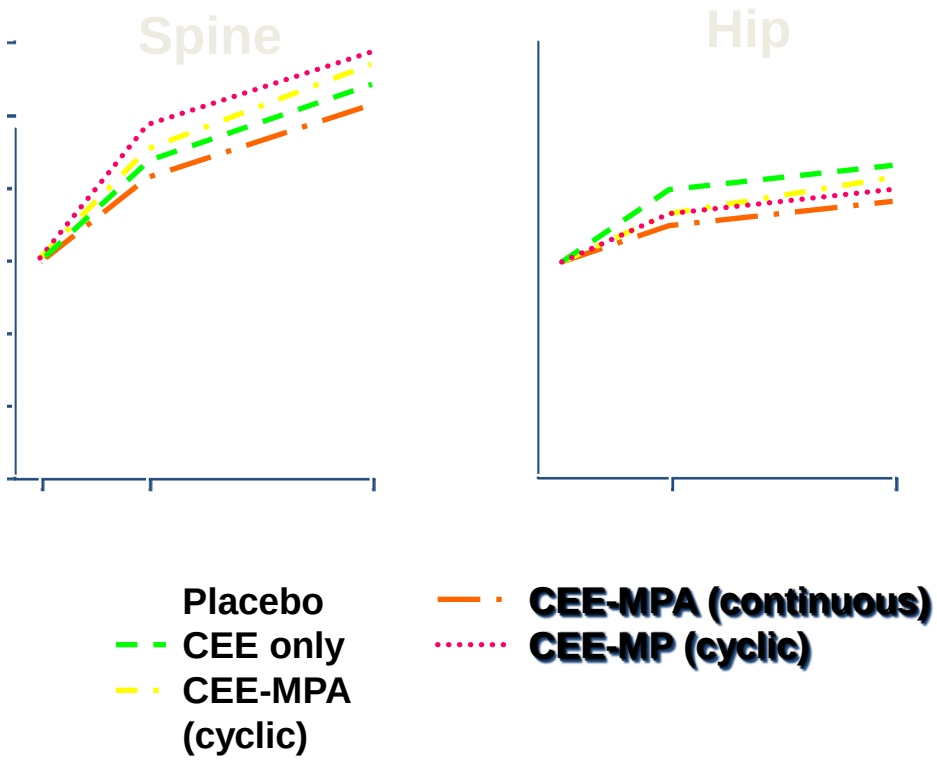
- Normal diet 200IU/day
- Minimal non-toxic dose 2000IU /day
- Day in the sun 10000 IU/ day


JUNE 26, 1995
BOSNIA: INTO BATTLE
TIME
INTERNATIONAL
Estrogen
EVERY WOMAN'S DILEMMA

HRT: Benefits

- **Improvement or maintenance in bone mass**
- **Relief of vasomotor symptoms**
- **Risk reduction of cardiovascular disease?**
- **Potential benefits for:**
  - **Alzheimer's disease**
  - **Age-related macular degeneration**
  - **Colon cancer**

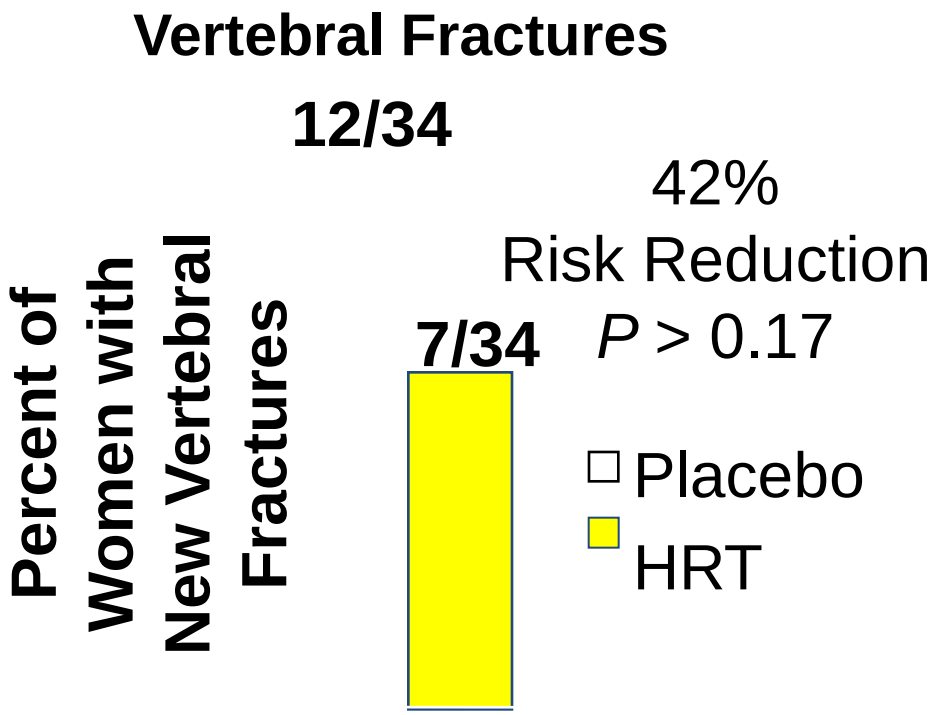
HRT: Effect on BMD Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial



CEE, conjugated equine estrogen; continuous administration (daily throughout the month); cyclic administration (days 1–12 of each month); MPA, medroxyprogesterone acetate; and MP, micronized progesterone.

The Writing Group for the PEPI Trial. *JAMA.* 1996;276:1389-1396.

HRT: Effect on Fracture Reduction



When analyzed using the numbers of fractures method, a 61% risk reduction was observed ($P = 0.04$)

Hip Fractures

- **No prospective data studying hip fracture risk reduction with HRT**
- **Thought to be reduced by 50%, based on epidemiological data**

4 Years of HRT Had No Effect on the Risk of Non-spine Fractures

Type	E + P	Placebo	RH	p-value
Hip	**12**	**11**	**1.1**	**.82**
Any	**130**	**138**	**1.0**	**.70**

