# MALATTIE METABOLICHE DELL'OSSO

*Osteoporosi*

*Osteomalacia*

*Osteodistrofia renale*

*Osteopetrosi*

# SINDROME OSTEOPOROTICA
# CLASSIFICAZIONE (I)

## *OSTEOPOROSI PRIMITIVE*

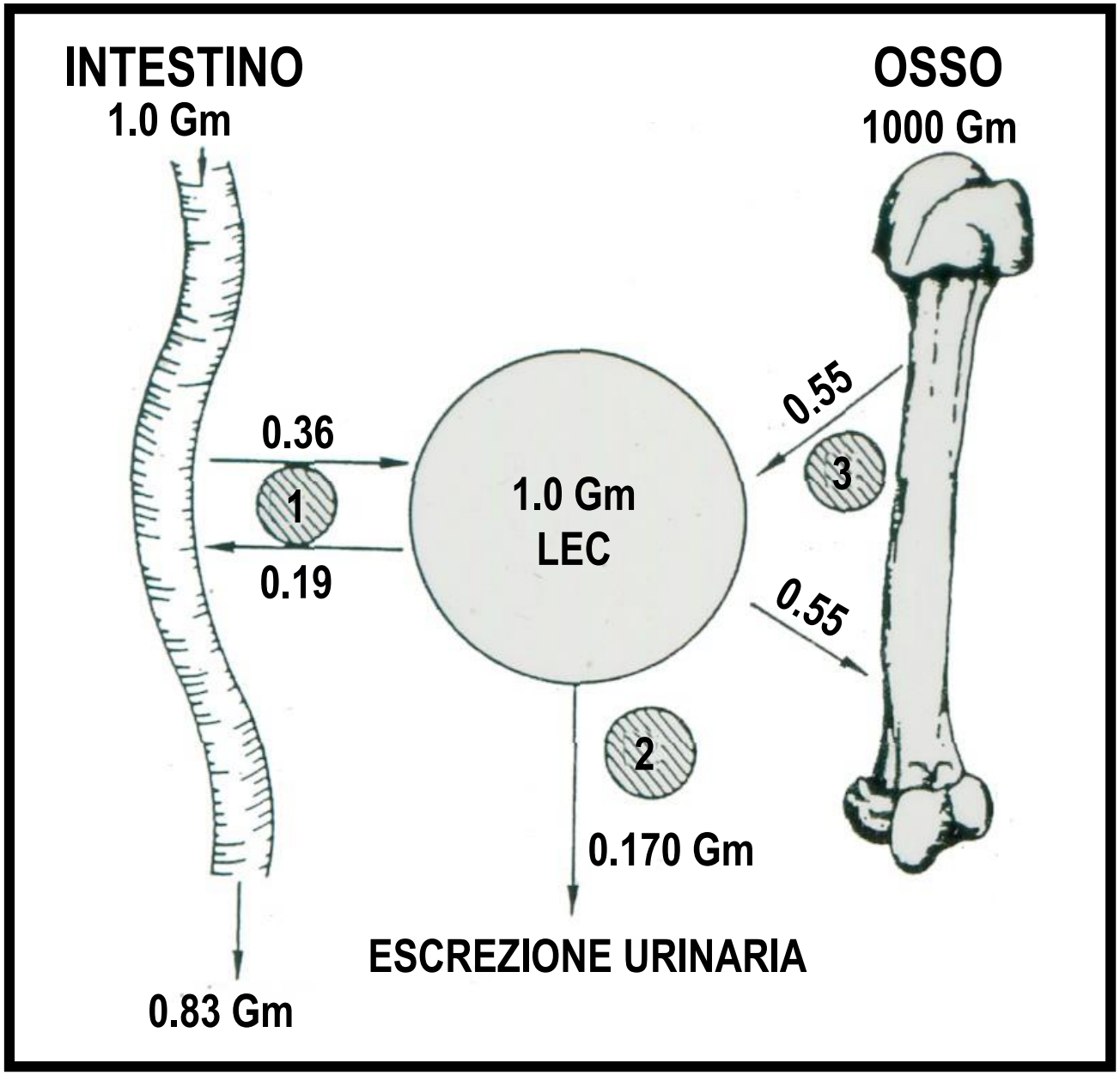
- *Osteoporosi idiopatica*
- *Osteoporosi involutiva postmenopausale*
- *Osteoporosi involutiva senile*

# SINDROME OSTEOPOROTICA
# CLASSIFICAZIONE (II)

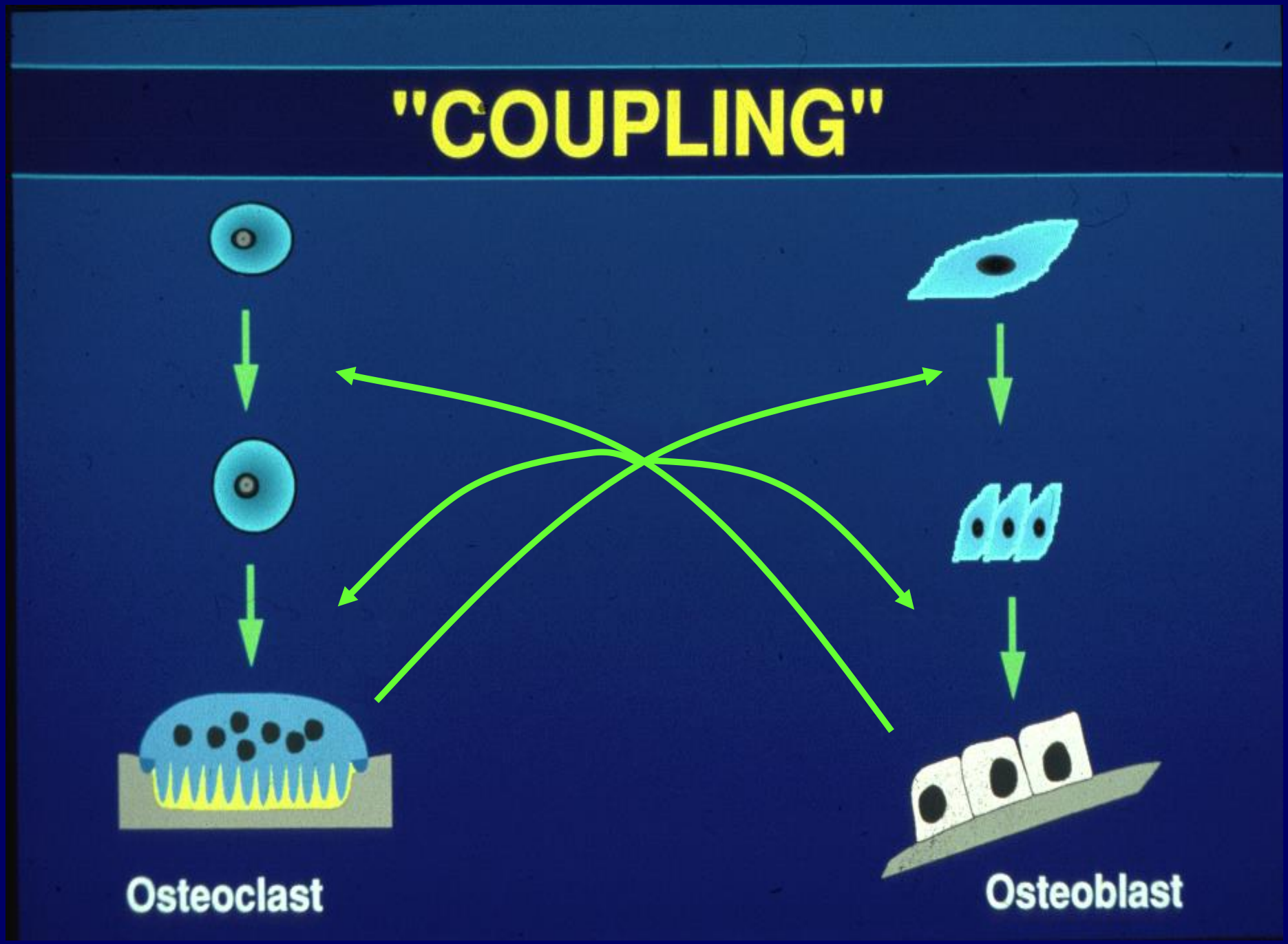
## *OSTEOPOROSI SECONDARIE*

- *Malattie genetiche*
- *Malattie endocrino-metaboliche*
- *Malattie osteoarticolari*
- *Insufficienza renale cronica*
- *Malattie ematologiche*
- *Malattie neoplastiche*
- *Malattie dell'apparato digerente*
- *Iatrogene*
- *Immobilizzazione*

