Journées Francophones de Nutrition

Bordeaux 11-13 décembre 2013

SYMPOSIUM SATELLITE

CERIN

Mécanismes des Fractures Ostéoporotiques: Quels Points d'Impact pour la Prévention Nutritionnelle ?

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HUG Hôpitaux Universitaires de Genève

**** Centre Collaborateur de l'OMS dans la Lutte contre l'Ostéoporose***

Conceptual definition of osteoporosis

Hip fracture incidence worldwide

Meta-analyses on calcium ± vitamin D and dairy on osteoporotic fractures

Hierarchy of evidence strength among types of study

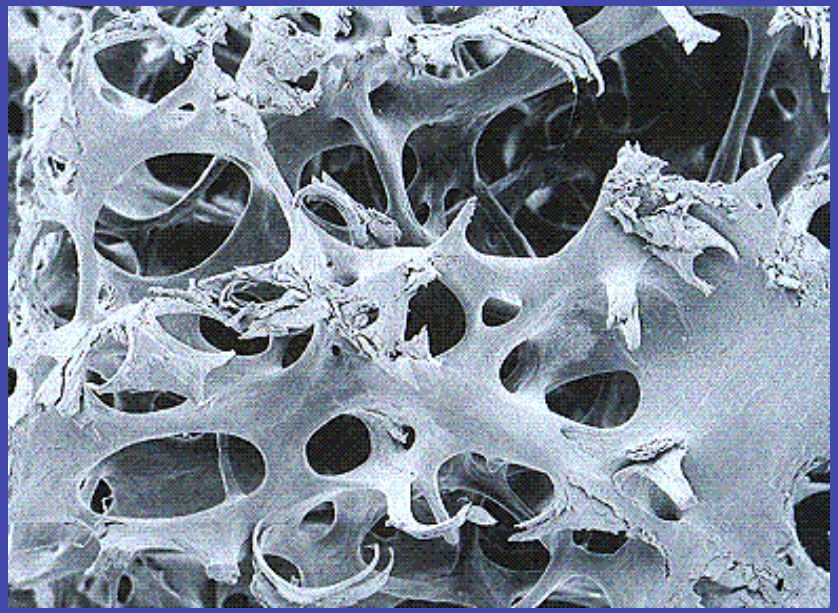
Hip fracture: a stochastic and very rare event:
Non significant effect not only in nutritional epidemiologic studies but also in intervention RCTwith strong antiosteporotic medications

Operational definition of osteoporosis by DXA measured-BMD T-score:
Majority of fractures above -2.5 T-score, threshold of osteoporosis definition. Hence:
1) Introduction of clinical risk factors (FRAX)
2) Development of technical tools for better risk fracture prediction

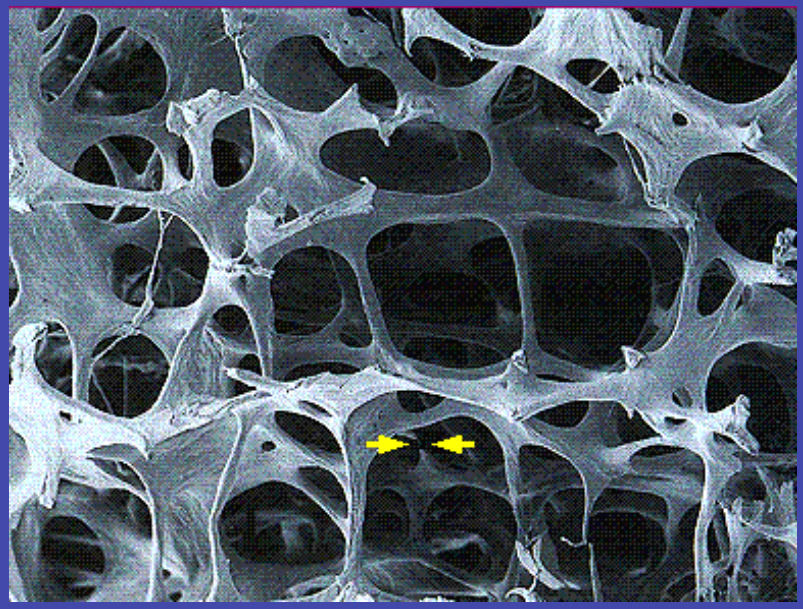
Nature and importance of bone remodelling on bone structure and components:
Change at the menopause; microarchitecture deterioration,
age-dependent reduction in bone strength > bone mineral mass

Définition of Osteoporosis

"A disease characterized by
low bone mass and microarchitectural deterioration of bone tissue,
leading to enhanced bone fragility
and a consequent increase in fracture risk" [1)]



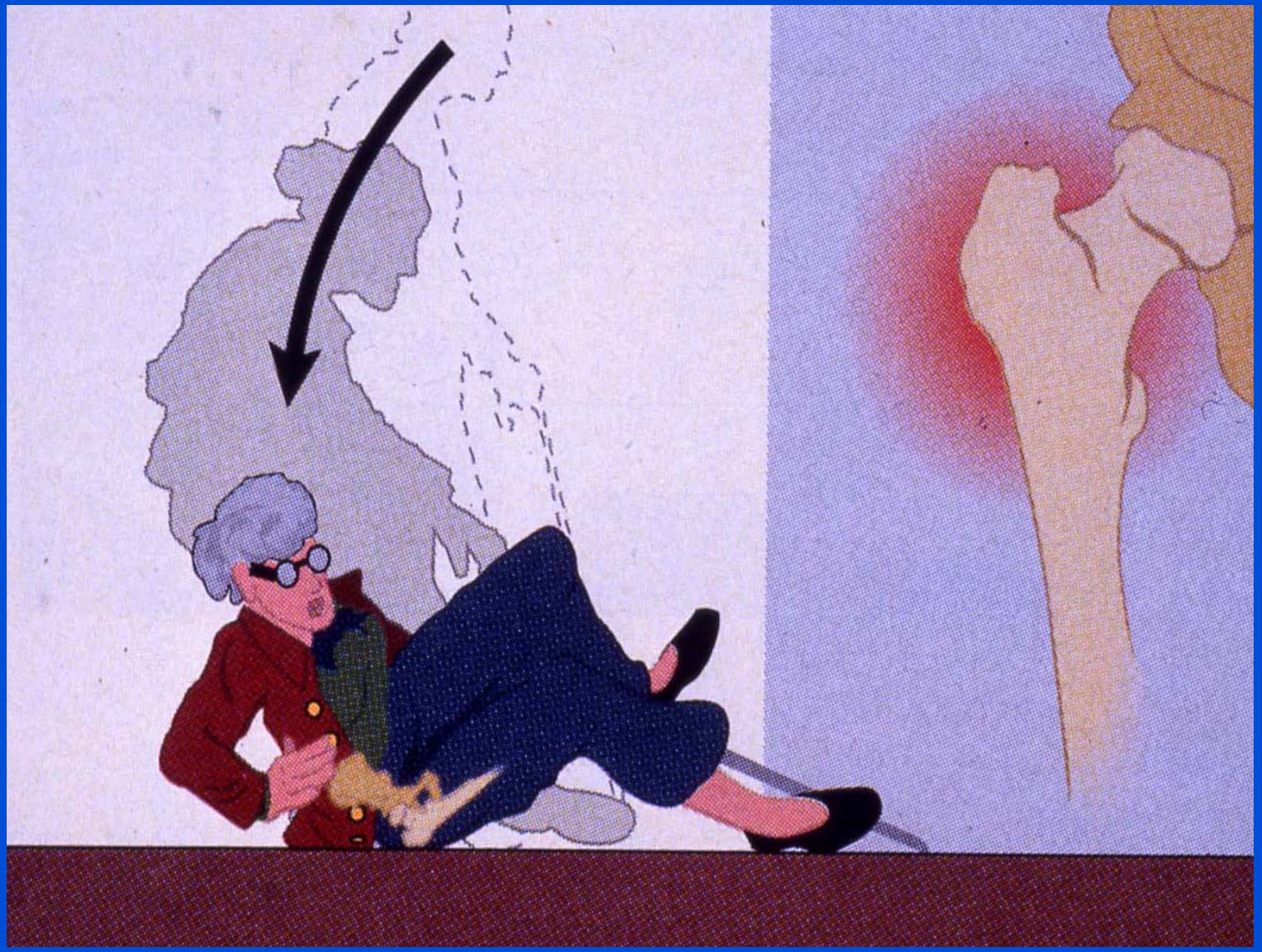
Normal [2)]



Ostéoporose [2)]

1. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. 1994. Report of a WHO study group. WHO Technical Report Series; No 843.
2. Dempster DW et al, J Bone Miner Res. 1986; 1: 15-21 0

Hip Fracture



A systematic review of hip fracture incidence and probability of fracture worldwide