Hormone replacement therapy

Clinical Synthesis Panel on HRT

Lancet1999:354;152-155

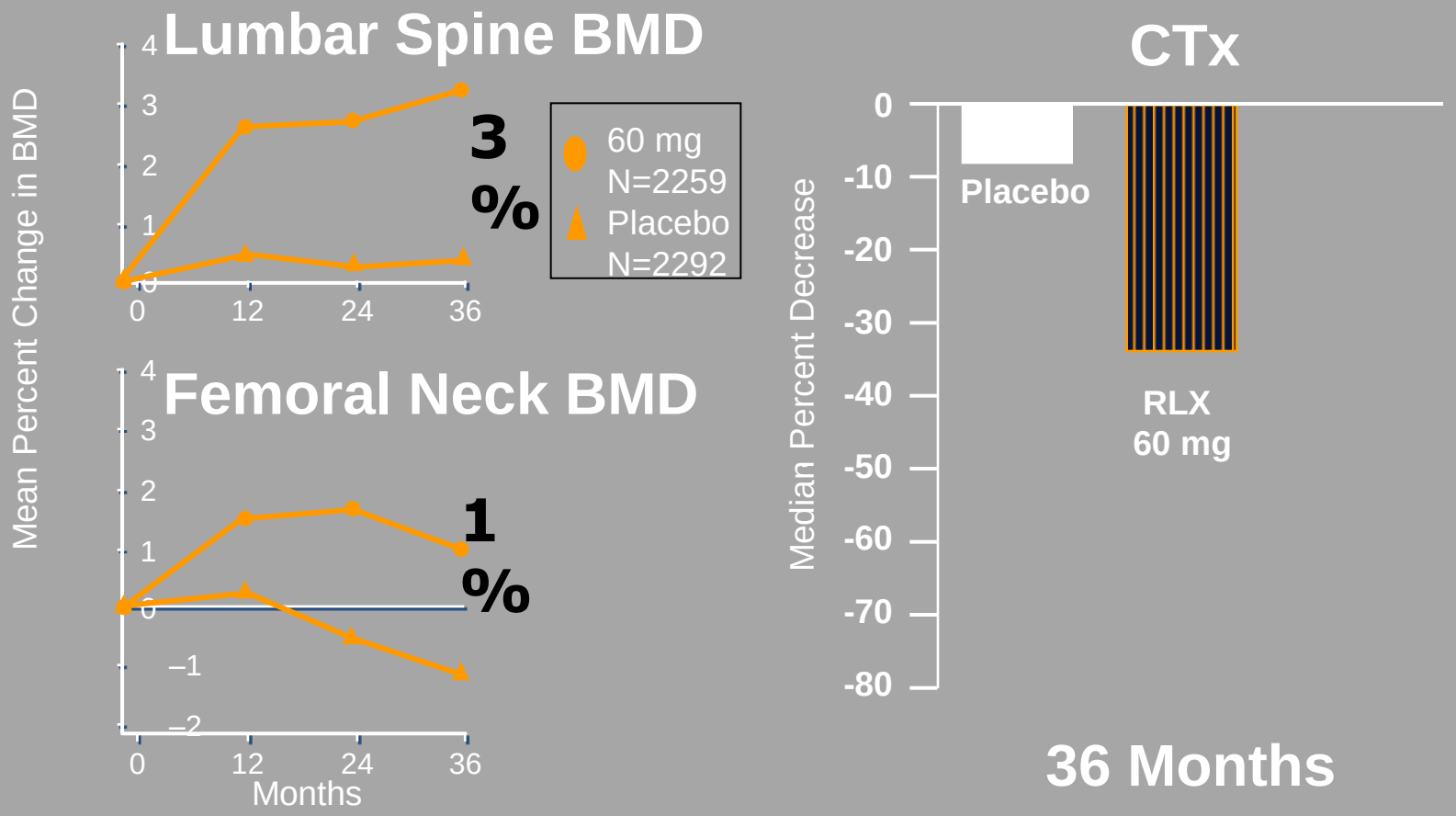
- Few prospective controlled trials
- Lowest dose that adequately prevents fracture unknown
- Long term use necessary to reduce fractures

Selective Estrogen Receptor Modulators (SERMs)

TAMOXIFEN (Nolvadex)

RALOXIFENE (Evista)

Raloxifene: Effect on BMD and Bone Turnover (MORE)



Ettinger B et al. *JAMA.* 1999;282:637-645.

Raloxifene: Benefits and Risks

Benefits

- Improved bone mass
- Reduced number of vertebral fractures
- No breast tenderness
- No uterine bleeding or spotting
- Potential for reduced risk of breast cancer

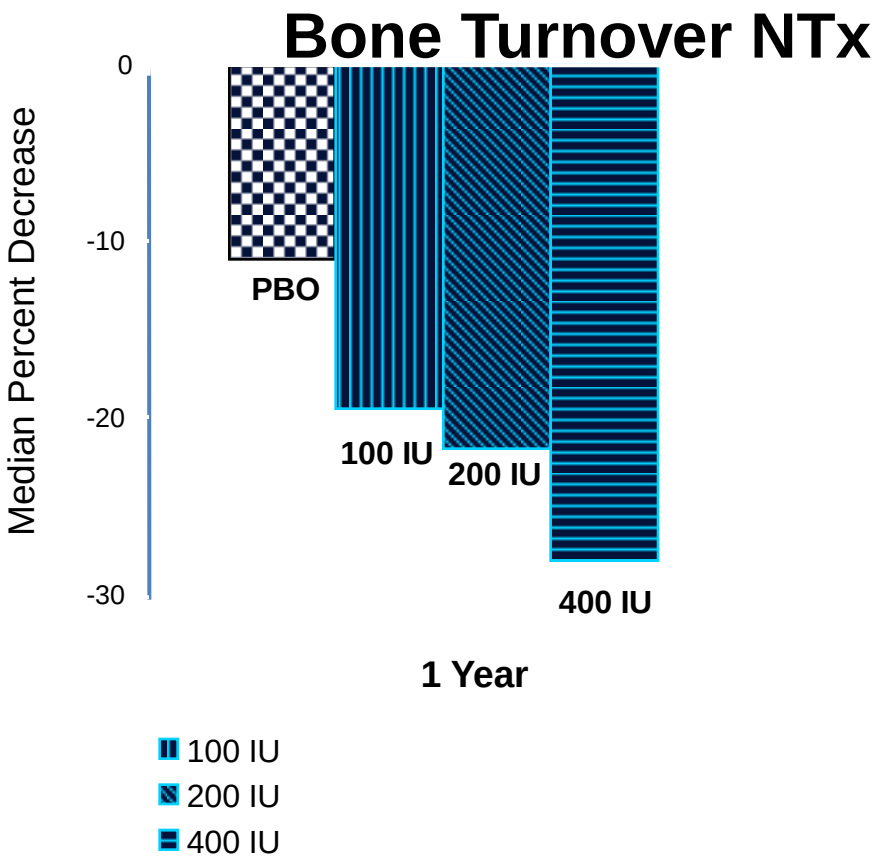
Risks

- Hot flashes
- Leg cramps
- Deep vein thrombosis and pulmonary embolism

Nasal Calcitonin: Effect on BMD and Bone Turnover (PROOF)