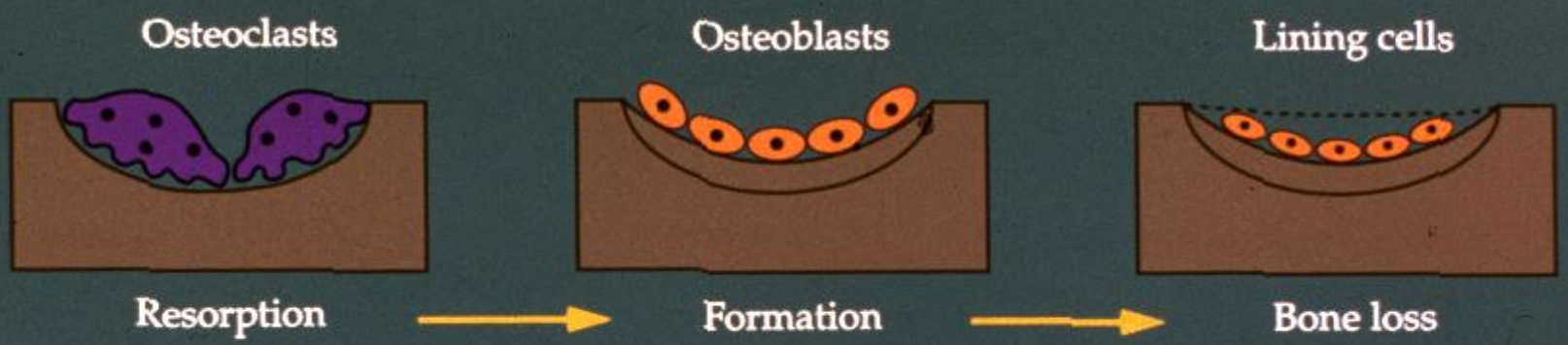
# SISTEMA DI OMEOSTASI DEL RICAMBIO CALCICO