Kanis et al Osteoporos Int 2012; 23:2239-56

Ten-year probability of hip fractures

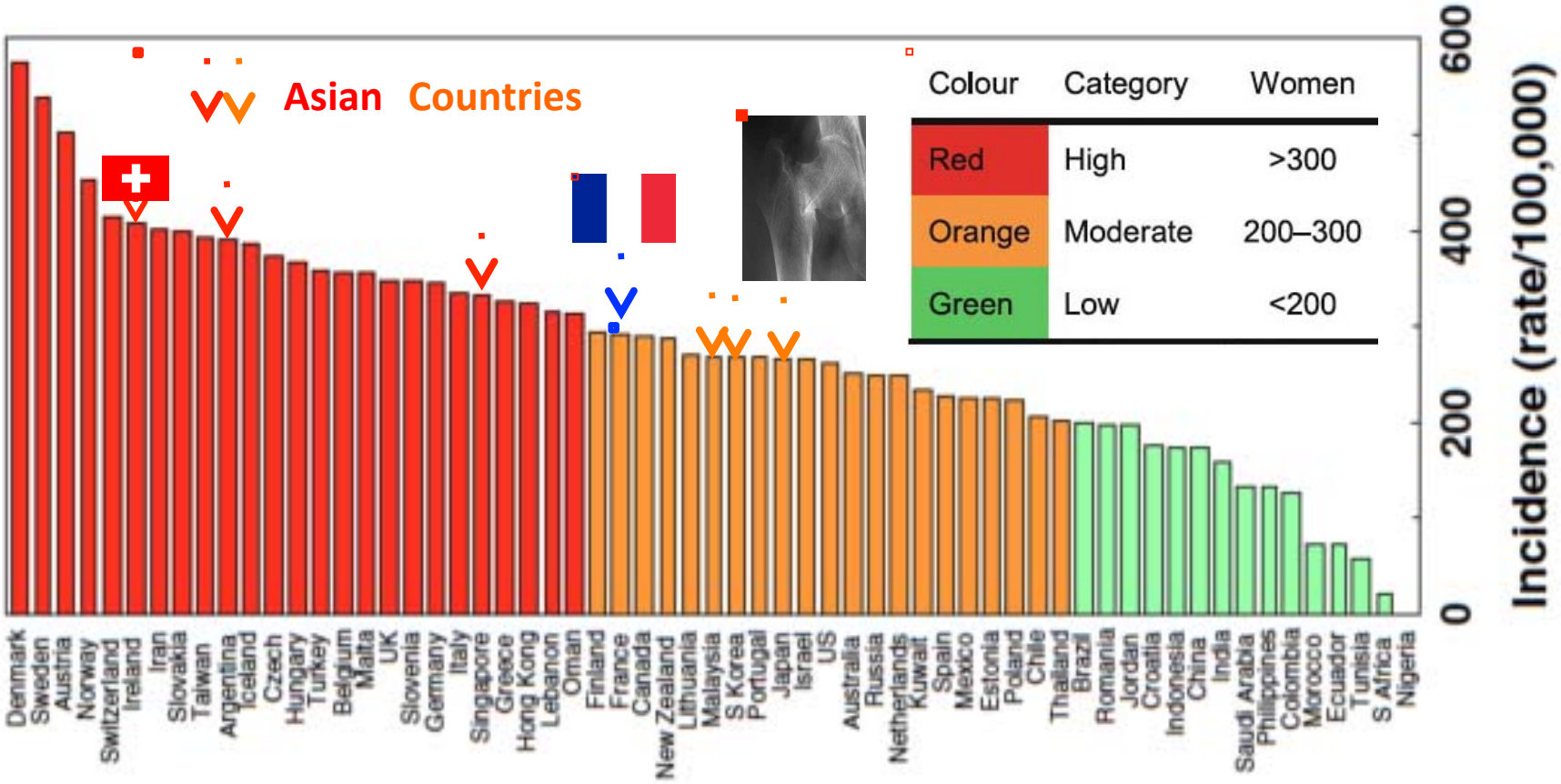


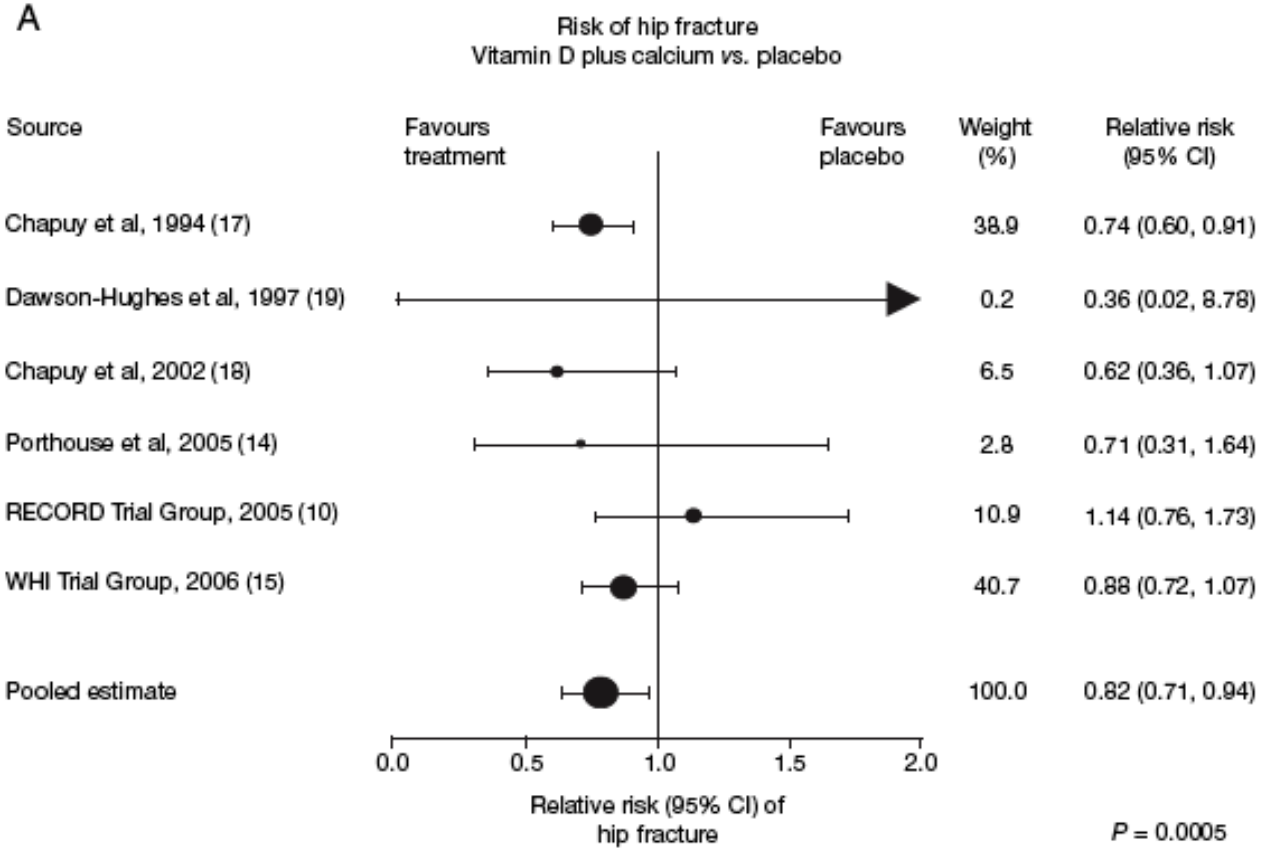
Fig 1. Age-standardized annual incidence of hip fractures in women (/100,000) according to country together with colour codes

Need for Additional Calcium to Reduce the Risk of Hip Fracture with Vitamin D Supplementation: Evidence from a Comparative Metaanalysis of Randomized Controlled Trials

Steven Boonen, Paul Lips, Roger Bouillon, Heike A. Bischoff-Ferrari, Dirk Vanderschueren, and Patrick Haentjens

JCEM 2007

A



CI = confidence interval
RECORD = Randomised Evaluation of Calcium Or vitamin D
WHI = Women's Health Institute

Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis

Benjamin M P Tang, Guy D Eslick, Caryl Nowson, Caroline Smith, Alan Bensoussan

The Lancet 2007; 370:657-66

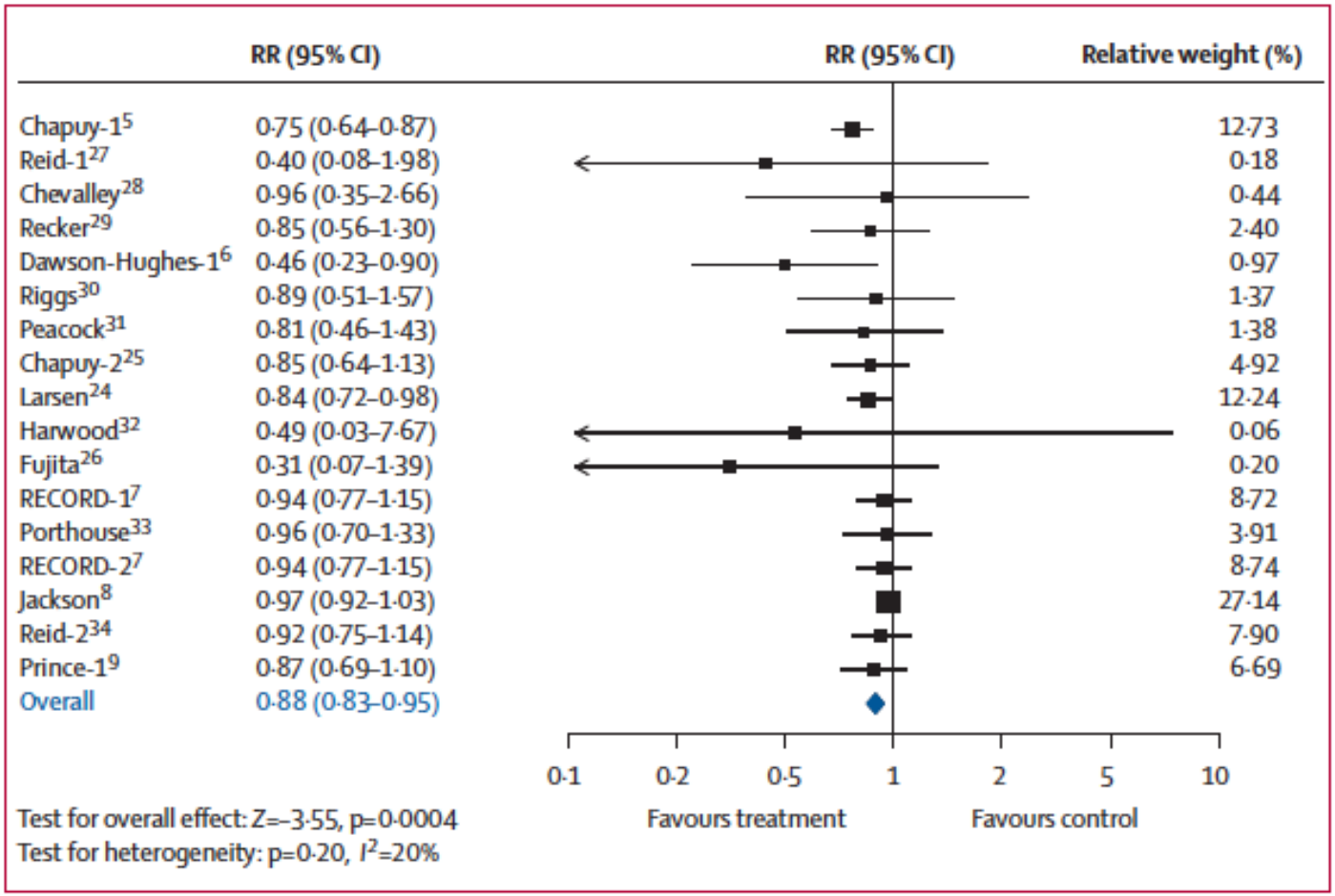


Figure 2: **Effect of calcium and calcium in combination with vitamin D on fracture risk**
RR=risk ratio. Size of data markers are proportional to the weight of every study in the forest plot. Horizontal bars=95% CI.

Milk Intake and Risk of Hip Fracture in Men and Women: A Meta-Analysis of Prospective Cohort Studies

Heike A Bischoff-Ferrari,[1,2] Bess Dawson-Hughes,[3] John A Baron,[4] John A Kanis,[5] Endel J Orav,[6] Hannes B Staehelin,[7] Douglas P Kiel,[8] Peter Burckhardt,[9] Jana Henschkowski.[1] Donna Spiegelman,[10] Ruifeng Li,[10] John B Wong,[11] Diane Feskanich,[12] and Walter C Willett[13] *JBMR 2011*

Original Investigation

Milk Consumption During Teenage Years and Risk of Hip Fractures in Older Adults

Diane Feskanich. ScD: Heike A. Bischoff-Ferrari, MD, DrPH; A. Lindsay Frazier, MD; Walter C. Willett, MD, DrPH

JAMA Pediartrics 2013

Evidence Based Medicine

Montori and Guyatt. Respiratory Care 2001; 46:1201-1212

Hierarchy of Evidence Strength

1) **N of 1 randomized controlled trial** *

2) **Systematic review of randomized trials**

3) **Single randomized trial**

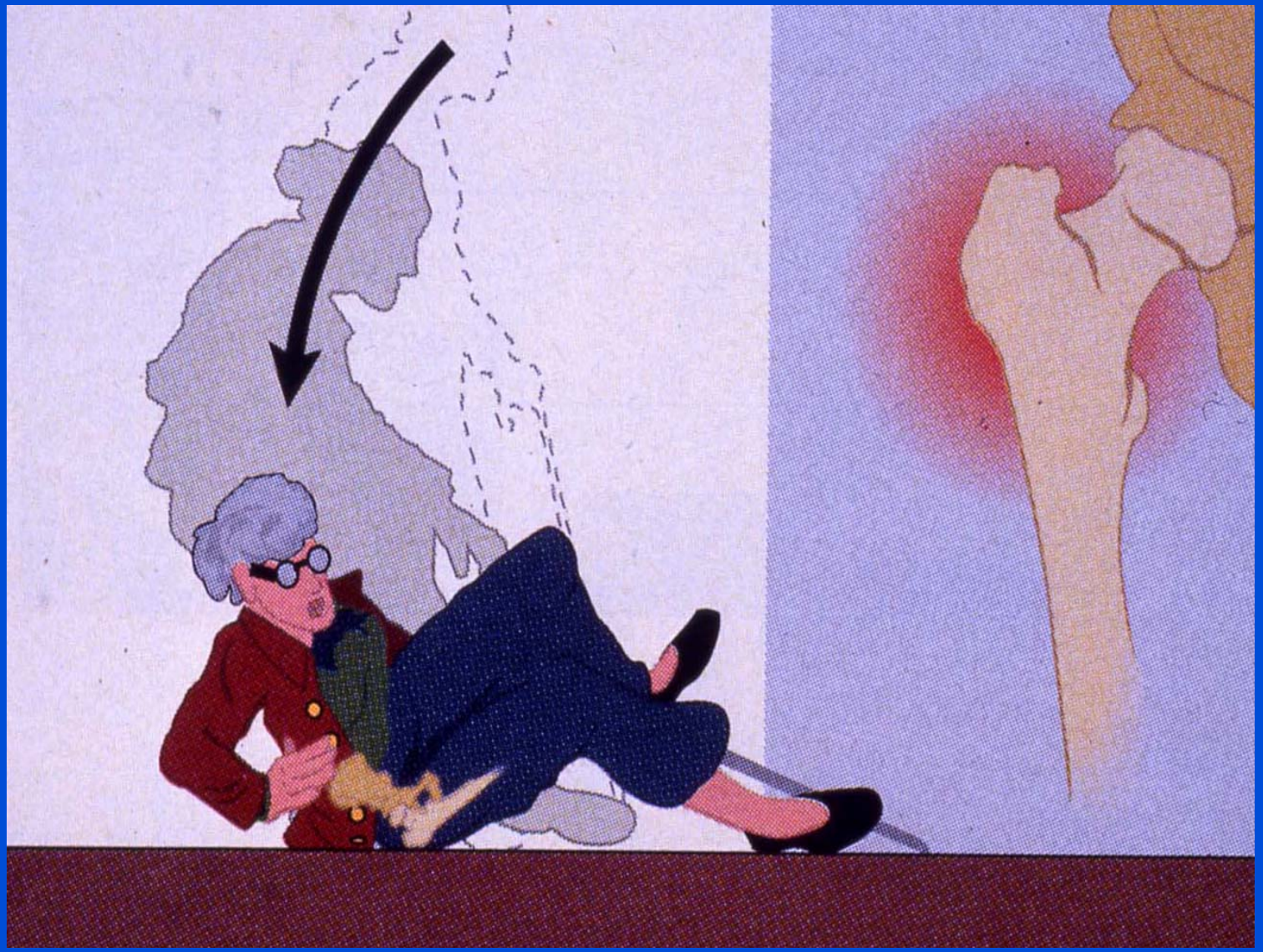
4) Systematic review of observational studies adressing patient-important outcomes