- **Mean age 68**
- **N = 1255**

Treatment	Mean Change in Lumbar Spine BMD from Baseline (%)
Placebo	0.5
100 IU	1.0
200 IU	1.2
400 IU	1.5

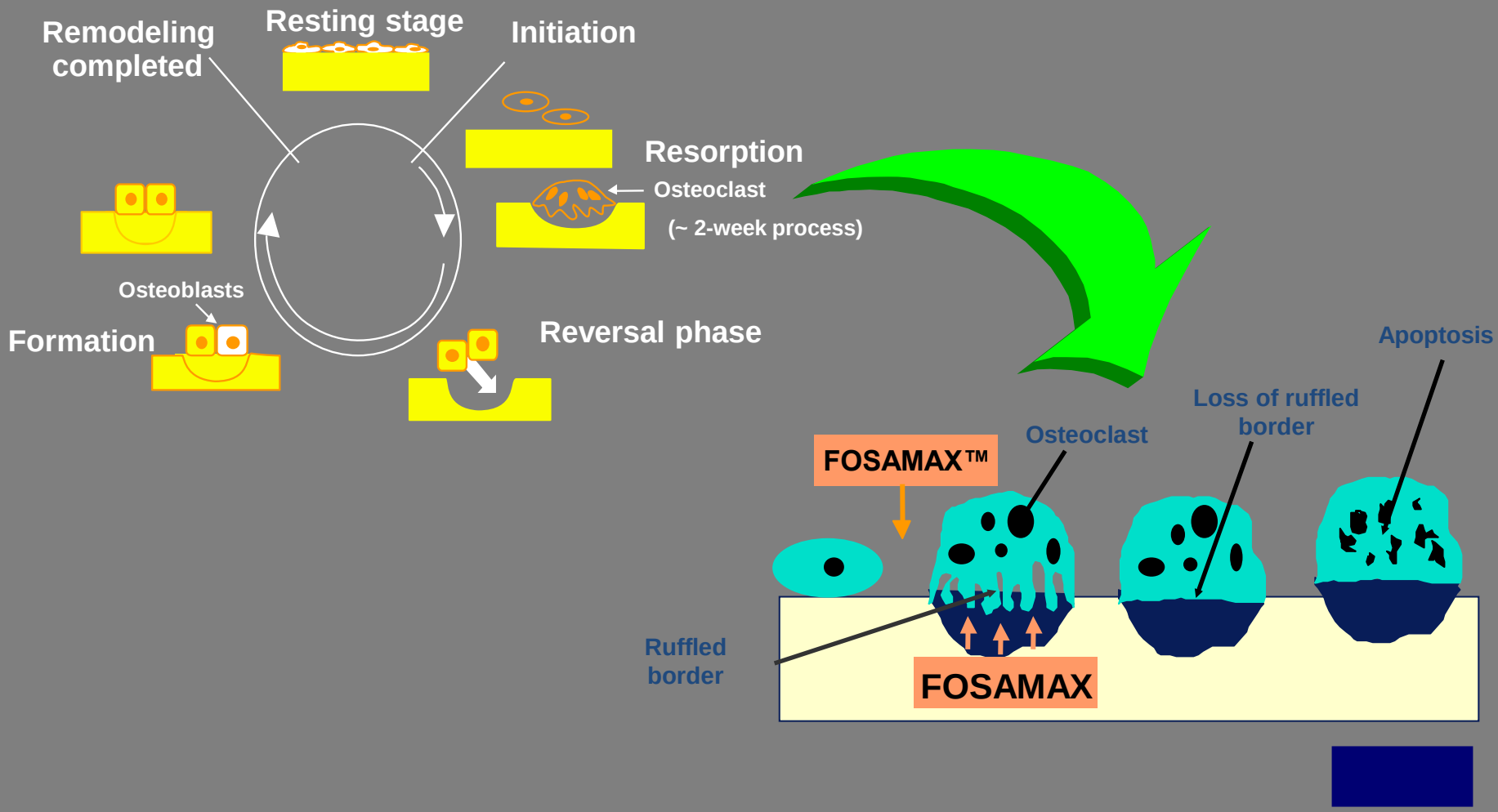


Chesnut CH III et al. *Am J Med.* 2000;109:267-276.

Bisphosphonate treatment

- Most of these agents are very effective for treating patients with osteoporosis
  - Vertebral fracture by 60-70%
  - Multiple vertebral fractures by 75-96%
  - Hip fracture by 40-50%
  - Non-vertebral fracture by 20-35%
- In general are well tolerated
- In clinical trials, have been very safe

Bone Remodeling and Mechanism of Action



Bone et al. *Clin Ther*, 2000.

Bisphosphonates: Benefits and Risks

Benefits

- **Fracture reduction**
- **BMD increase**
- **Non-hormonal**

Risks

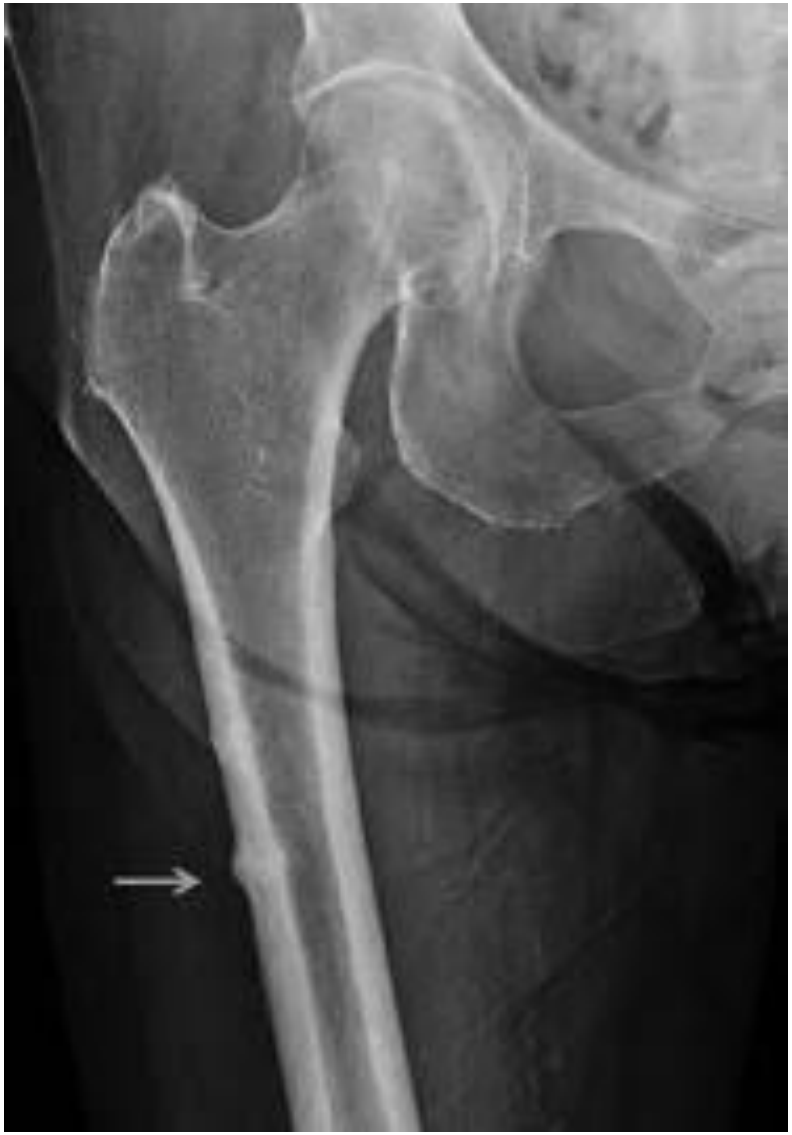
- **Nausea**
- **Upper gastrointestinal irritation**
- **Myalgias and arthralgias**