# "COUPLING"

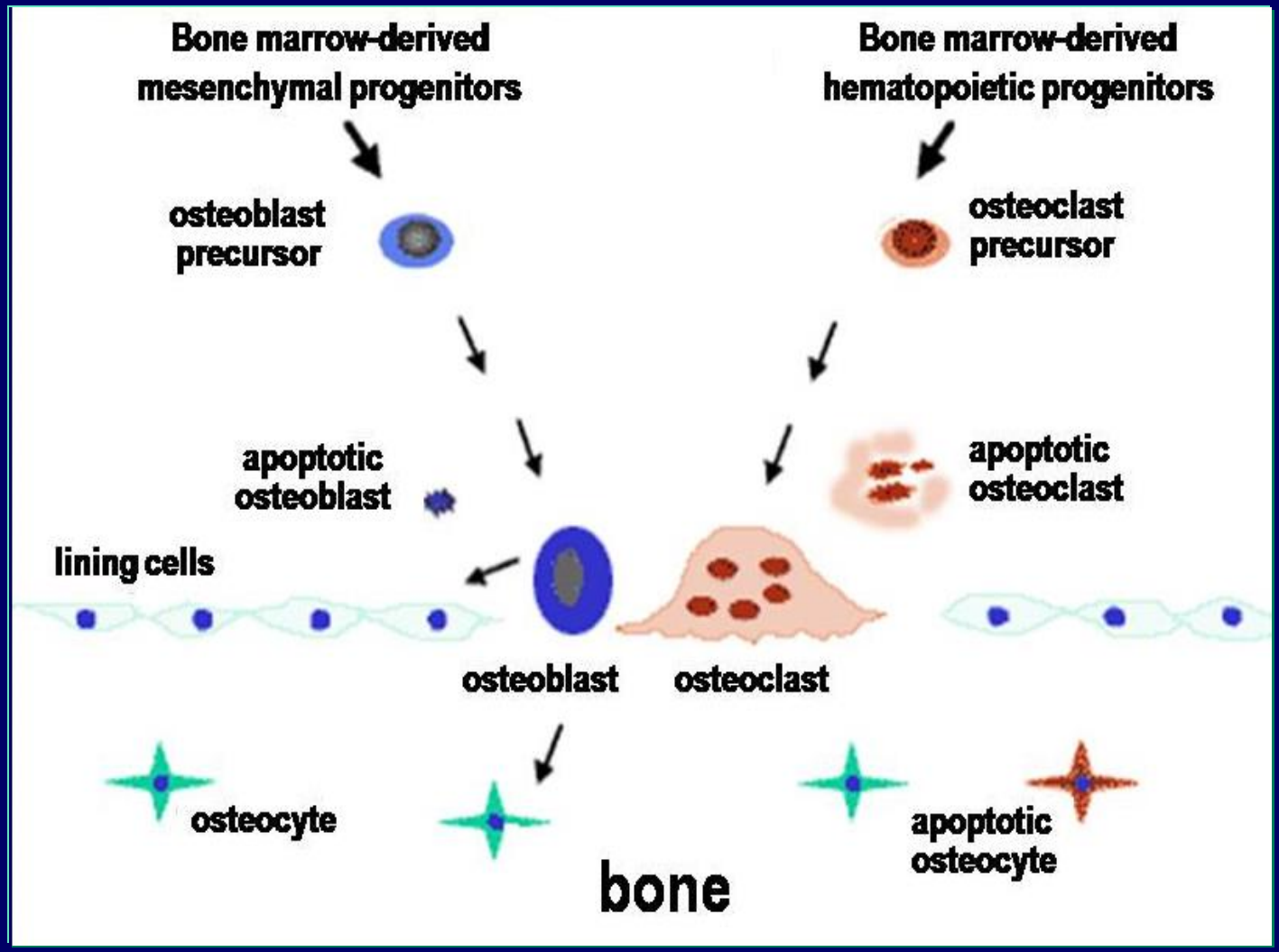


# Bone turnover in a remodeling unit in adults

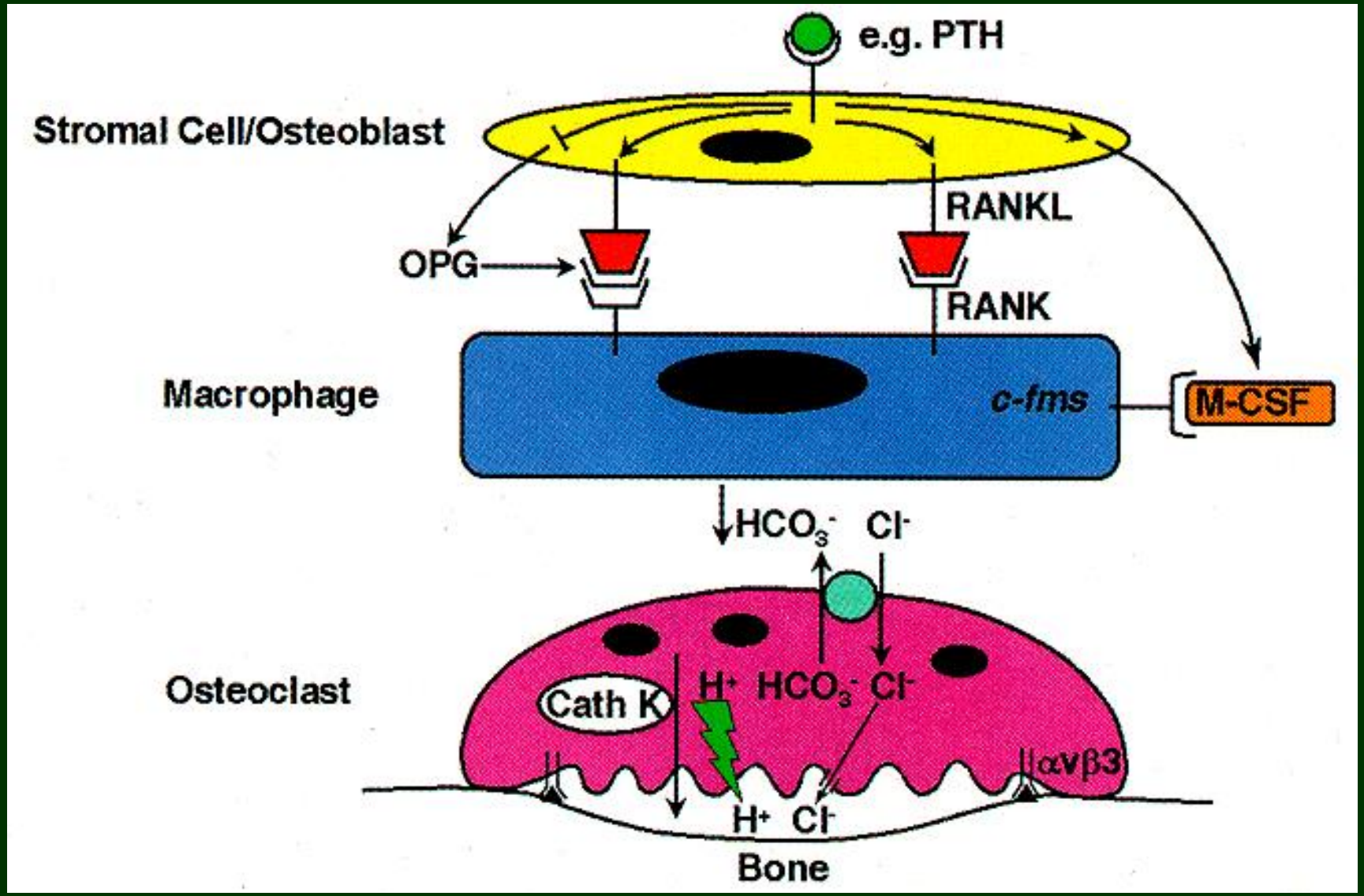


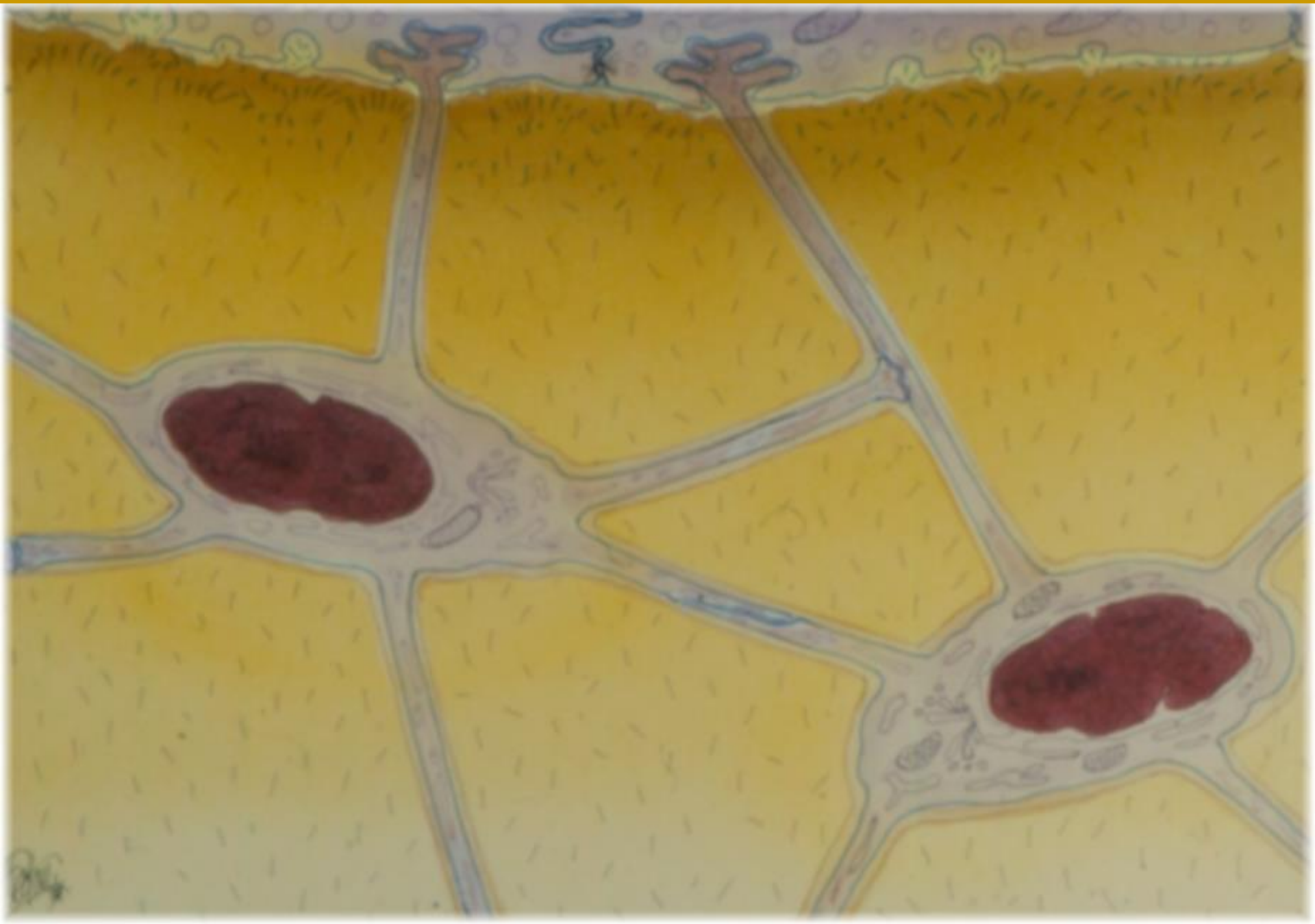

| | |
|---|---|
| Trabecular bone | 20% of the skeletal mass<br>80% of the turnover |
| Cortical bone | 80% of the skeletal mass<br>20% of the turnover |