5) **Physiological studies**

6) **Unsystematic clinical observations**

** Patients undertake pairs of treatment periods: one with target tt; the other with placebo or alternative tt.*

Hip Fracture: A Stochastic Event



Odd ratio (CI) 95% for Hip Fracture:

Randomized Placebo Controlled Trials in Postmenopausal Women

Drug: 402 Fx /28500 = 1.4%

vs

Placebo: 430 Fx/22628 = 1.9%

Hopkins et al.BMC Musculoskeletal Disorders 2011

Alendronate

Black 1996. 0.43 (0.23-1.01) **?**

Cummings 1998. 0.79 (0.43-1.45) **NS**

Denosumab

Cummings 2009. **0.60** (0.37-0.98)

Raloxifen

Ettinger 1999. 1.12 (0.64-1.95) **NS**

Risedronate

McKlung 2001

W 70-79 y + OP + VF: **0.60** (0.20-0.80)

W 70-79 y + OP – VF: 0.6 (0.3-1.2) **NS**

W >80 y + 1 Clin.Risk Factor: 0.8 (0.6-1.2) **NS**

Strontium

Reginster 2008. 0.89 (0.66-1.19) **NS**

Teriparatide

Neer 2001. 0.50 (0.09-2.75) **NS**

Zoledronate

Black 2007. **0.59** (0.42-0.83)

Evidence Based Medicine

Montori and Guyatt. Respiratory Care 2001; 46:1201-1212

- **Hierarchy of Evidence Strength**

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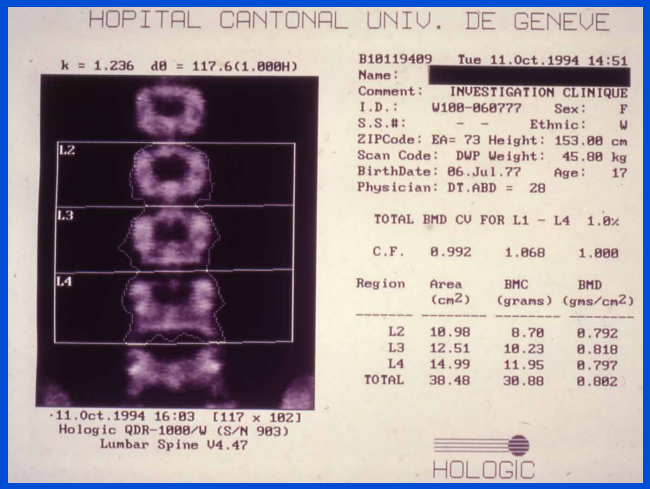
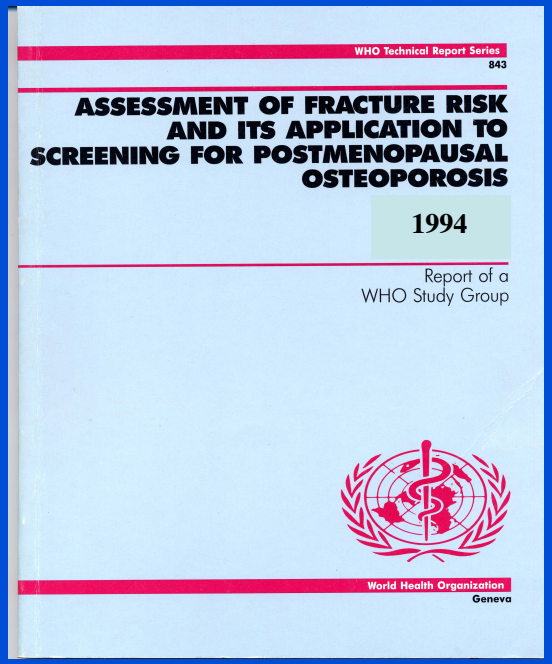
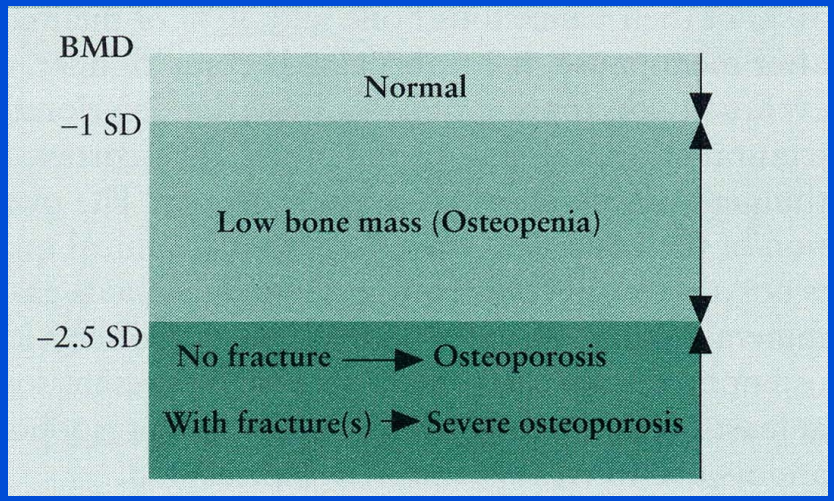
DXA Measurement and Fracture Prediction

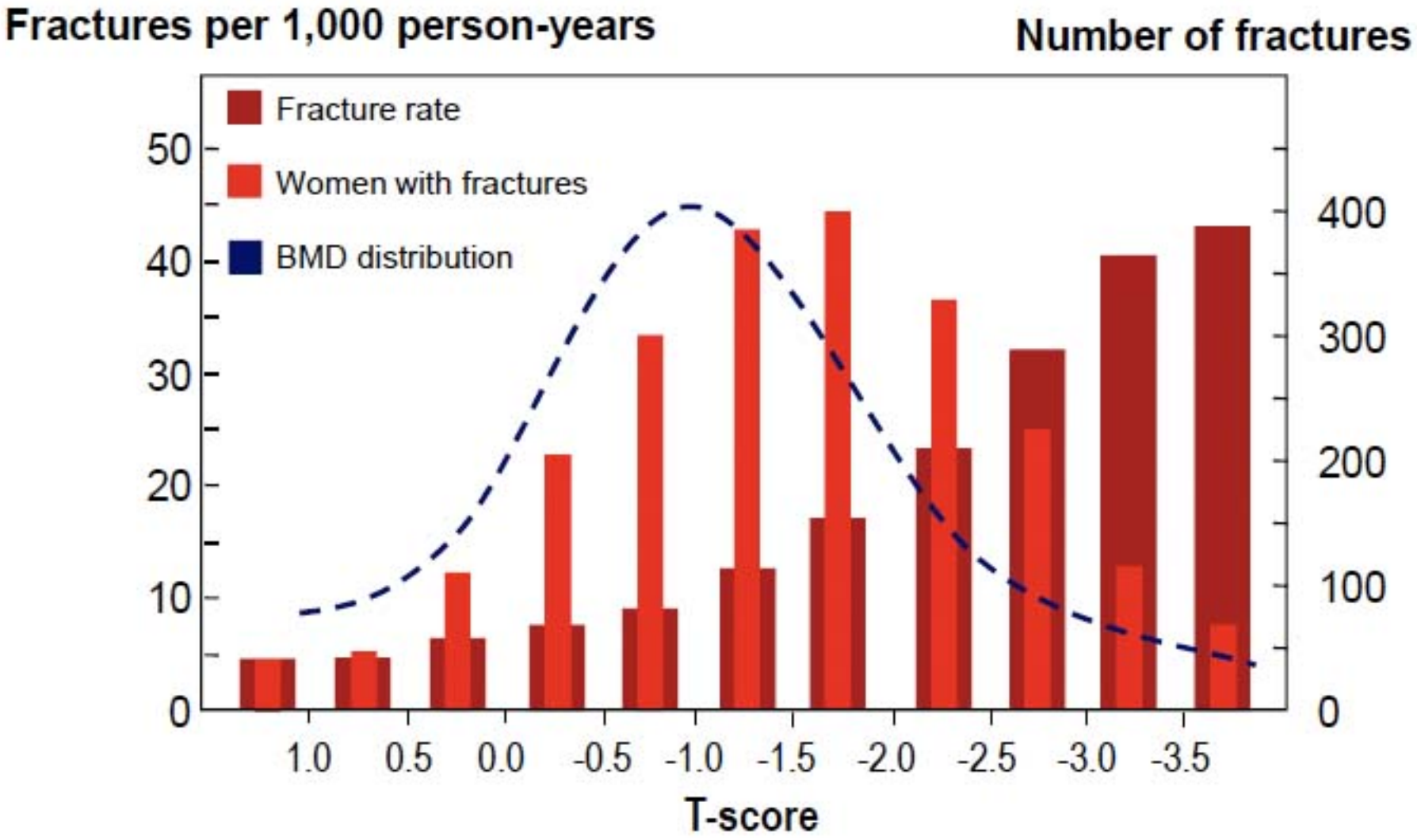




Relative Risk



Bone Mineral Density and Fractures



E.Siris et al. Arch Intern Med. 2004; 164:1108-1112

Prediction of Osteoporotic Fractures

- Clinical
- Approach
- Technical

Determinants of Bone Mechanical Strength

(Besides Bone Mass)

Structural Elements

- Macro-architecture
  - Size
  - Geometry
- Micro-architecture
  - Trabecular Thickness
  - Trabecular Distribution
  - Cortical Thickness
  - Cortical Porosity

▲

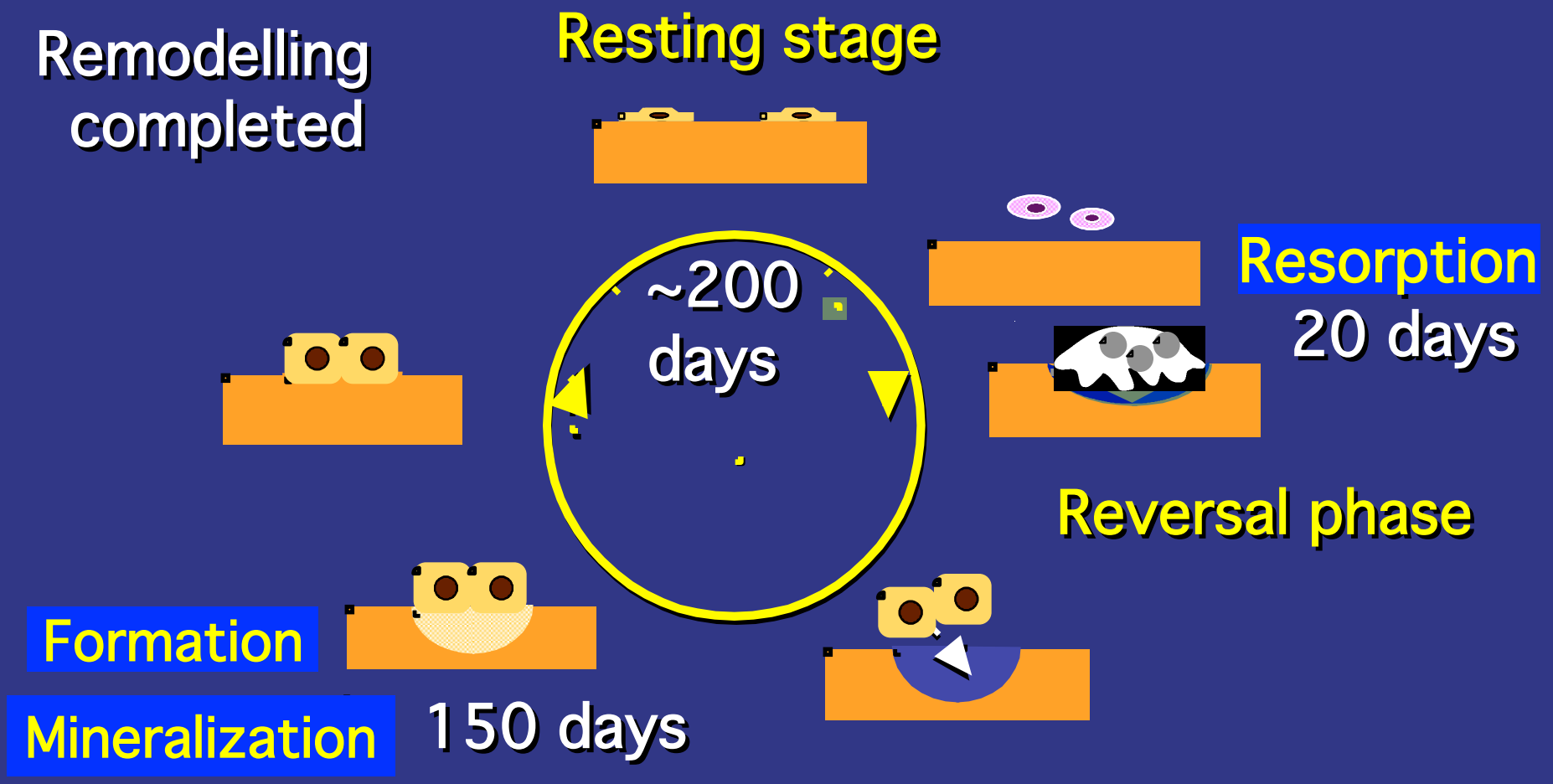
Physical & Chemical Elements

- Mineral Quality
  - Density
  - Crystal Size
- Collagen Quality
  - Cross-links
- Microcracks ?