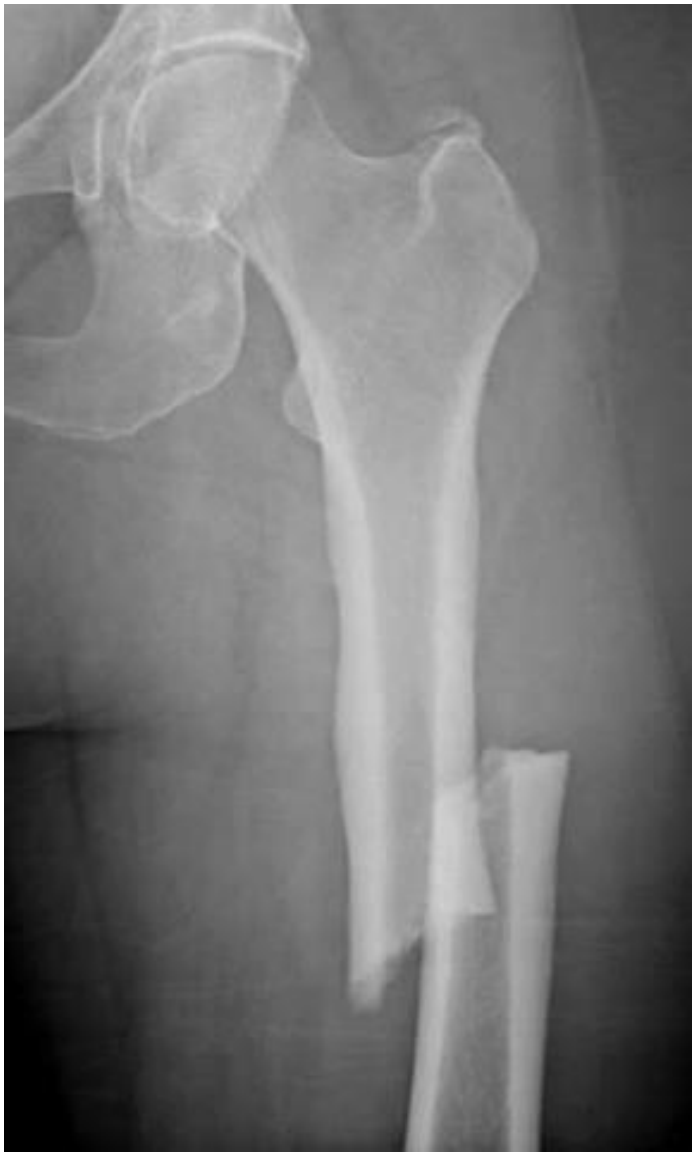
Negative effects of bisphosphonates

- Oesophageal irritation
- Muscle and bone pain
- Atrial fibrillation
- Long term skeletal safety

Atypical femoral fracture

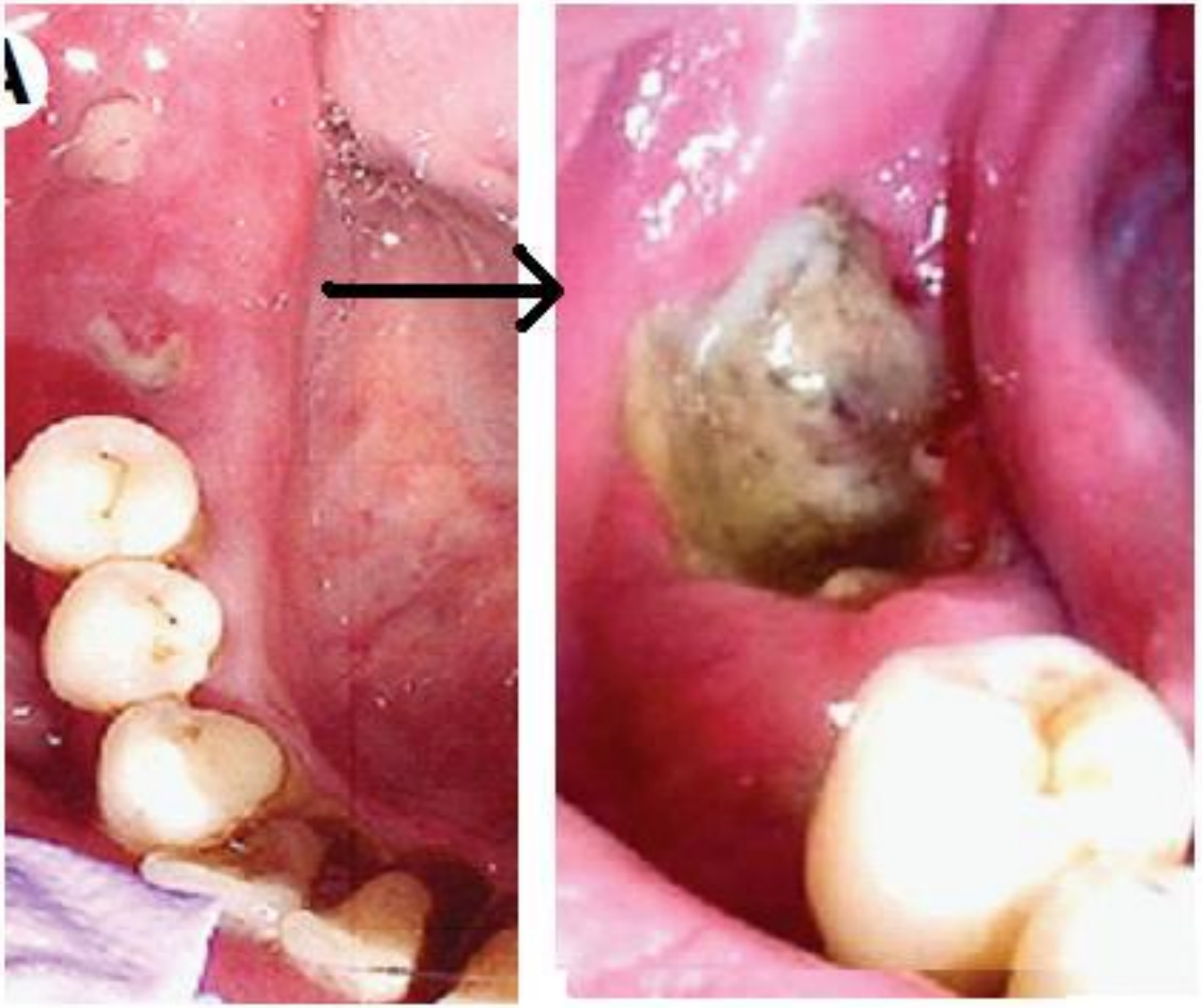
- Link to bisphosphonates:
  - Bone suppression with bisphosphonates
- Minor and major features
- Starts as unicortical fracture
- Associated with prolonged use of bisphosphonates