# The Complexity of the Bone Remodelling Microenvironment

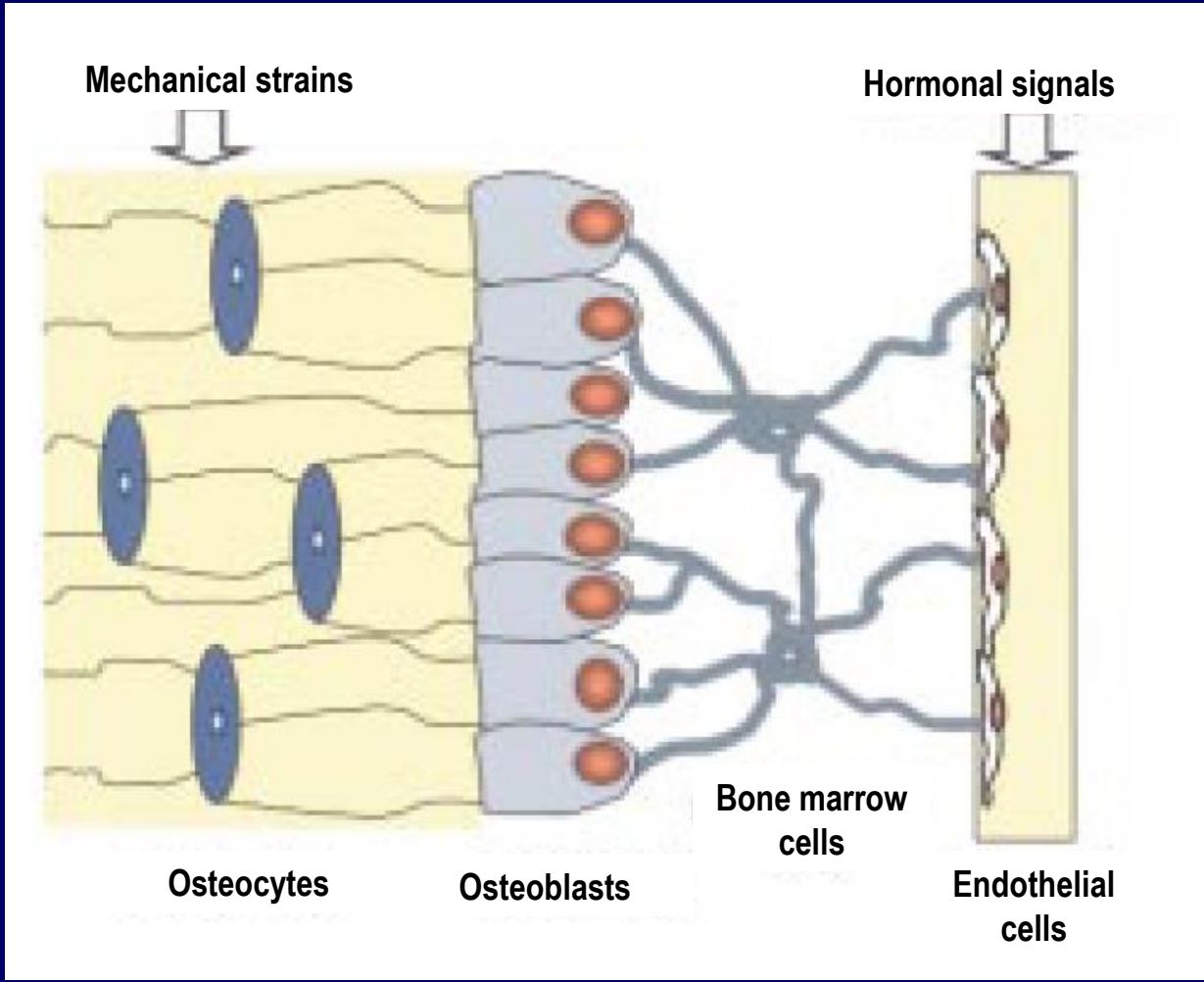


# Mechanisms of osteoclastogenesis and osteoclastic bone resorption





# Functional syncytium comprising osteocytes, osteoblasts, bone marrow stromal cells, and endothelial cells




Adapted from:JCI 104:1363, 1999

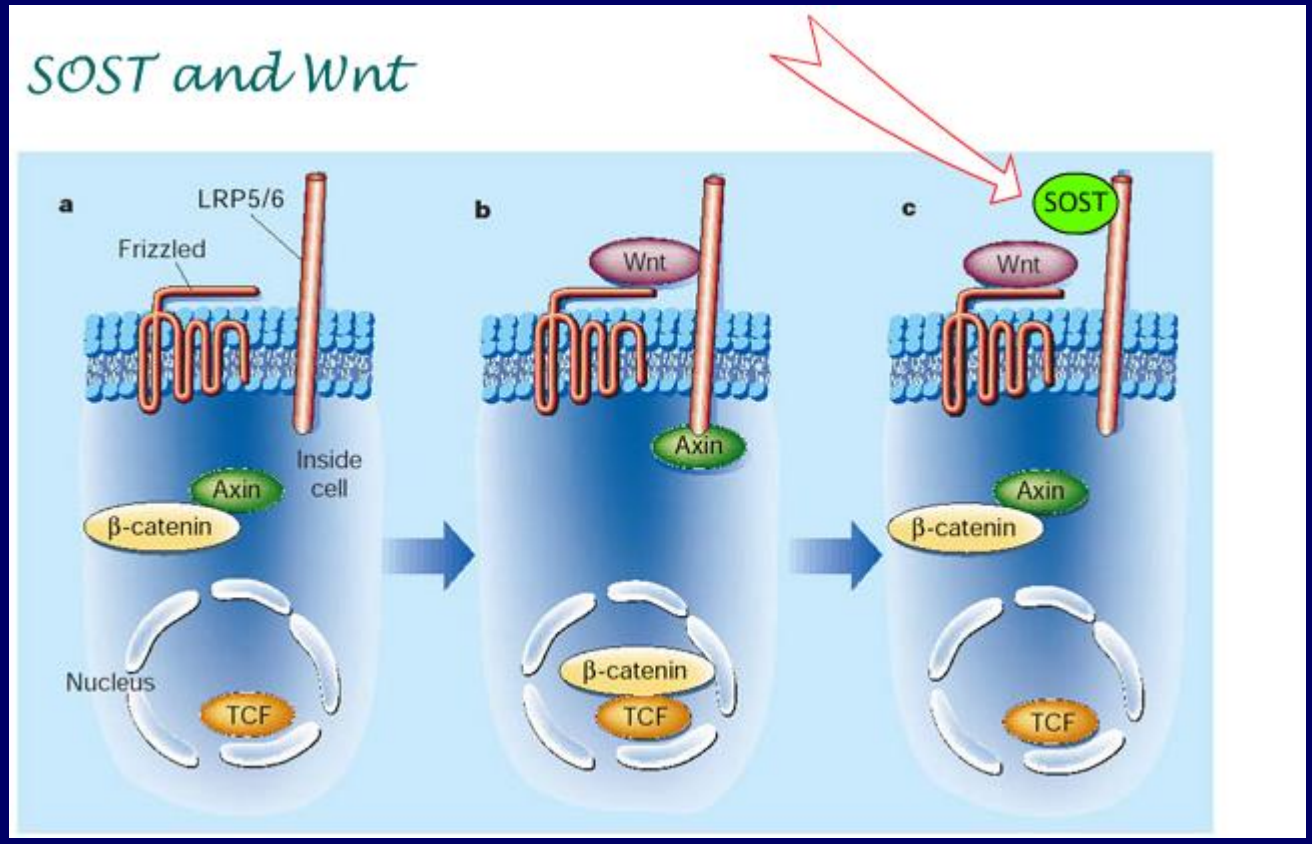
# OSTEOCYTES AS MULTIFUNCTIONAL CELLS

- Osteocyte Conversion of Mechanical Strain into Biochemical Signals
- Osteocyte Modification of Their Microenvironment
- Osteocytes as Regulators of Mineralization and Phosphate and Calcium Homeostasis
- Osteocyte Can Move

# Osteocyte Markers

| *Marker* | *Expression* | *Function* |
|---|---|---|
| E11/gp38 | Early, embedding cell | Dendrite formation? |
| CD44 | More highly expressed in osteocytes compared with osteoblasts | Hyaluronic acid receptor associated with E11 and linked to cytoskeleton |
| Fimbrin | All osteocytes | Dendrite branching? |
| Phex | Early and late osteocytes | Phosphate metabolism |
| OF45/MEPE | Late osteoblast through osteocytes | Inhibitor of bone formation / regulator of phosphate metabolism |
| DMP1 | Early and mature osteocytes | Phosphate metabolism and mineralization |
| Sclerostin | Late embedded osteocyte | Inhibitor of bone formation |
| FGF23 | Early and mature osteocytes | Induces hypophosphatemia |

# SOST and Wnt



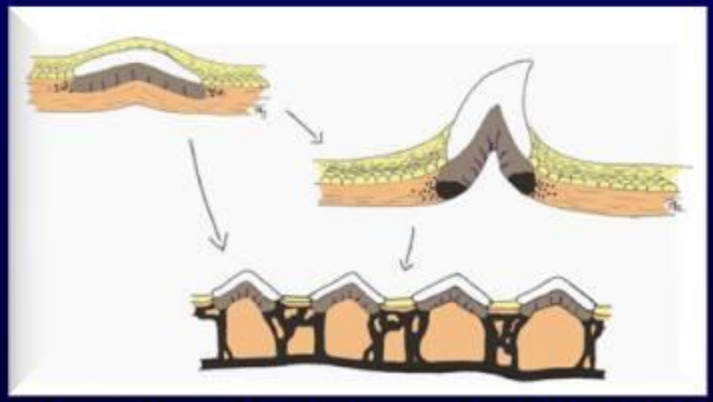

SOST is a homolog of WISE, which binds to LRP-6. SOST binds to LRP-5 which is a co-receptor in the Wnt-signalling pathway. Thus, SOST inhibits Wnt-signalling pathway, similar to Dkk inhibition.