▲

Bone Remodelling

Bone Remodelling



The Osteoporosis Continuum

Healthy spine

50 Menopausal

Experiencing vasomotor symptoms

55+ Postmenopausal

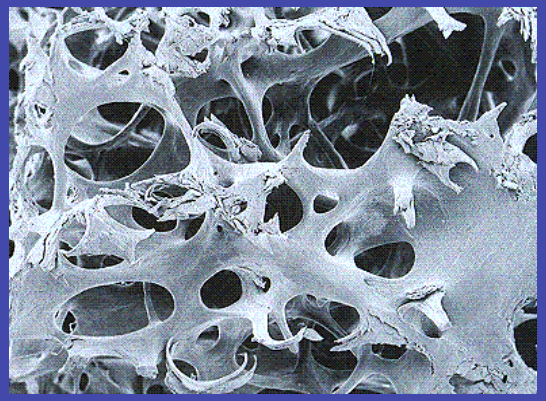
At greater risk for vertebral fracture than any other type of fracture

70-75+ Kyphotic

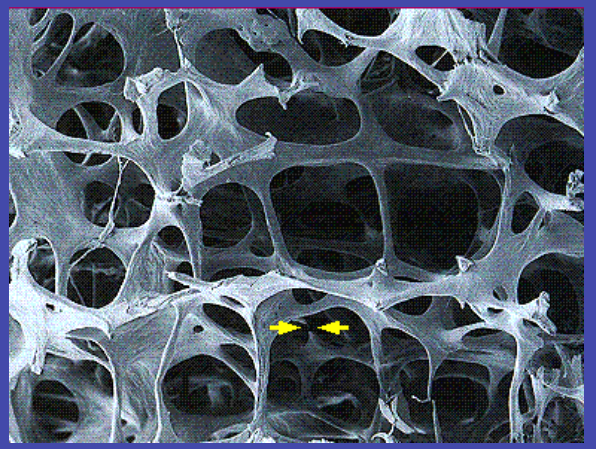
At risk for hip fracture and other types of nonvertebral fracture

Kyphotic spine

Premenopause



Postmenopause



Increase in Bone Remodeling

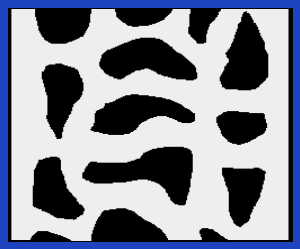
Resorption > Formation

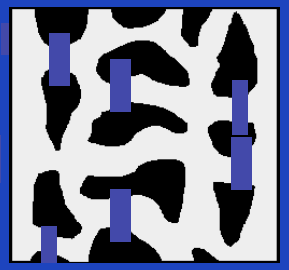
Determinants of Bone Strength

Load Resistance

- Bone mass
- Macro-architecture

- Micro-architecture





Non-invasive technics to assess microstructure and strength:
-HR-pQCT showing micro-architecture of distal radius

Mechanic concepts of structure resistance: siffness and failure load: the relation stress/strain

Eg: difference in bone structure & strength in premenopausal women with ± a fracture history.

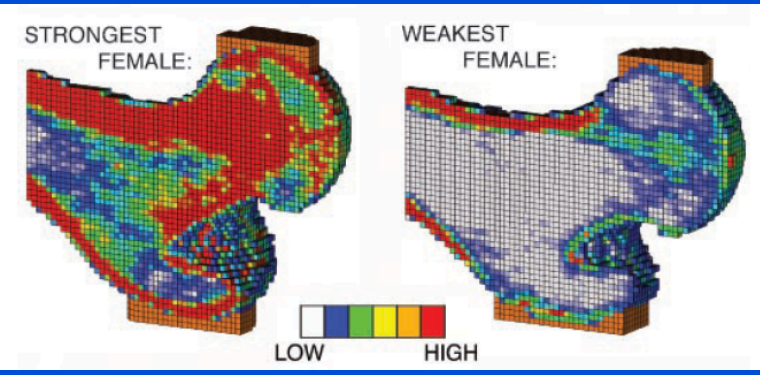
Impact of Antiosteoporotic Medications on Bone Remodeling

Early change in bone remodelling (turnover) predicts change BMD and future fracture: reduce bone resorption and stimulate bone formation, targets of intervention with medications and nutritional products.

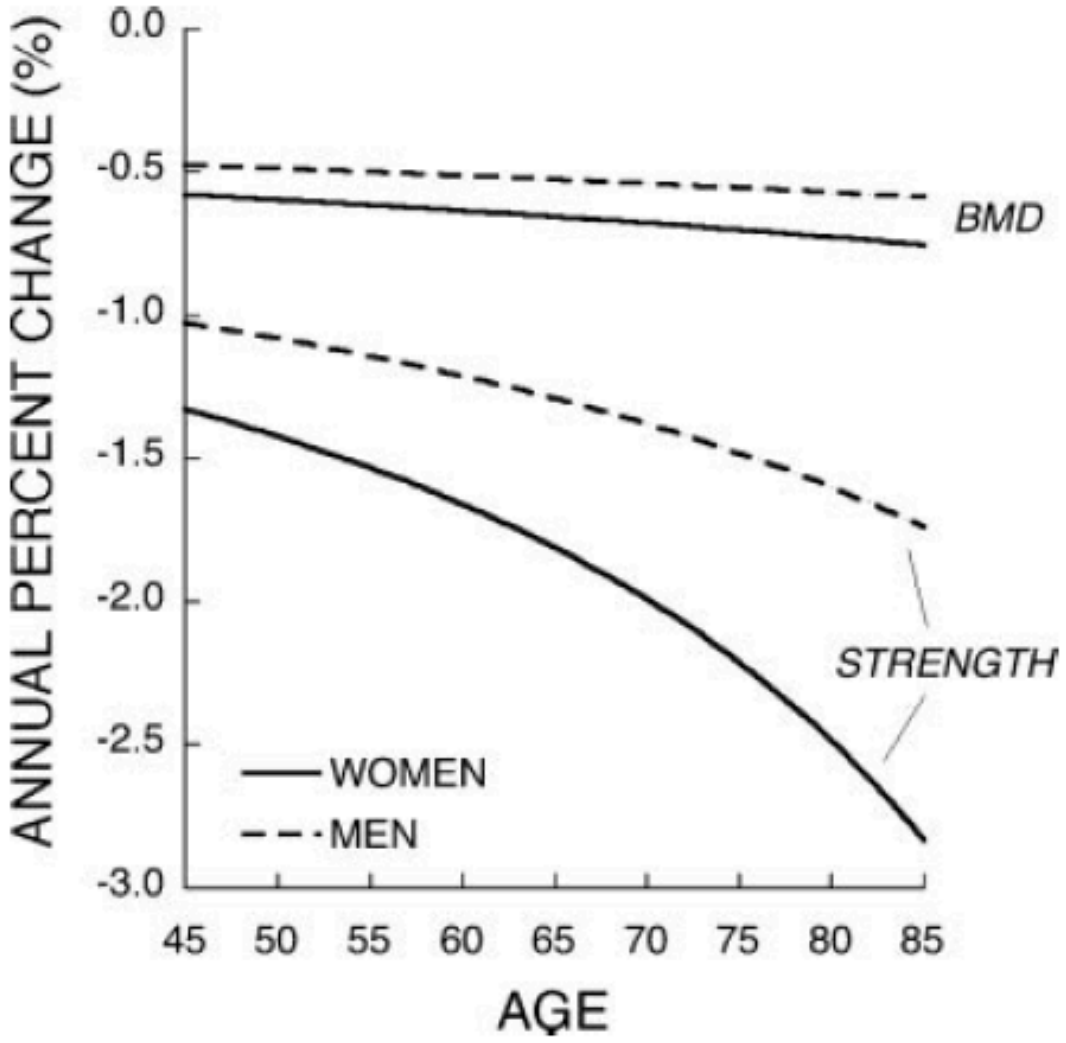
Eg: milk intervention on bone remodelling, using a cross-over design, first in the hierarchy of evidence strength.

Impact of Ca, Pi, protein and vitamin D on bone and skeletal muscle health.

Age-related loss of bone strength at hip exceeds loss of aBMD



Hip FEA



Kaeveny, JBMR 2010

Trabecular Architecture in Vivo with High Resolution pQCT

Xtreme CT, Scanco

~ 80 μm^3 voxel size

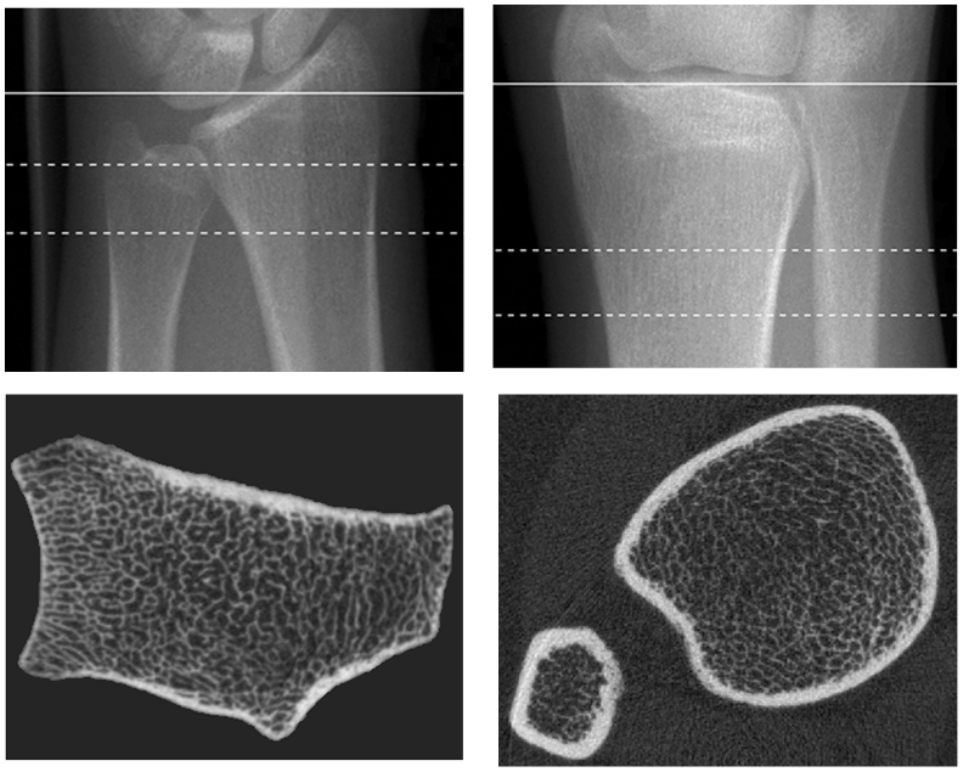
~ 3 min scan time, < 4 µSv

Distal radius and tibia only

Reproducibility:

density: 0.7 - 1.5% *

µ-architecture: 1.5 - 4.4% *



* Boutroy et al. J Clin Endocrinol Metab. 2005; 90:6508-15

STRUCTURES
OR WHY THINGS DON'T FALL DOWN

J.E. GORDON

Penguin Books 1991

s ·

Steel

Aluminium

Bone

Stress

Wood

•

Strain *e*

s / e = Young's modulus of elasticity

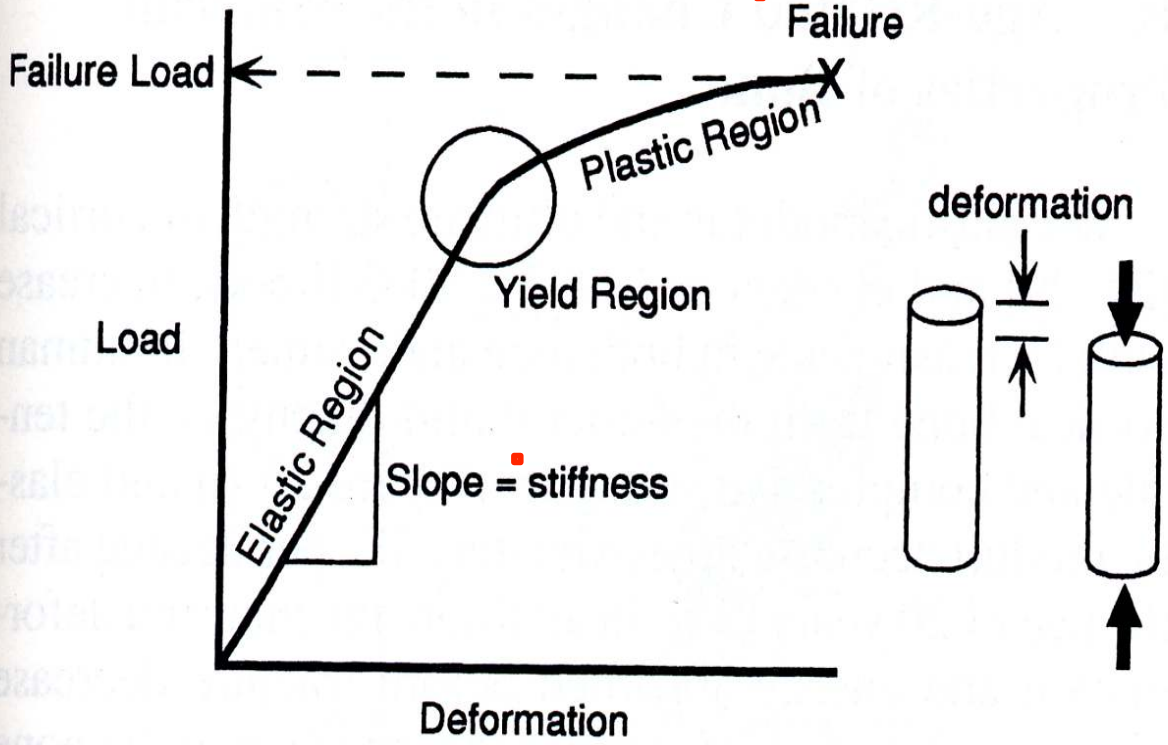


FIGURE 23-2 The load versus deformation plot is used to describe the structural behavior of a specimen. The elastic region is distinguished from the plastic region by the yield region. In the elastic region, when the load is removed there will be no residual deformation and the bone will return to its original shape. In contrast, in the plastic region, the bone will undergo permanent deformations that will remain even if the load is removed.

Bouxsein M. Biomechanics of Age-Related Fractures in Osteoporosis, p.601-623, Editors: Marcus et al., Elsevier AP, 2008

Fracture History of Healthy Premenopausal Women is Associated with a Prevailing Reduction of Cortical Microstructural Components at the Distal Radius

T. Chevalley, J.-P Bonjour, B. van Rietbergen, S. Ferrari, R. Rizzoli

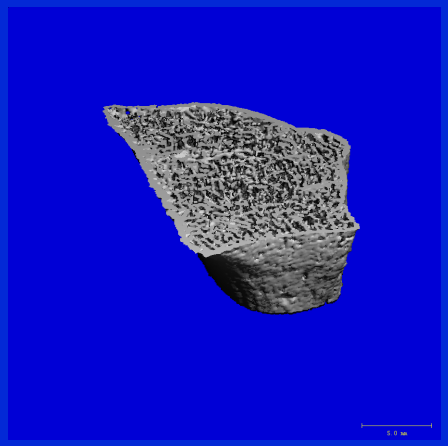
Division of Bone Diseases,
University Hospitals and Faculty of Medicine of Geneva

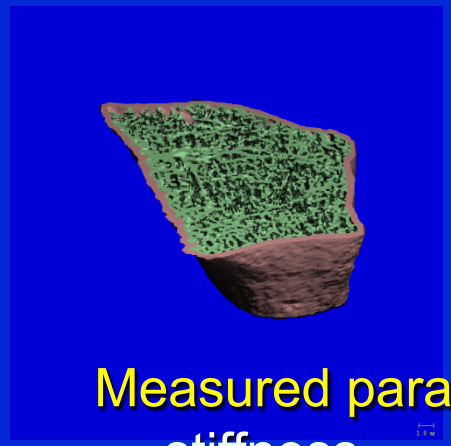
ASBMR - October 6 2013

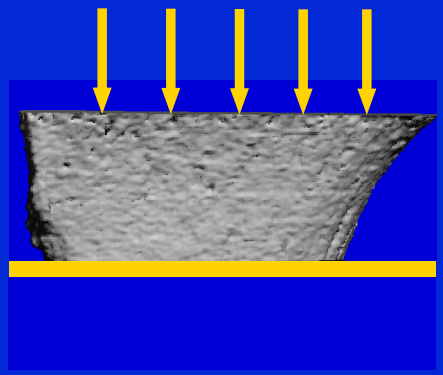
Chevalley et al. Bone 2013;55:377-83

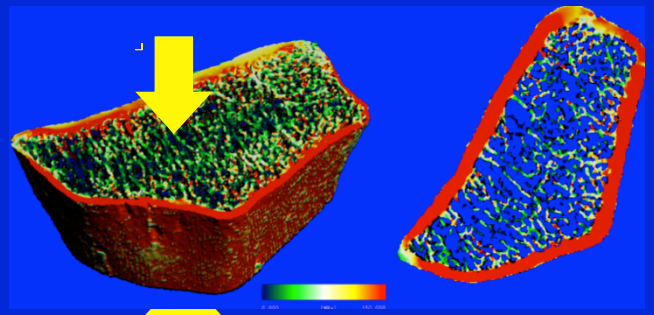
Finite elements analysis

- HR-pQCT measurement
- Separation of cortical and trabecular bone
- Compression test in the axial direction







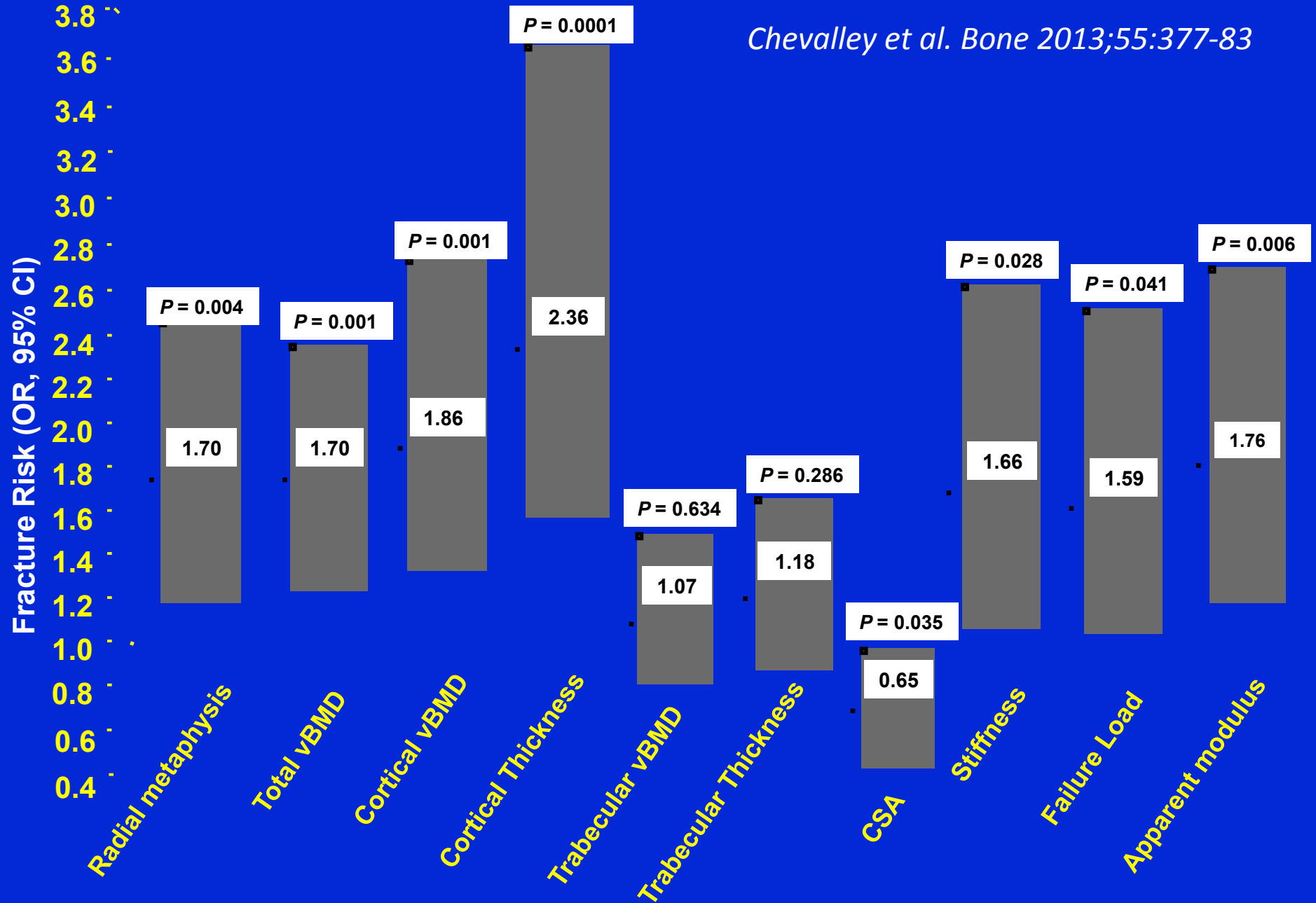


Measured parameters:

- stiffness
- estimated failure load
- Apparent modulus
- % load carried by trabecular and cortical bone
- % load carried by cortical/trabecular bone distal and proximal

Risk of Fracture in Healthy Premenopausal Women for 1 SD ↓ in radial aBMD or in Microstructure and Strength Variables of the Distal Radius

Chevalley et al. Bone 2013;55:377-83

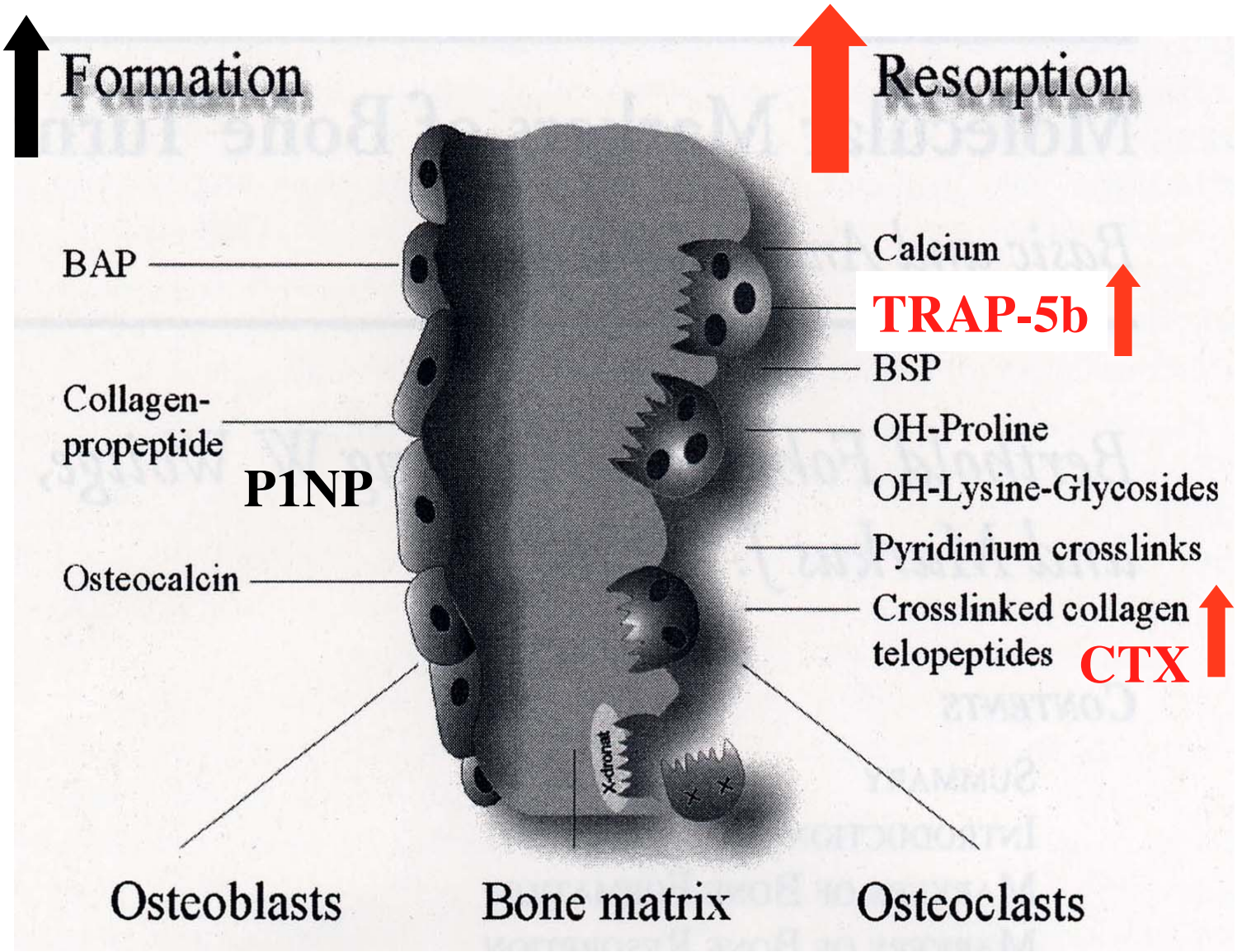


Fracture Risk Evaluation

- Low BMD = important risk factor for fracture,
  - In 50% of subject with new fracture, BMD above diagnostic BMD-threshold
  - Changes in BMD on antiresorptive treatment explains only partially the reduction in fracture risk