Osteonecrosis of the jaw

- ? Predilection for the jaw
  - Mechanical stress
  - High bone turnover
  - Related to infection with actinomyces
    - Forms a biofilm in mouth
  - Jaw bone formed by intramembranous ossification


A

Do we stop the bisphosphonates after 5 years?

Bone forming agents:

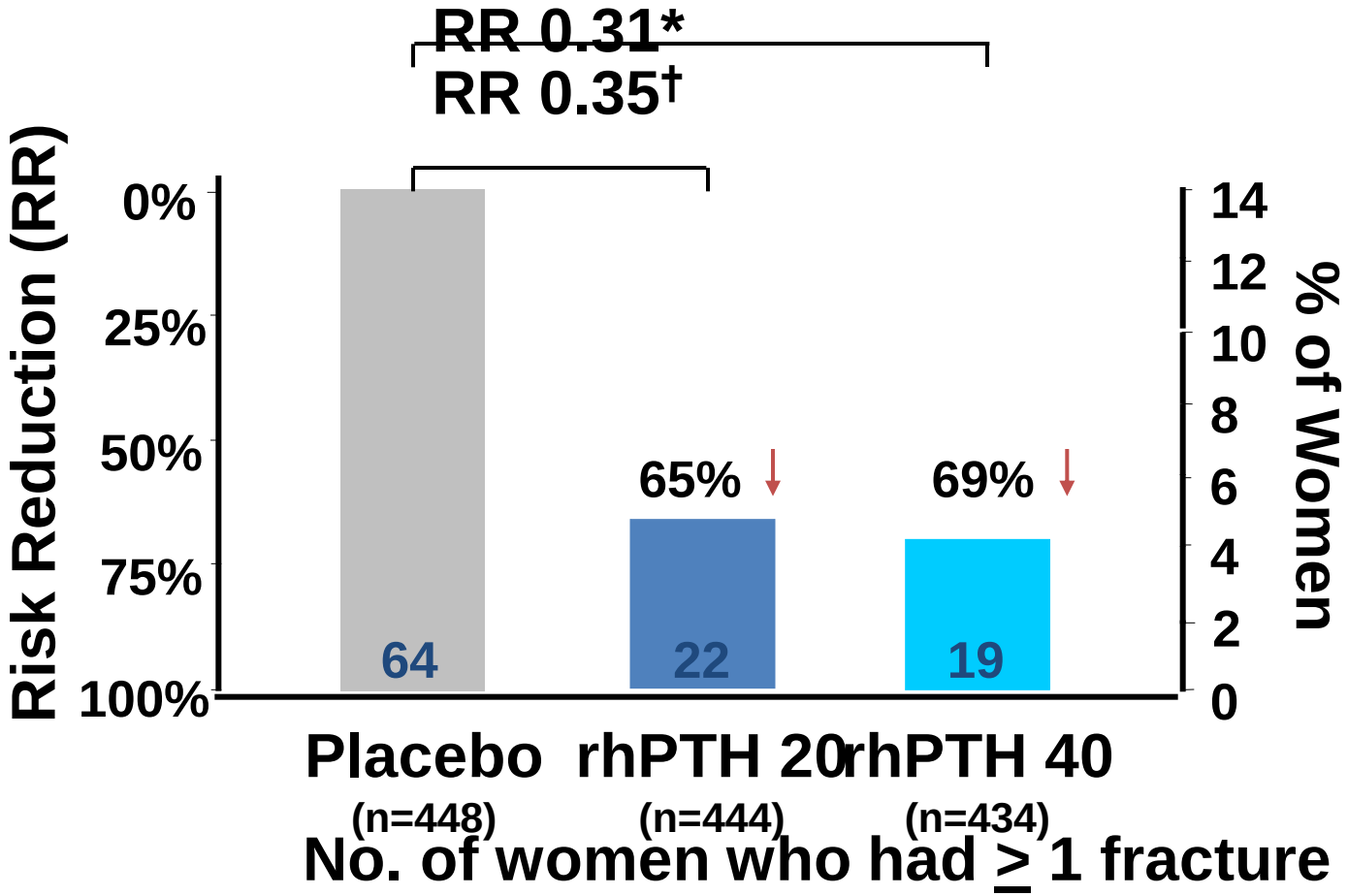
- Selectively increase population and/or activity of the osteoblasts
- Induce a positive bone tissue balance.

Parathyroid hormone:

- Intermittent injections of 1-34 PTH
- Increases the amount of bone matrix
- Restores connectivity of cancellous bone
- Increases cortical thickness
- This is associated with a decrease in the degree of mineralization

Effect of PTH on the Risk of New Vertebral Fractures

*P<0.001 vs. Placebo



*95% CI, 0.19-0.50 †95% CI, 0.22-0.55

Neer R et al. *N Engl J Med*. 2001;344:1434-1441.