# La Mineralizzazione

# Where Did Bone Come From?

- Following the violent moves of tectonic plates (1.5 billion years ago) large amount of minerals were washed in the ocean
- This led to the sharp increase in the diversity of multicellular organisms (a little more than 0.5 billion years ago) → The "Cambrian Explosion"
- From exoskeletons made of calcium carbonate to calcium hydroxyapatite. Why? Hydroxyapatite is a more stable mineral than a calcitic material (i.e. pH changes)

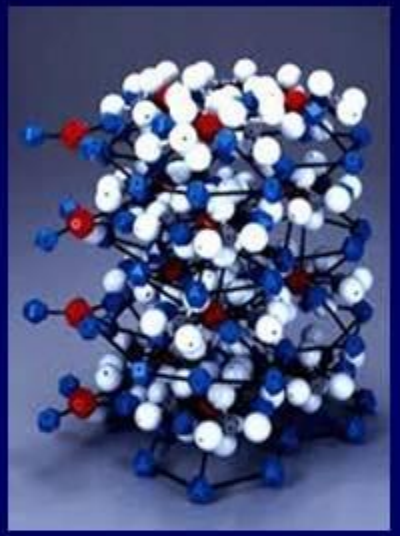
The origin of bone. Precipitation of hydroxyapatite around the basal membrane of the skin gave rise to enamel- and dentine-like tissues that formed odontodes, which became the progenitors of teeth and scales. Spread of mineralization deeper in the dermis formed shields consisting of acellular—and later cellular—bone



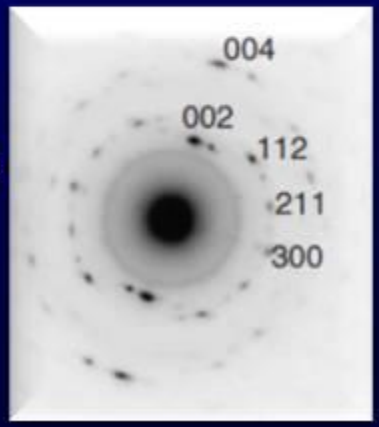
Adapted from: Acta Orthopaedica 82:393, 2011

# Skeletal Mineral Crystallites

- Bone contains ≈60-70% (w/w) of calcium phosphate mineral, ≈20-30% of organic matrix, and 10% of water
- Mineral phase of mature bone tissue consists of poorly crystalline nonstoichiometric carbonated hydroxyapatite (DAHLLITE) with hexagonal crystal structure
- Bone crystallites are the smallest biogenic crystals known: 2-6 nm thick, 30-50 nm wide, and 60-100 nm long → EXTREMELY HIGH SURFACE TO BULK RATIO with consequent increased interactions with organic matrix

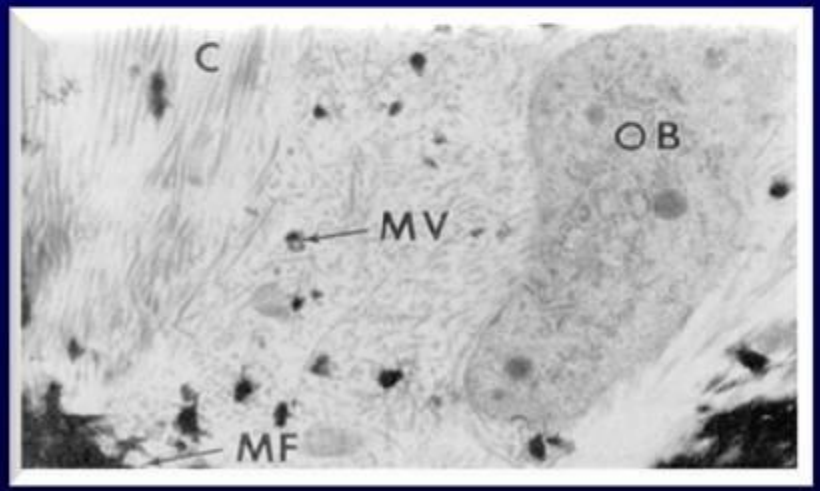


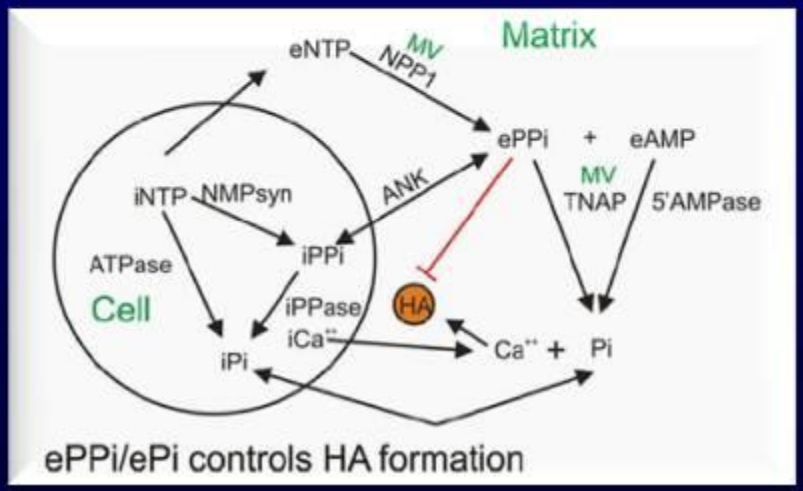
- Despite their small size they are very stable and resistant to dissolution
- Bone crystallites are anisotropic with consequent "mechanical anisotropy"
- The compressive elastic modulus of the bone crystallites is ≈40GPa, lower that of geological apatites (≈100-120 Gpa)
- The mineral particles are aligned along the collagen fibril axis