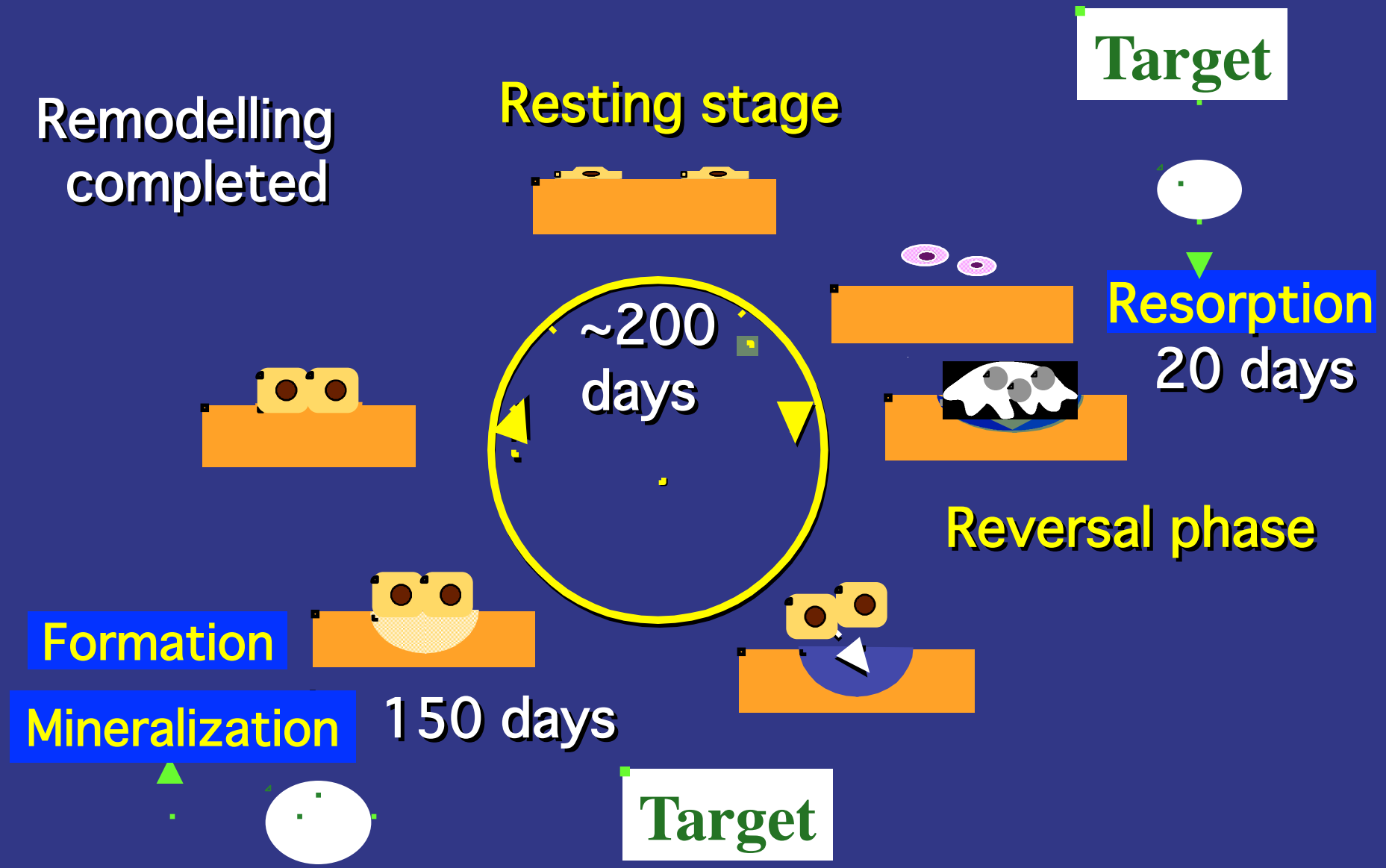
- Risk factors for fractures independent of BMD:
  - Age
  - Low BMI
  - Prevalent fracture
  - Family history of hip fracture
  - Falls
  - **Bone Turnover: Early Change Predicts BMD & Fracture**

Increased Biochemical Markers of Bone Resorption (+++) after Menopause

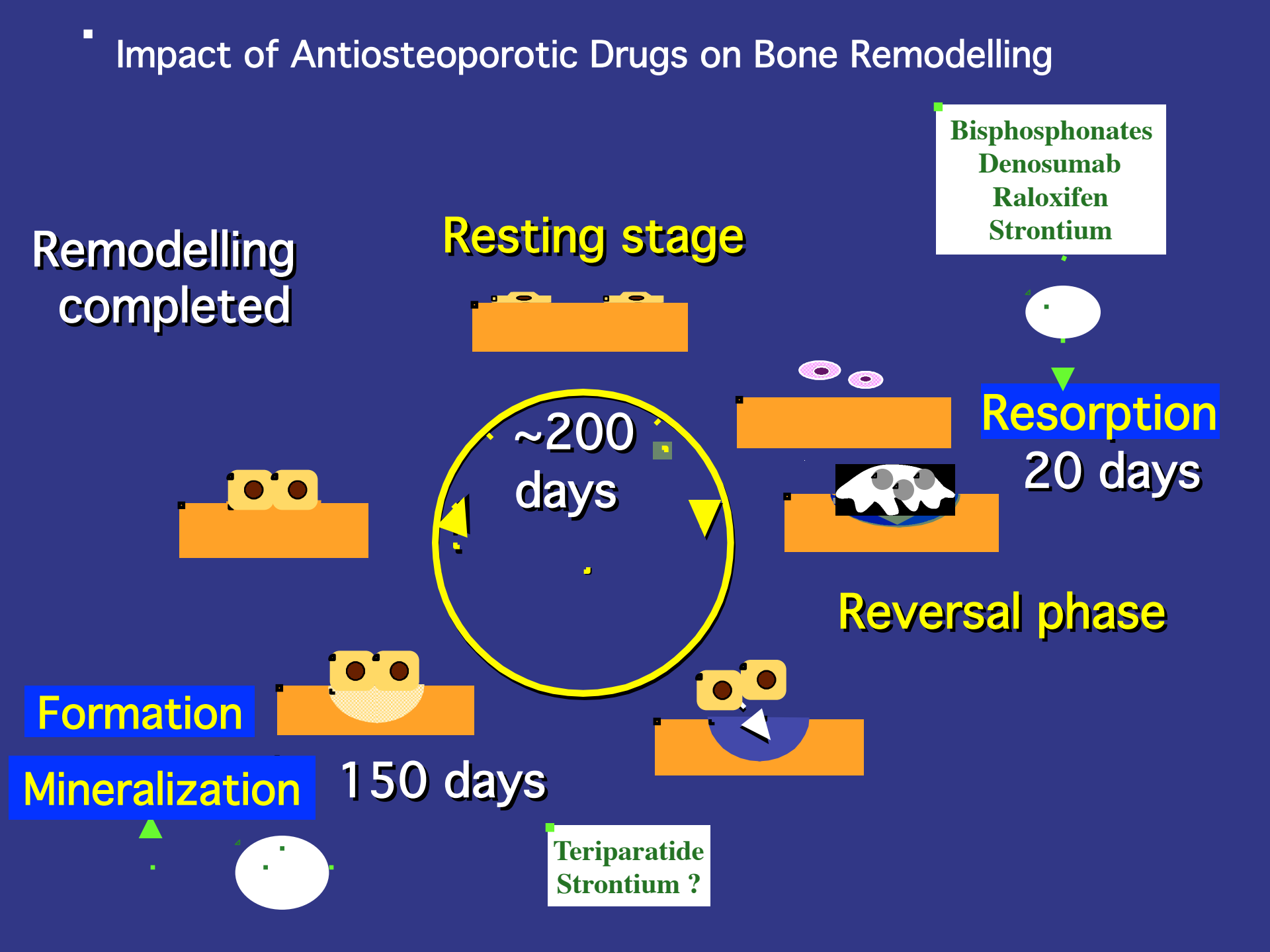


Adapted from Fohr in Osteoporosis, Pathophysiology and Clinical Management, Eds Orwoll 2003

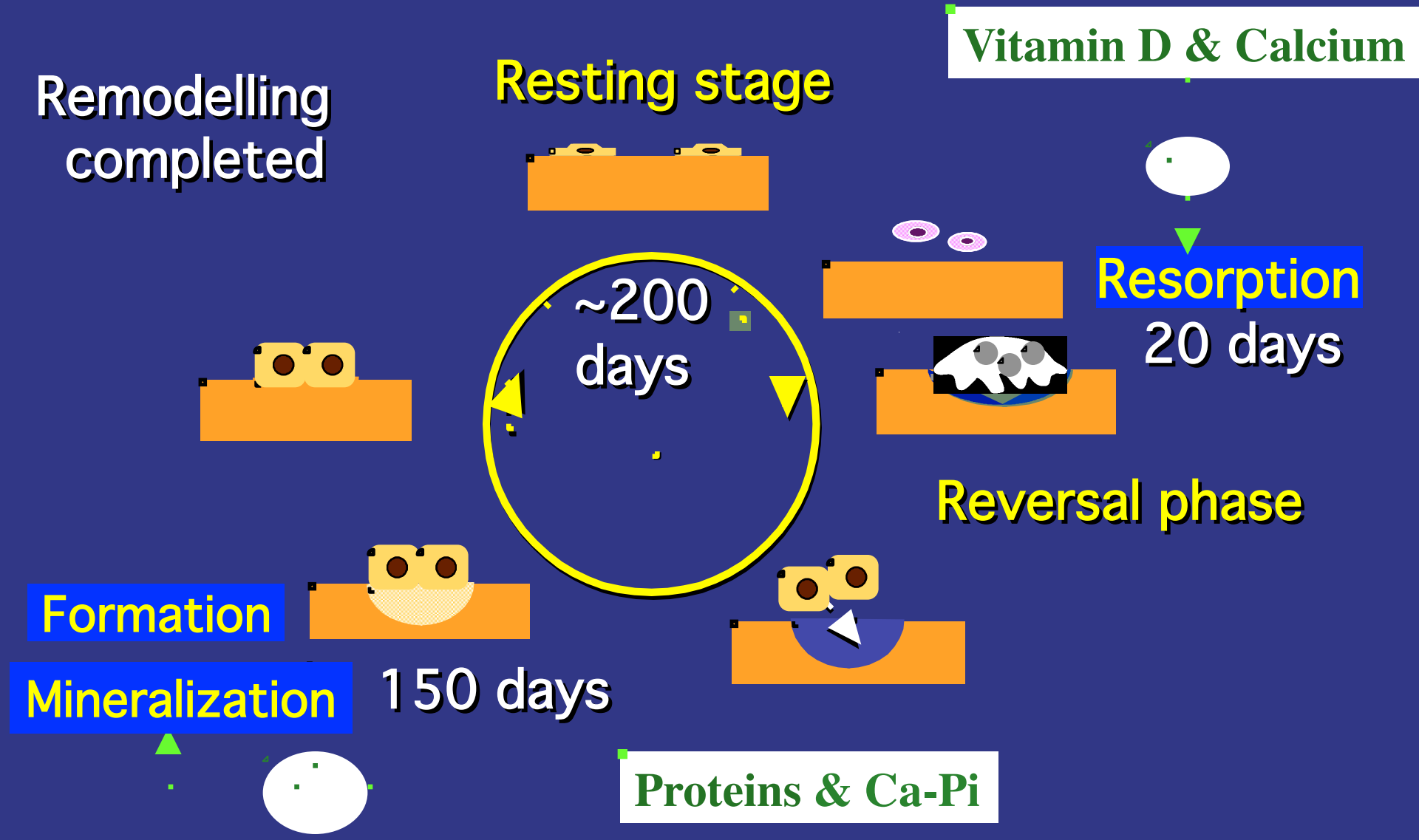
Impact of Antiosteoporotic Intervention on Bone Remodelling