NOFSA GUIDELINES ON PTH USE

NOFSA has provided the following guidelines for the use of teriparatide:

- Severe established osteoporosis as defined by low BMD and at least 2 prevalent fractures
- Failed anti-resorptive treatment as defined by an incident fragility fracture while compliant to anti-resorptive treatment for at least 12 months or unacceptable loss of BMD on two occasions while on treatment
- Duration of therapy is presently limited to 18 months and should be followed by maintenance therapy with an anti-resorptive drug

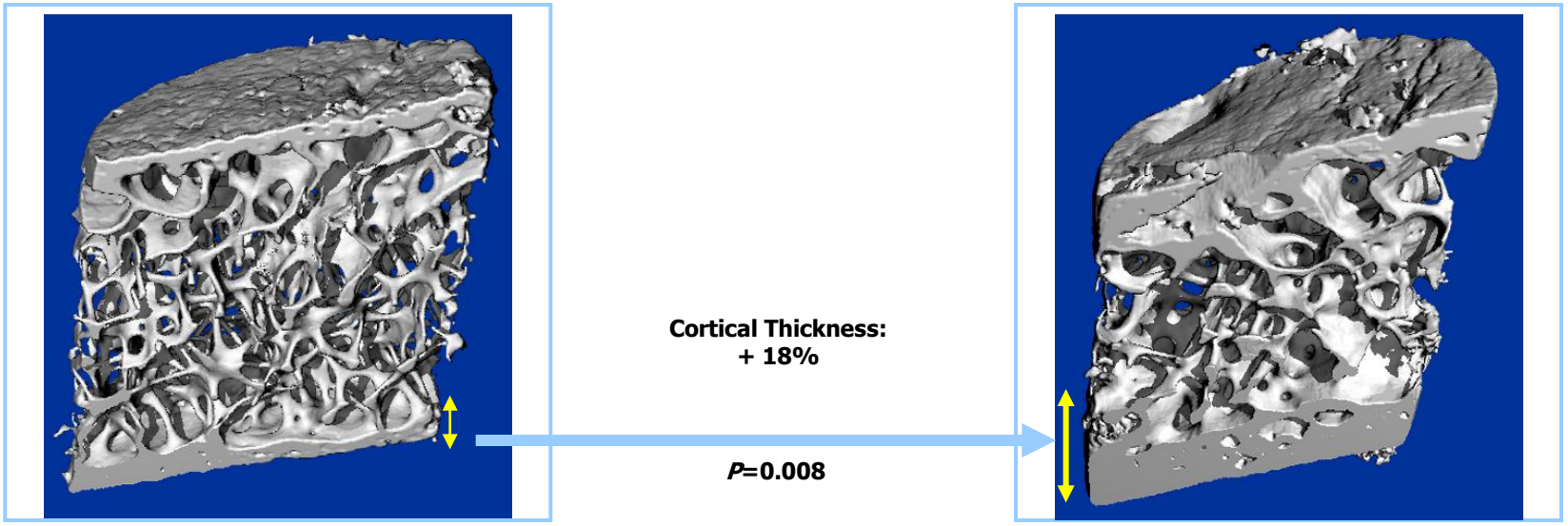
Other anabolic agents

- Strontium ranelate
  - Antiresorptive effect with stimulation of osteoblastic activity

  - An uncoupling of bone remodeling resulting in a bone anabolic effect

STRONTIUM RANELATE IMPROVES TRABECULAR & CORTICAL MICROARCHITECTURE

Strontium Ranelate 36 Mo

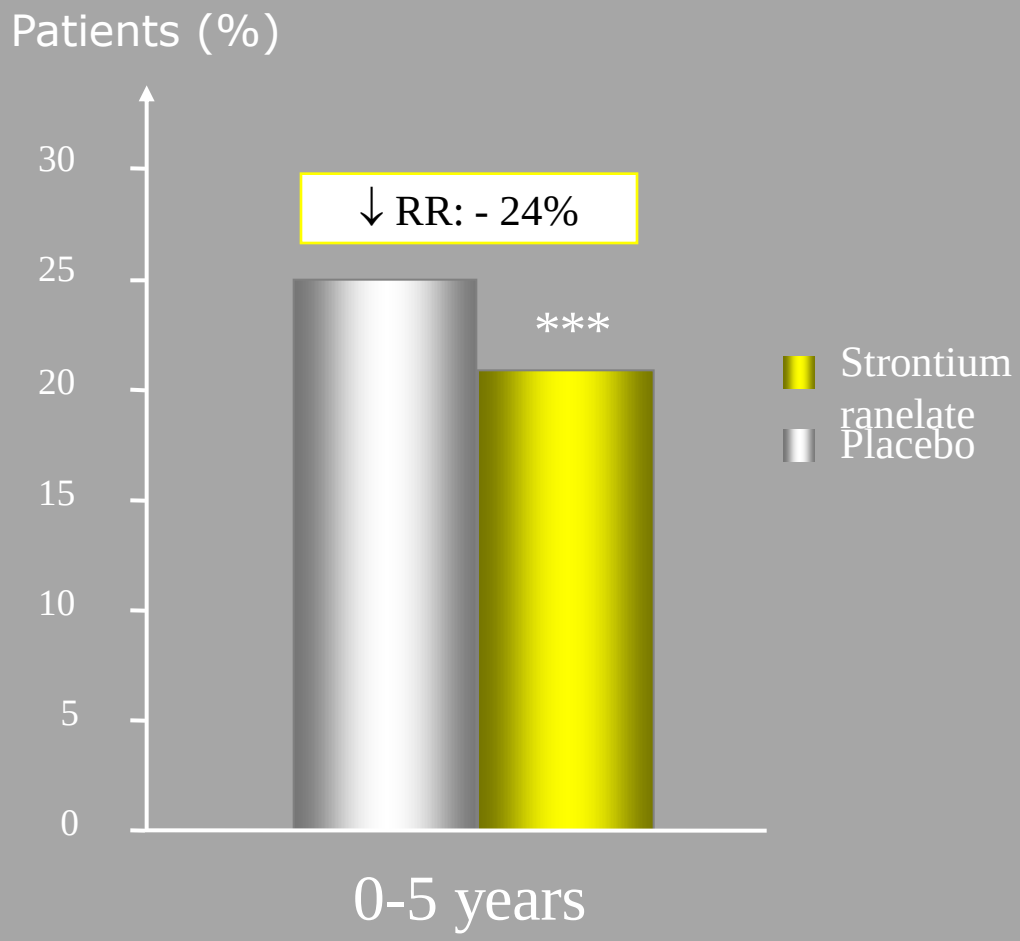


	BPHs	Strontium ranelate
Structural Model Index	NA (AL) NS (RIS)	- 22%
Trabecular separation	NS	- 16%
Cortical Thickness	NS	+ 18%