# Phosphate: Role in Mineralization

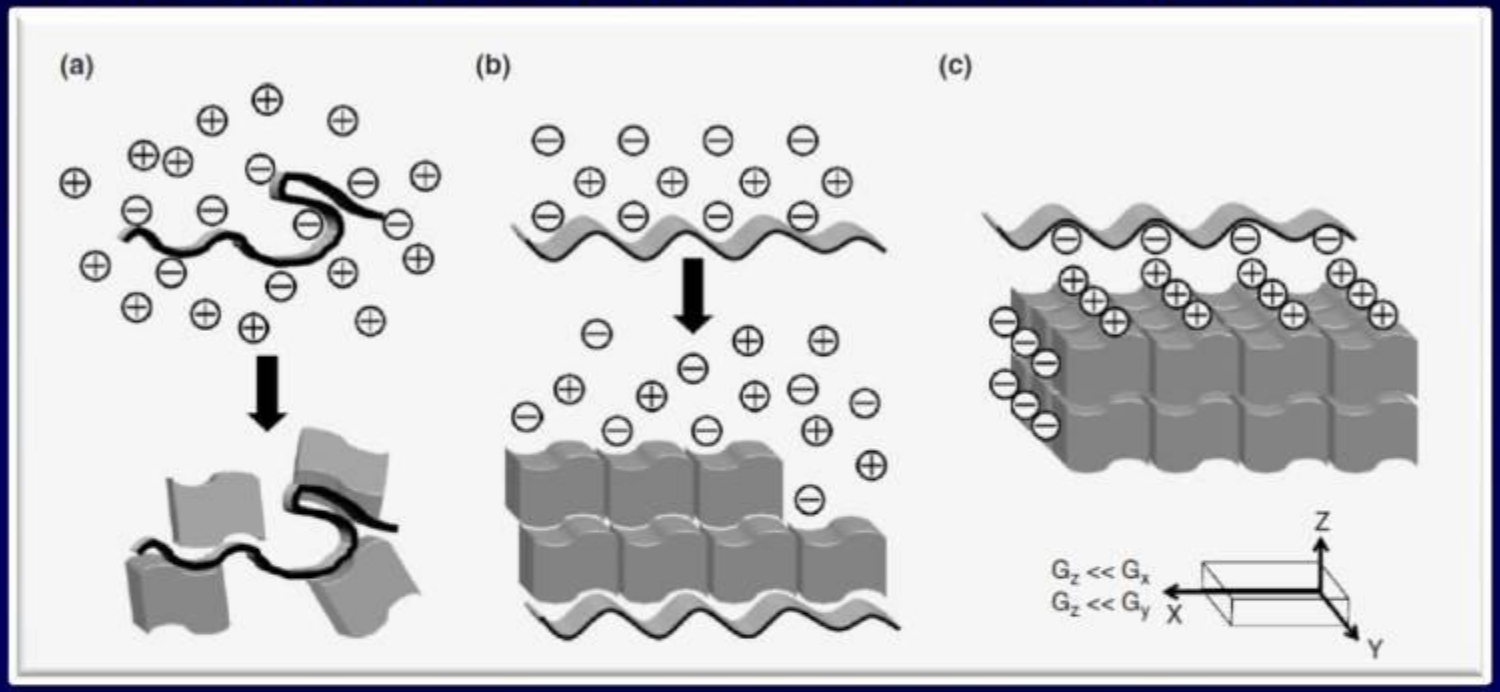
- Cellular $PO_4^{3-}$ levels are in the range of 5 mM (is required for metabolic reactions!) vs. 0.1 µM [$Ca^{2+}$]
- Pyrophosphate is formed in a number of ATP requiring reaction and transported into the matrix by the progressive ankylosis protein
- Mineralization is triggered by alterations of the $PO_4^{3-}$ /pyrophosphate ratio




Adapted from: Semin Immunopathol 33:409, 2011

# The classical models of regulation of mineralization by acidic proteins

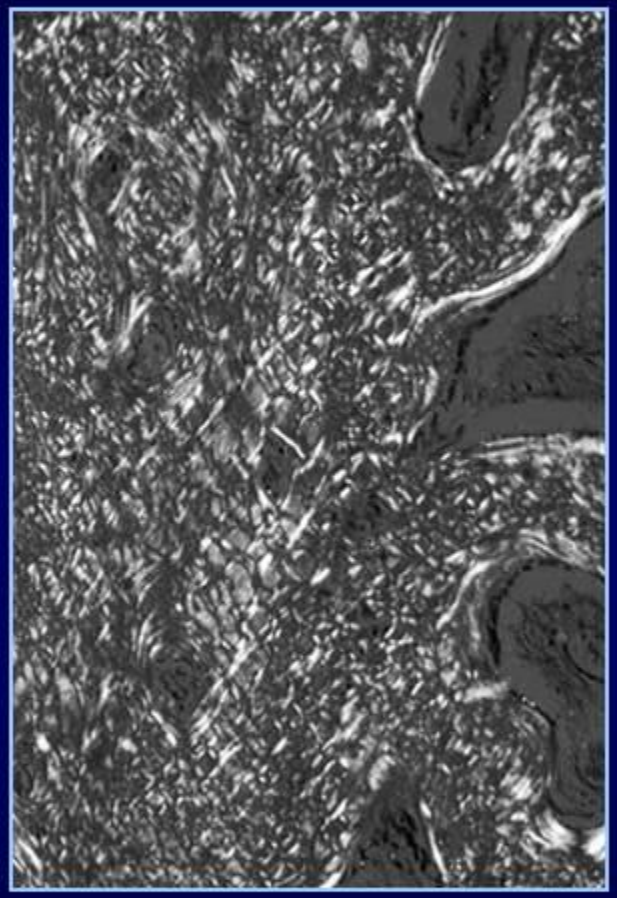



Adapted from: WIREs Nanomed Nanobiotechnol 3:47; 2011

## Effects of Bone Matrix Molecules on Mineralization In Vitro

| Promote or support apatite formation | Inhibit mineralization | Dual finction (nucleate and inhibit) | No published effect |
|---|---|---|---|
| Type 1 collagen | Aggrecan | Biglycan | Decorin |
| Proteolipid (matrix vesicle nucleational core) | a2-HS glycoprotein | Osteonectin | Lumican |
| BAG-75 | Matrix gla protein(MGP) | Fibronectin | Mimecan |
| Alkaline phosphatase | Osteocalcin | Bone sialoprotein Osteopontin | Tetranectin |
| | | MEPE | Osteoadherin |
| | | | Thrombospondin |

## Primary



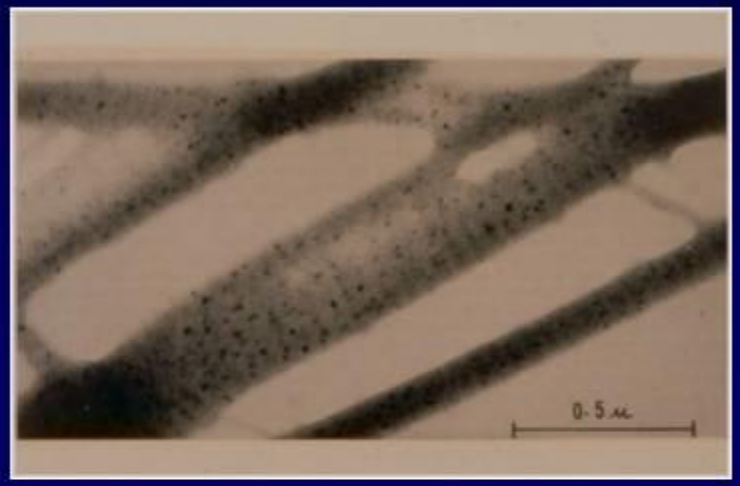
High water content
Fast mineralization
Low collagen/NCP ratio

## Secondary

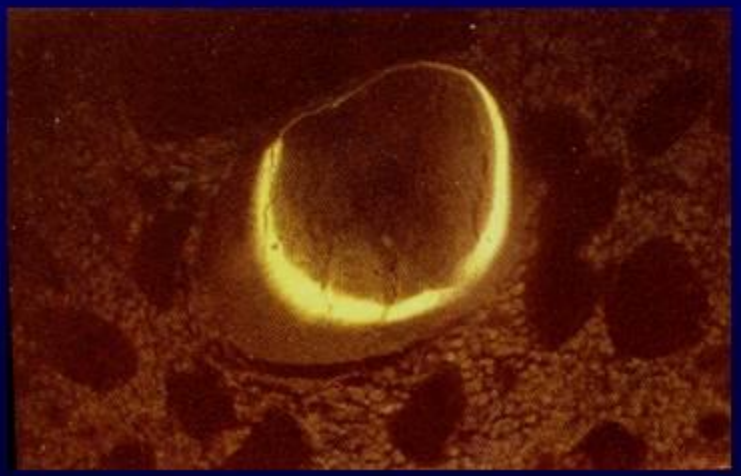
Low water content
Slow mineralization
High collagen/NCP ratio