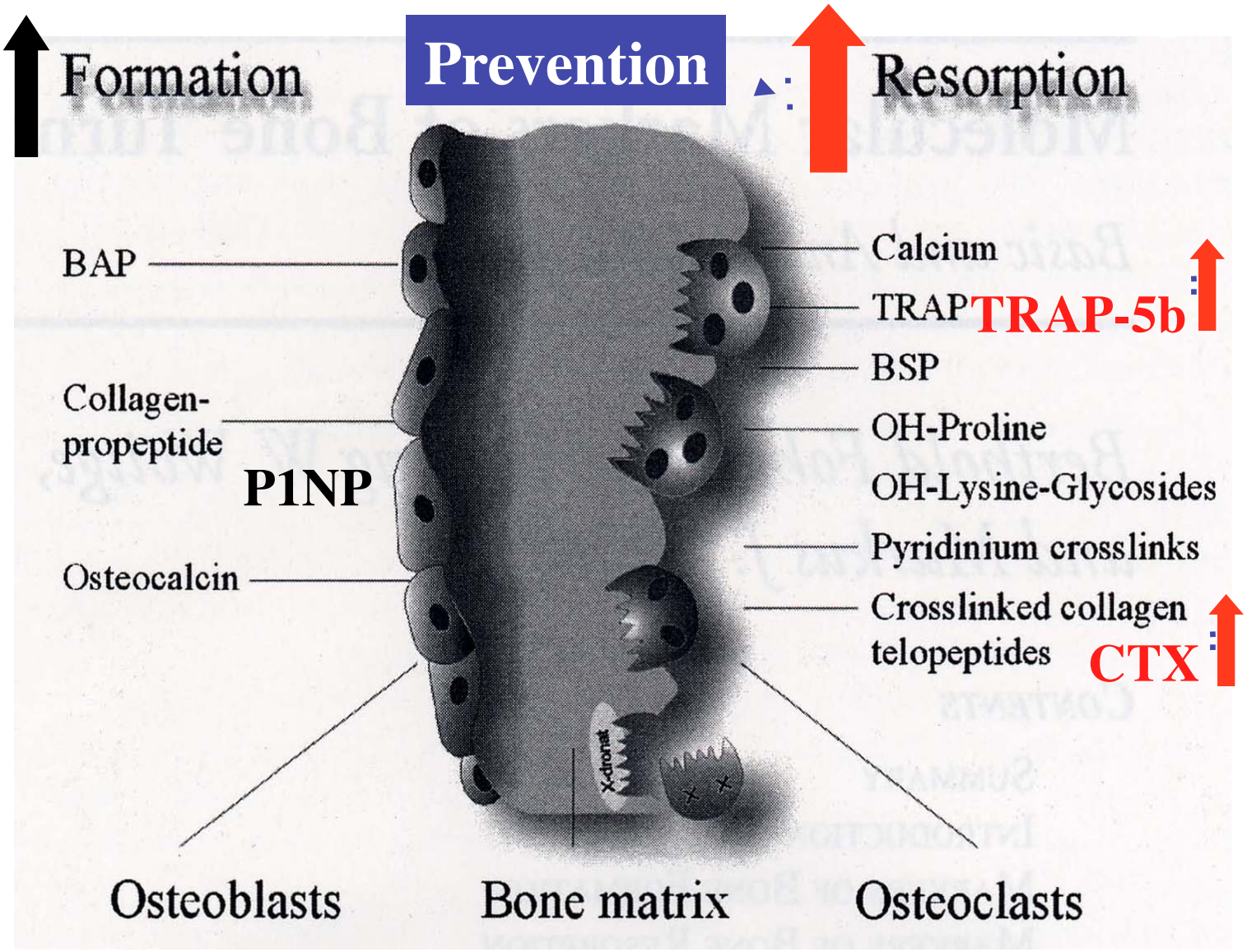
Impact of Antiosteoporotic Drugs on Bone Remodelling



Impact of Nutrients on Bone Remodelling



Nutritional Approach to Attenuate Bone Loss after Menopause



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Nutritional Inhibition of Bone Resorption

Healthy spine

50 Menopausal

Experiencing vasomotor symptoms

55+ Postmenopausal

At greater risk for vertebral fracture than any other type of fracture

70-75+ Kyphotic

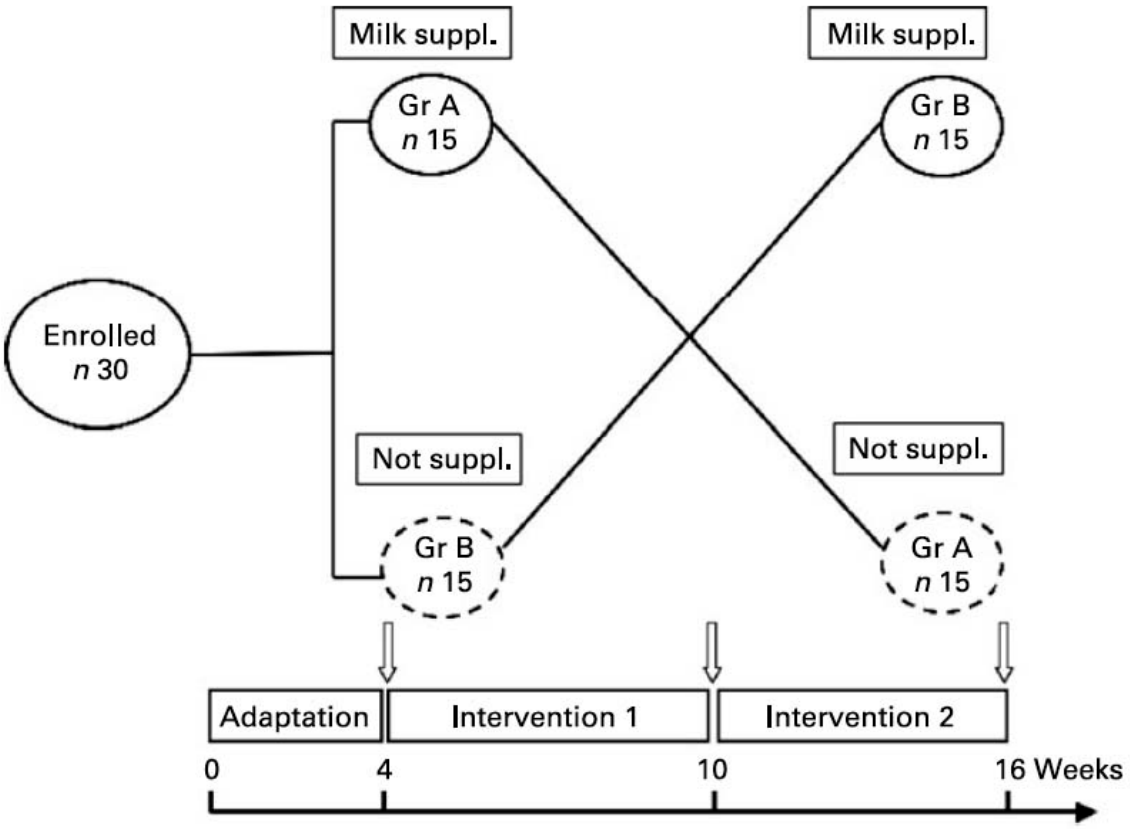
At risk for hip fracture and other types of nonvertebral fracture

Kyphotic spine

Inhibition of Bone Turnover by Milk Intake in Healthy 59 yrs Postmenopausal Women

British Journal of Nutrition 2008;100:868-87

BonjourJP, Brandolini-Bunlon M, Boirie Y, Morel-Laporte F, Braesco V, Bertière MC. Souberbielle JC



Milk suppl.

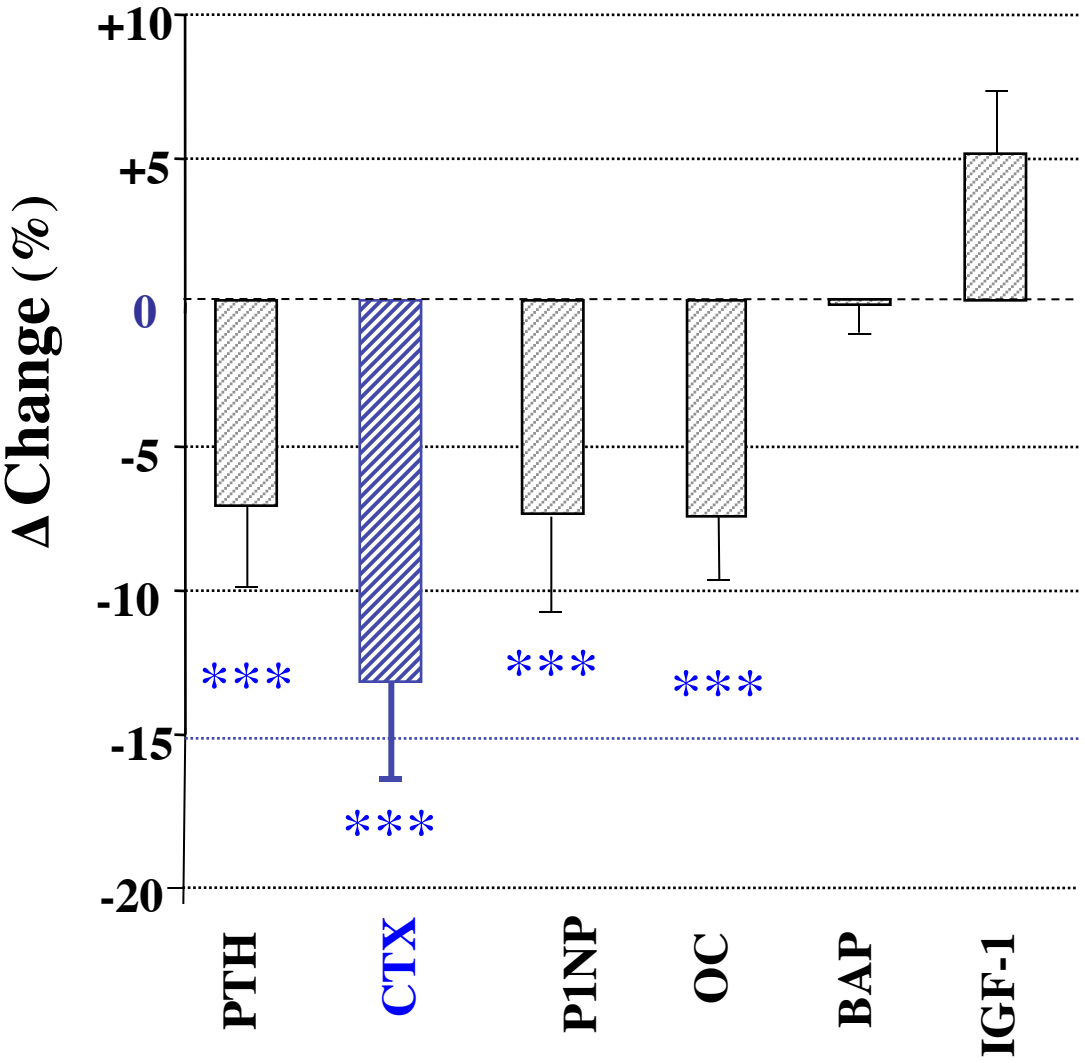
Energy (Kcal/d)	**+ 81 ns**
Protein (g/d)	**+ 11 ***
Ca (mg/d)	**+533 ***
P (mg/d)	**+352 ***
K (mg/d)	**+567 ***
Mg (mg/d)	**+ 31 #**

**** P < 0.0001***

 # P < 0.0025

Inhibition of Bone Turnover by Milk Intake in Healthy 59 yrs Postmenopausal Women