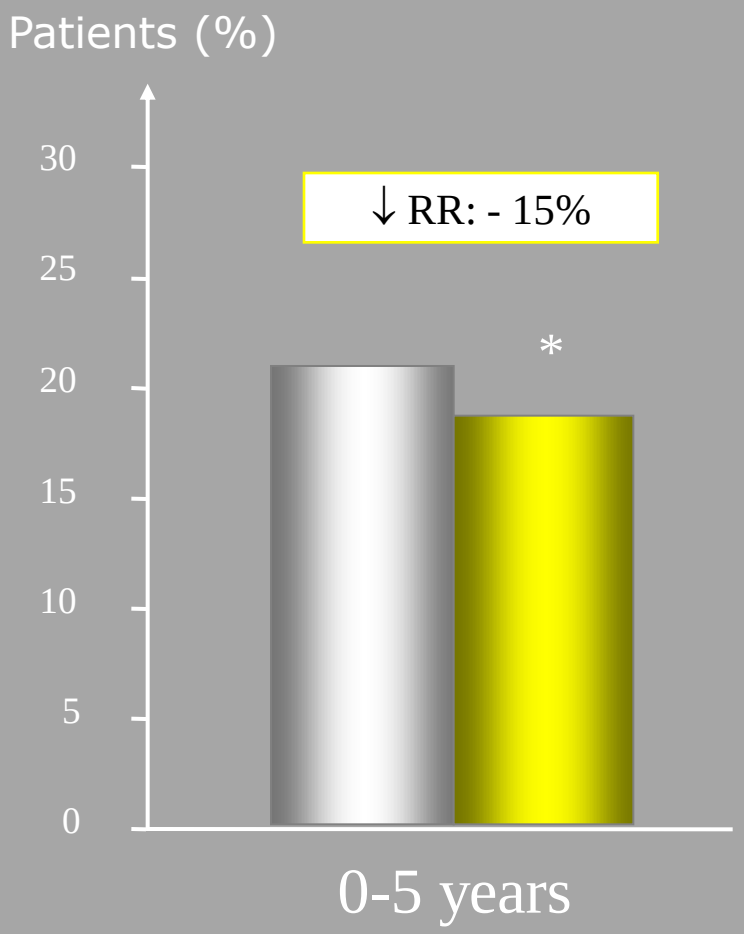
Arlot ME et al. J Bone miner Res 2008;23:215-222

Strontium ranelate efficacy over 5 years

Vertebral fractures



Non-vertebral fractures



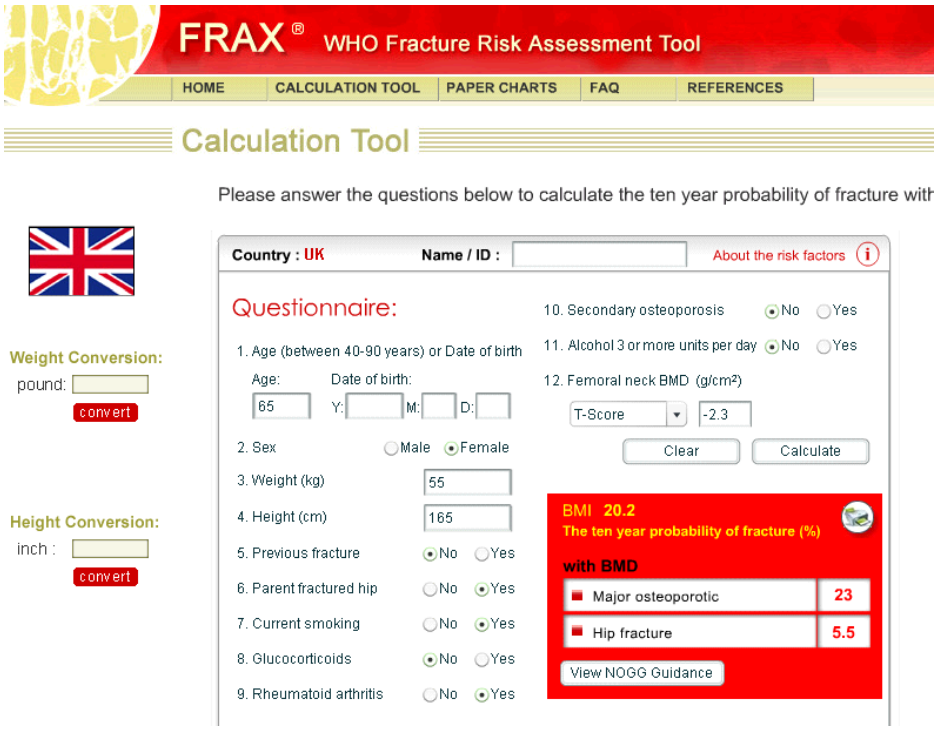
Reginster JY, et al. *Arthritis Rheum*. 2008;58(6):1687-1695.

*P<0.05, *** P<0.001

How we need to look at osteoporosis treatment outcomes

10-year fracture probability (FRAX)