# Defects of Mineralization

Intrinsic: altered bone matrix proteins




Extrinsic: mineral deficiency, pirophosphate concentrations, vitamin D



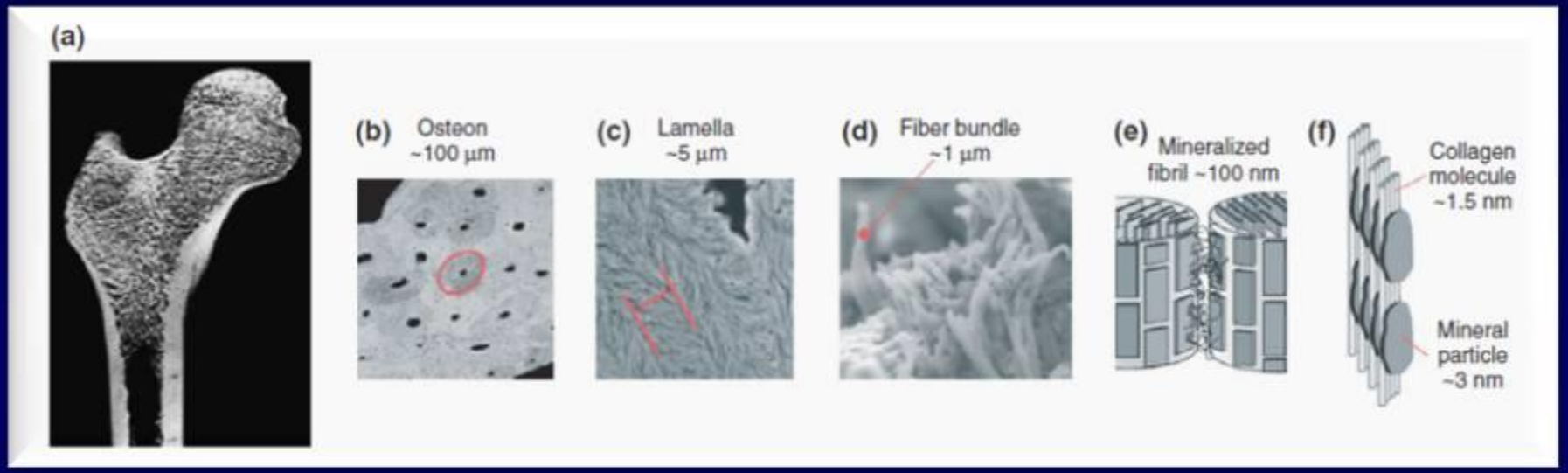


**BONE QUALITY**

**BONE DENSITY**

**BONE STRENGTH**

# Hierarchical organization of bone from macro- to nanoscale



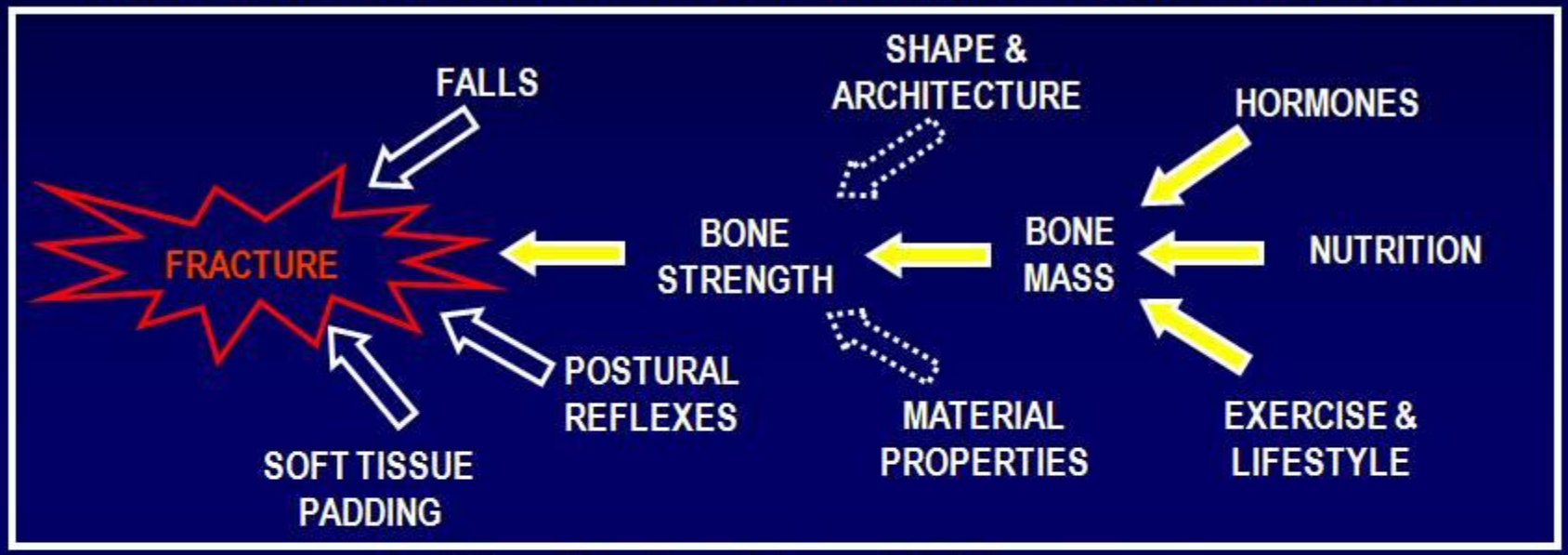

(a) Organ level—femoral bone. (b) Tissue level—haversian (osteonal) compact bone; red ellipse outlines an individual osteon. (c) Microscopic level—bone lamellae are the structural elements of lamellar bone tissues; red parallel lines outline one lamella. (d) Mesoscopic level arrays (bundles) of mineralized collagen fibrils. (e) Nanoscale level—mineralized collagen fibrils. (f) Molecular level—arrangements of collagen molecules and mineral crystallites in the mineralized collagen fibril

Adapted from: WIREs Nanomed Nanobiotechnol 3:47; 2011

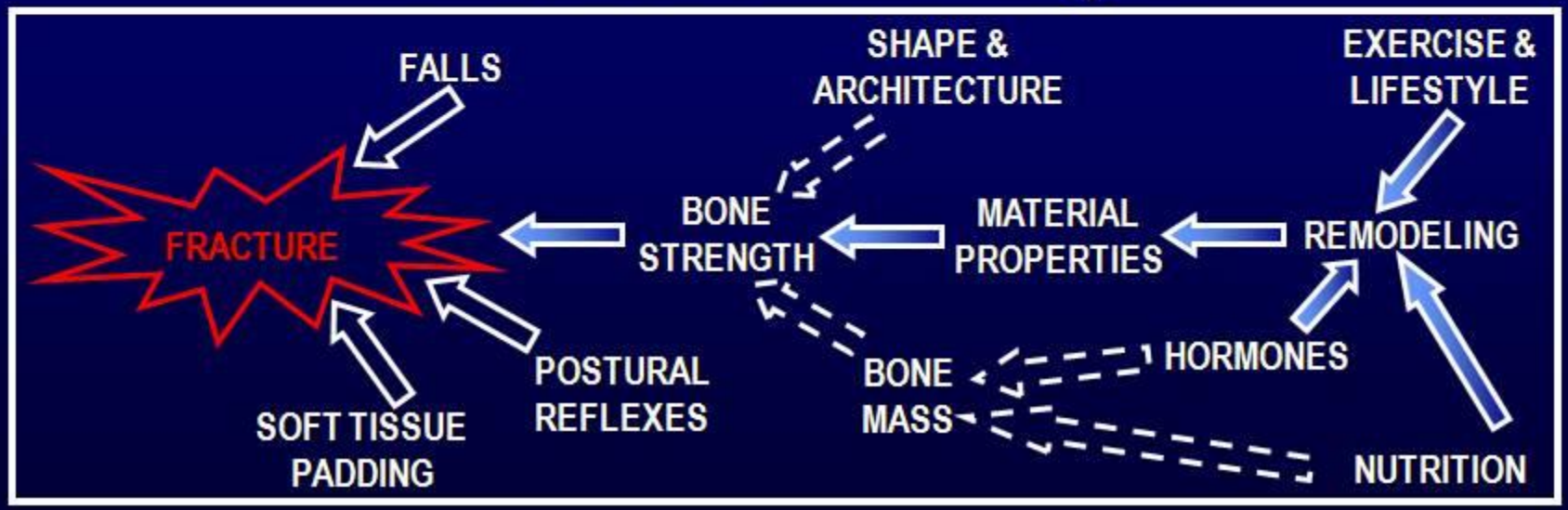
SOD Malattie del Metabolismo Minerale e Osseo