British Journal of Nutrition 2008;100:868-874



****P < 0.01*

Evidence Based Medicine

Montori and Guyatt. Respiratory Care 2001; 46:1201-1212

- **Hierarchy of Evidence Strength**

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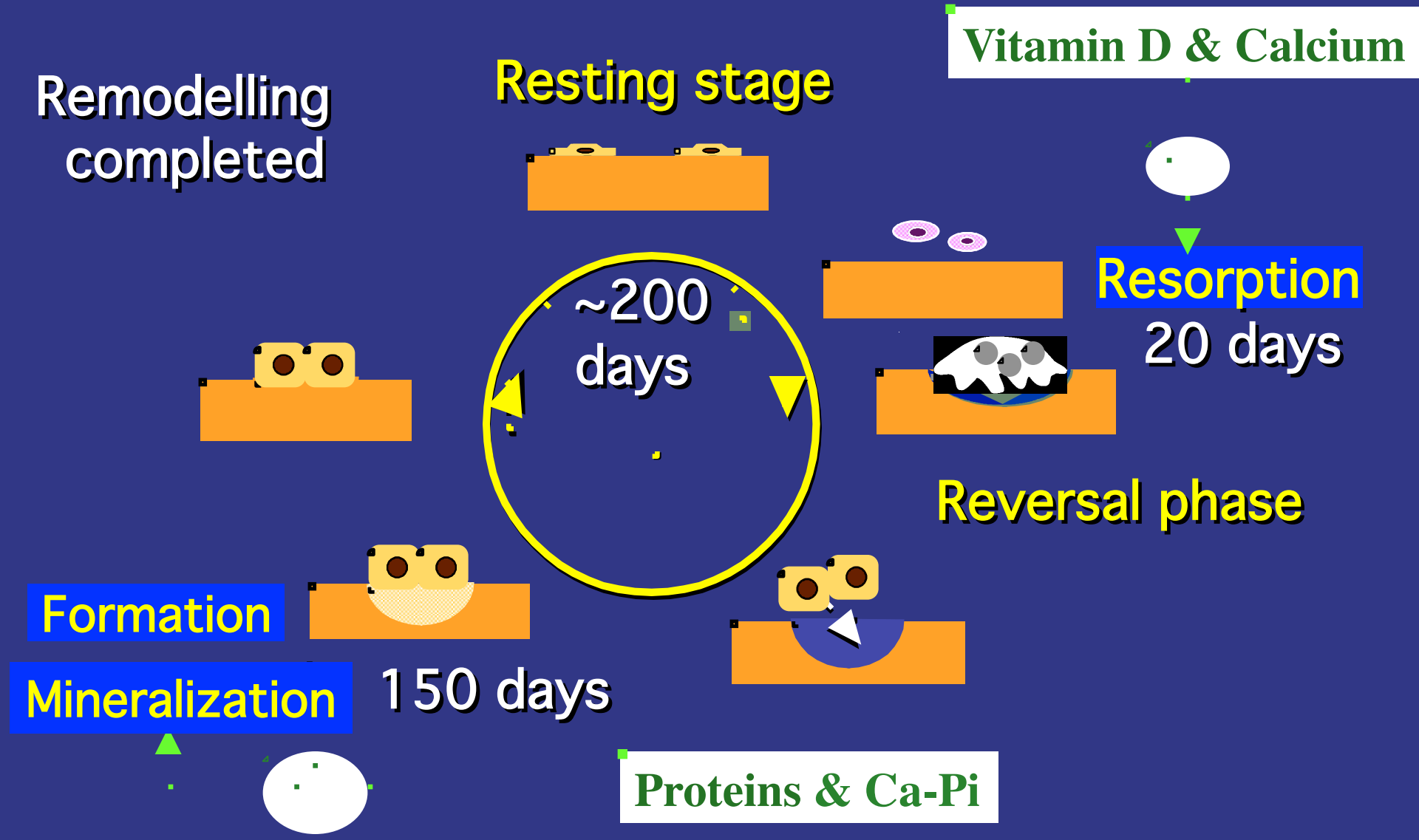
Nutritional Impact on Bone Remodeling



Nutritional Aspects of Bone Health

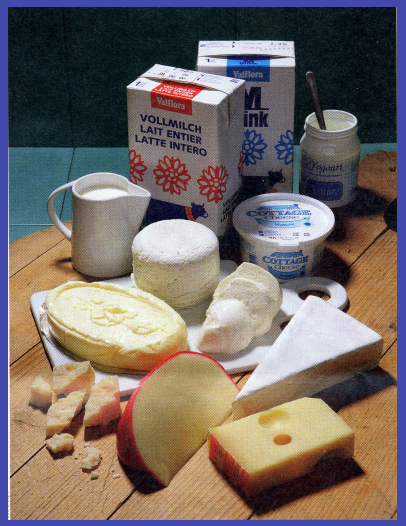
UV B (290-315 nm)

Skin Photosynthesis

Vitamin D

Food Fortification

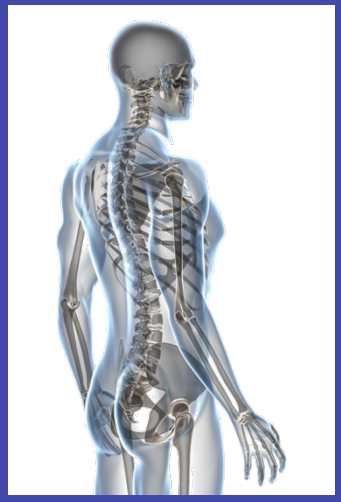
Dairy



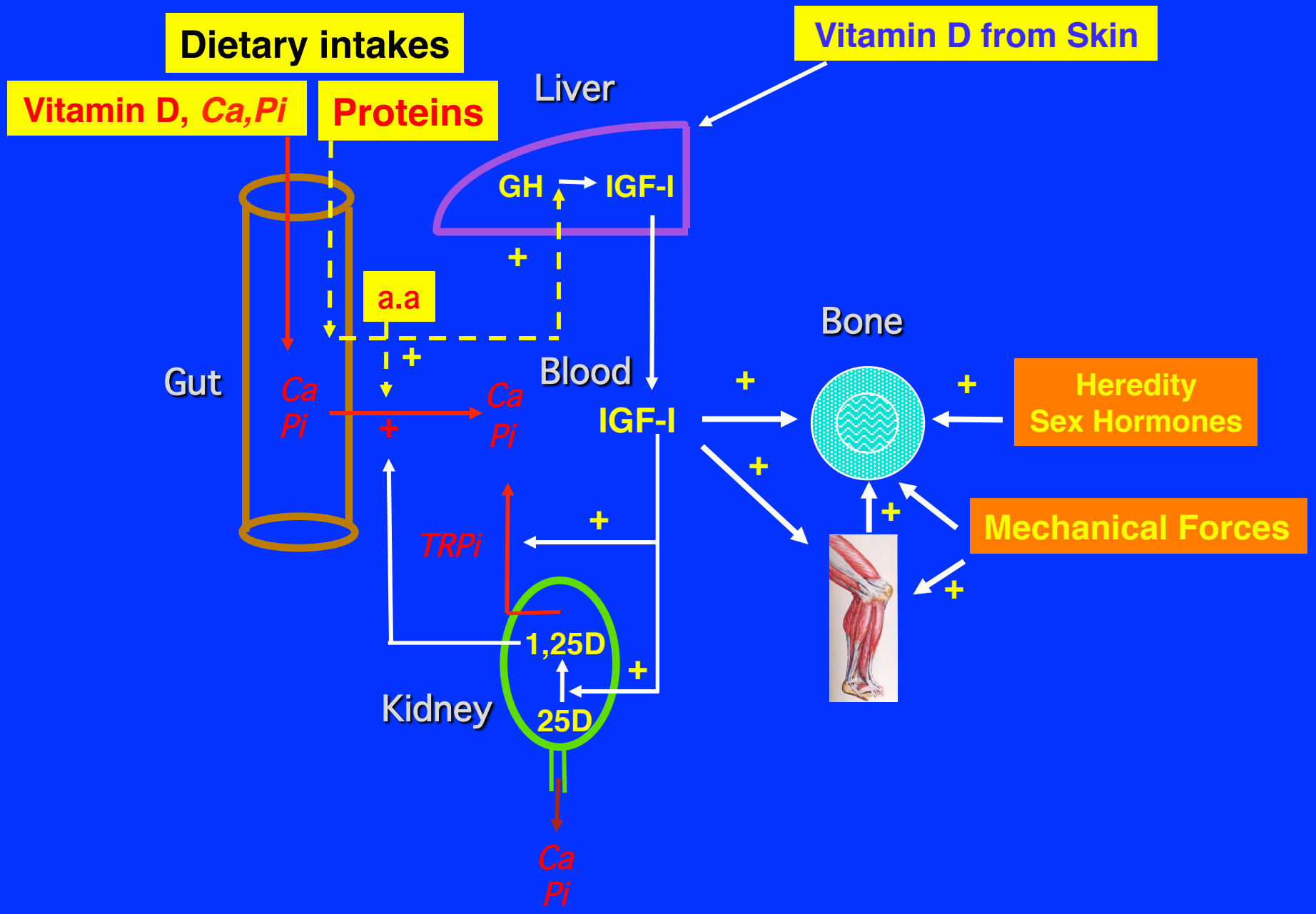
Three Essential Nutrients

Calcium
Phosphate
Proteins

Healthy Skeleton

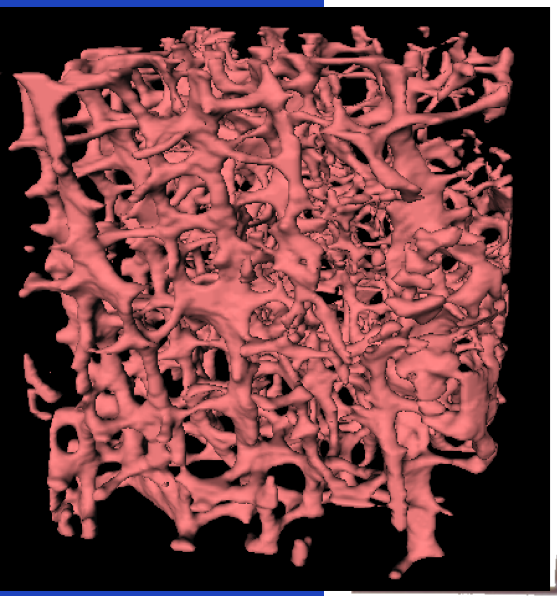


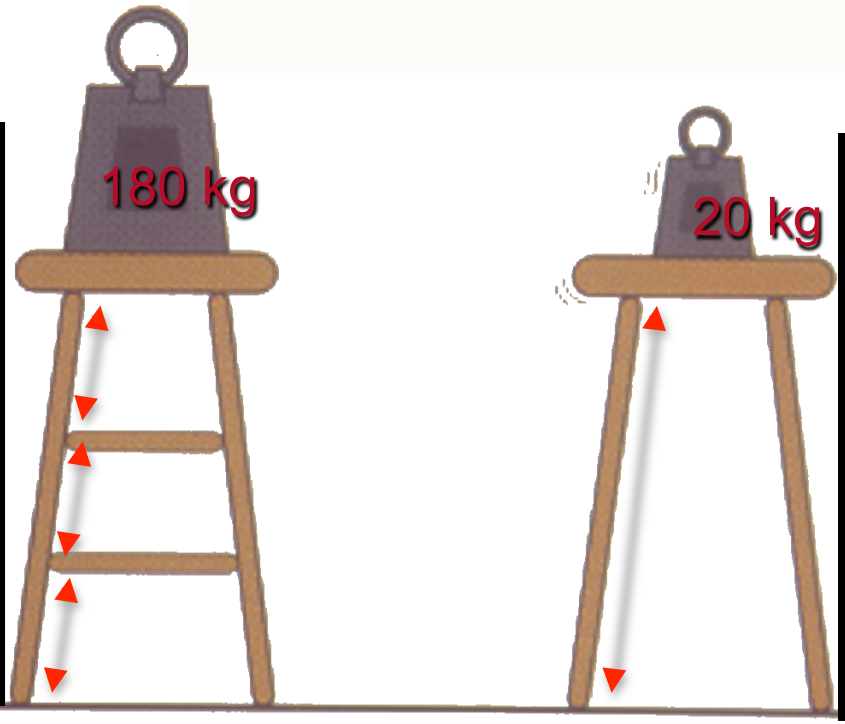
Role of Nutrients on Bone and Skeletal Muscle Health



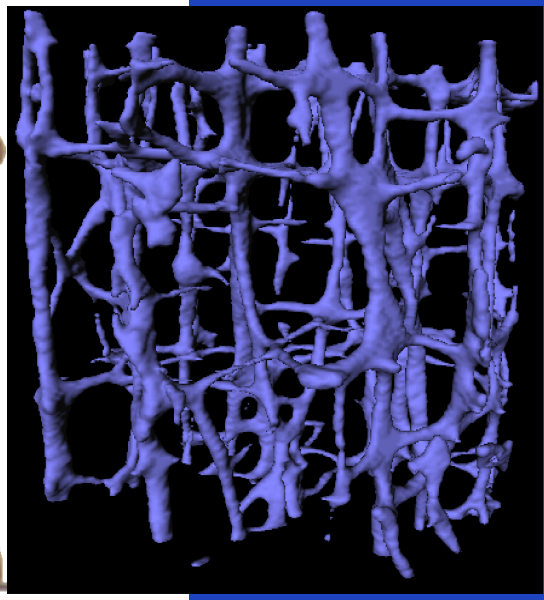
Microstructure and Bone Strength

37 Years





77 Years



Courtesy of R. Rizzoli