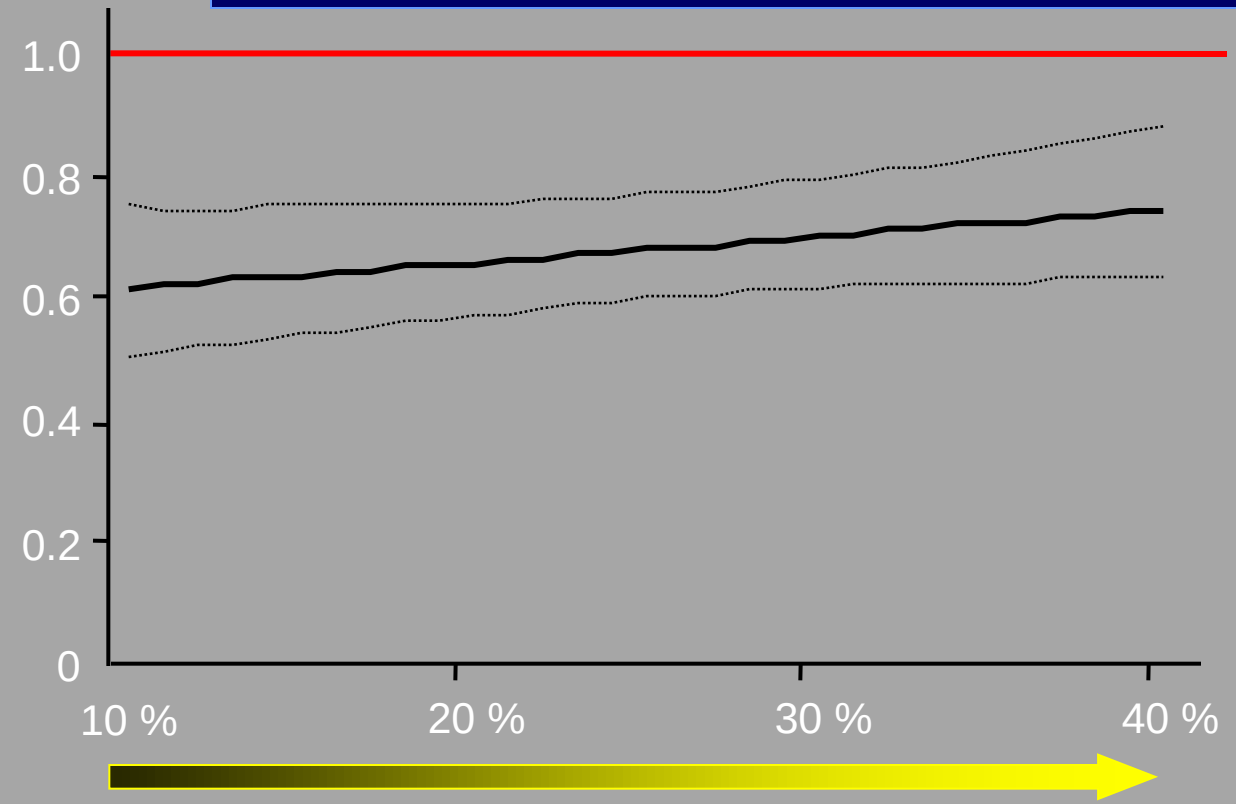
Efficacy against fractures



Efficacy of strontium ranelate on clinical fractures

Efficacy
(Hazard ratio)

Strontium ranelate is effective whatever the 10-year fracture probability (FRAX)



Kanis JA, et al. *Osteoporos Int*. 2011 (epub)

Emerging therapies for osteoporosis: Anti-resorptives

- Present therapies:
  - RANKL inhibition
    - Denosumab: 6 monthly injection
- New targets for antiresorptives:
  - Cathepsin K inhibition
    - Odanacatib

New anabolic agents for bone:

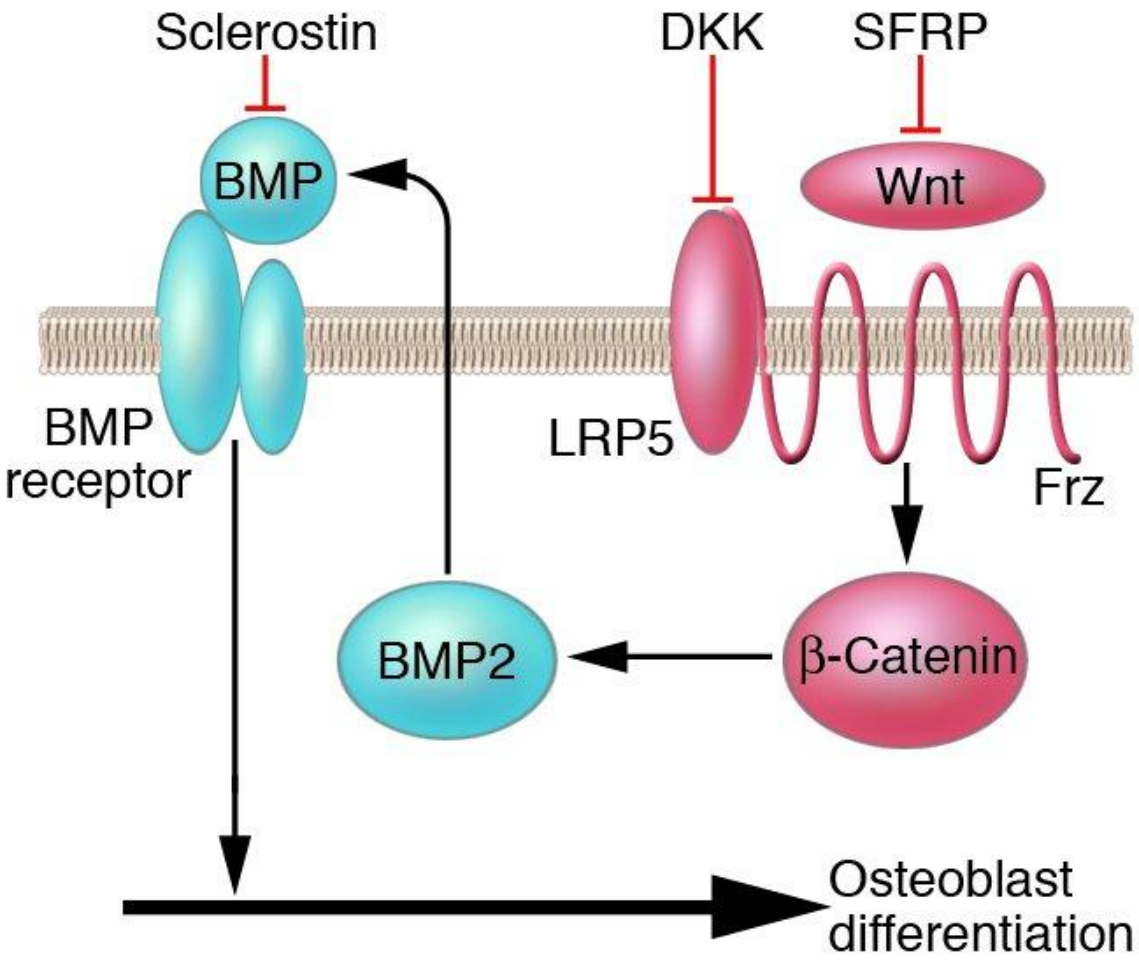
- PTH
  - Shortening of molecule
  - Stimulation of PTH secretion (didn't work)
- The Wnt signaling pathway

Looking for targets in rare diseases

- Sclerosteosis
- Hyperostosis corticalis

Sclerostin:

- Protein produced by osteocytes
- Produced in late stages of mineralisation
- Inhibits bone formation
- Bone loading decreases sclerostin
- Absent in sclerostosis and hyperostosis corticalis
- Target for medication:
  - Antibody to sclerostin


Sclerostin
DKK
SFRP
BMP
Wnt
BMP
receptor
LRP5
Frz
BMP2
β-Catenin
Osteoblast
differentiation

Sclerosteosis and Van Buchem Disease

- Associated with absence/reduced production of sclerostin
- Autosomal recessive disorders
- Characterized by endosteal hyperostosis
- Resistance to fracture
- Excessive height and syndactyly (sclerosteosis)

Courtesy of Wim van Hul