F.I.R.M.O. Fondazione Raffaella Becagli

## Hierarchical Arrangement of Factors Contributing to Osteoporotic Fracture Risk




## Revision of the Usual Hierarchical Arrangement



# Cosa Abbiamo Imparato di Pratico Da Tanta Ricerca?

# La diagnosi di osteoporosi

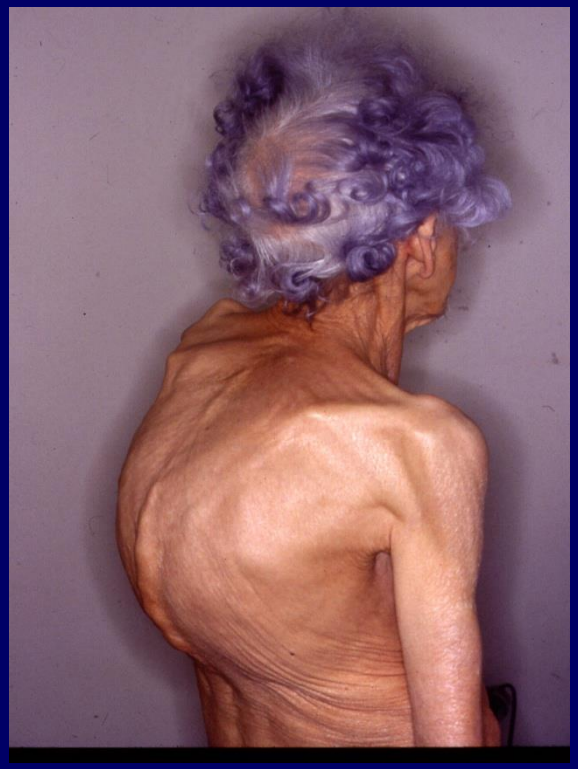
- **Valutazione clinica**
- Valutazione strumentale
- Valutazione metabolica

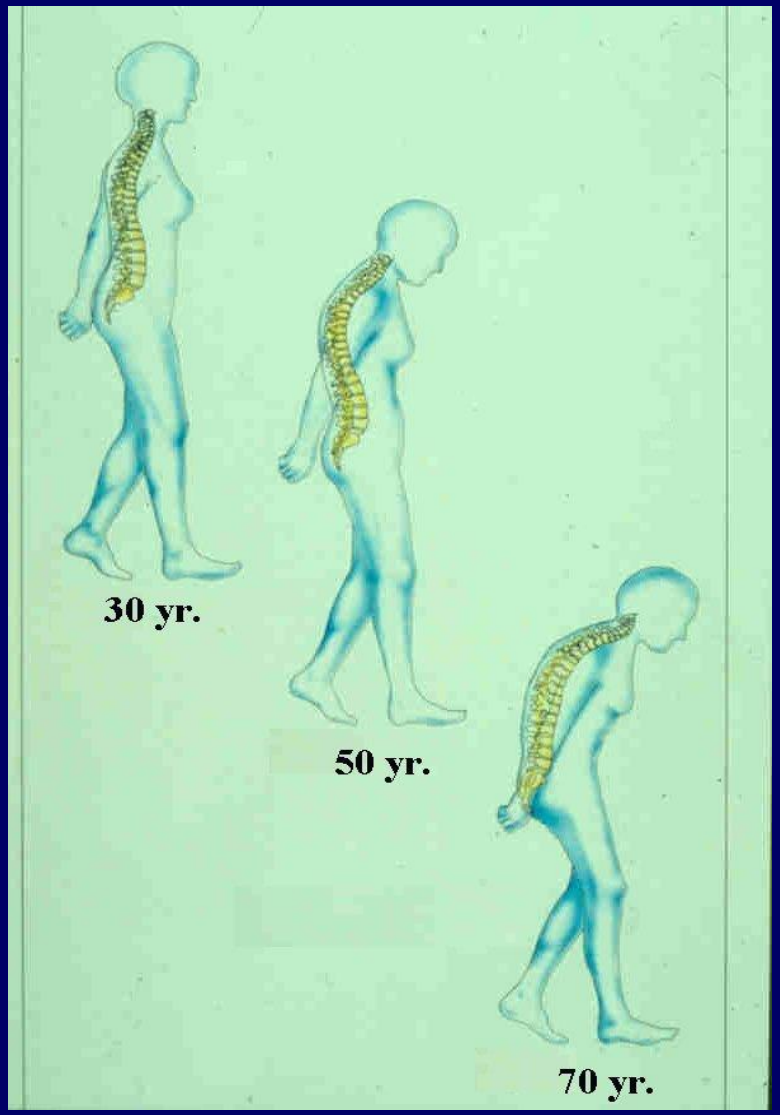
# Valutazione clinica

- Anamnesi
- Esame obiettivo
- Valutazione dei fattori di rischio

# Esame obiettivo

- Silente
- Astenia soprattutto la sera
- Riduzione dell’altezza
- Cifosi





# Considerare i Fattori di Rischio

## Fattori Immodificabili

- Razziali ed etnici
- Genetici
- Sesso femminile
- Età avanzata
- Salute mentale
- Uso di cortisonici

## Fattori Modificabili

- Bassa densità minerale
- Fumo
- Magrezza
- Sedentarietà
- Basso introito di calcio
- Deficit estrogenico
- Ipertiroidismo iatrogeno
- Cadute frequenti
- Osteoporosi secondarie

# La diagnosi di osteoporosi

- Valutazione clinica
- **Valutazione strumentale**
- Valutazione metabolica

# Diagnostica Strumentale dell'Osteoporosi
## Metodiche

- Radiologia tradizionale
- Tomografia Assiale Computerizzata
- Risonanza Magnetica
- Ultrasonografia Ossea
- Densitometria Ossea

# World Health Organization (WHO) Osteoporosis Guidelines

| | |
|---|---|
| Normale | T-score ≥ -1 |
| Osteopenia | T-score tra -1 e -2.5 |
| Osteoporosi | T-score ≤ -2.5 |
| Osteoporosi stabilizzata | T-score ≤ -2.5 + frattura |

Da studi epidemiologici la soglia di - 2.5 T-score rappresenta il livello di densità che identifica il maggior numero di donne che andranno incontro a frattura

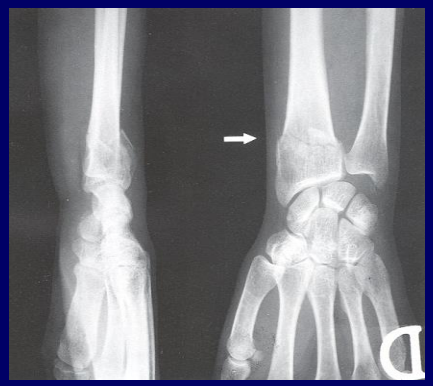
# Radiologia tradizionale

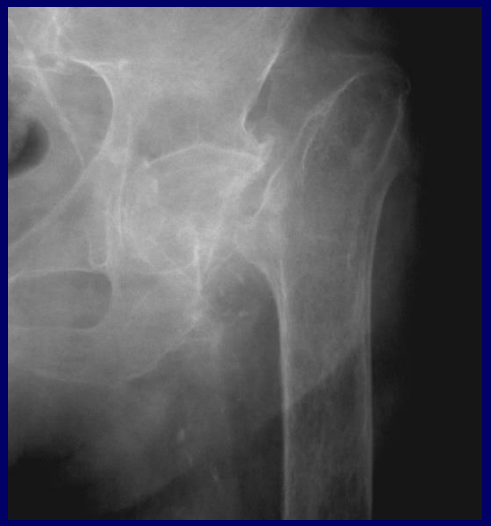
- Diagnosi differenziale
- Osteoporosi regionale
- Diagnosi di frattura

# Valutazione delle Fratture

## FRATTURE FEMORE E POLSO

- facilmente identificabili

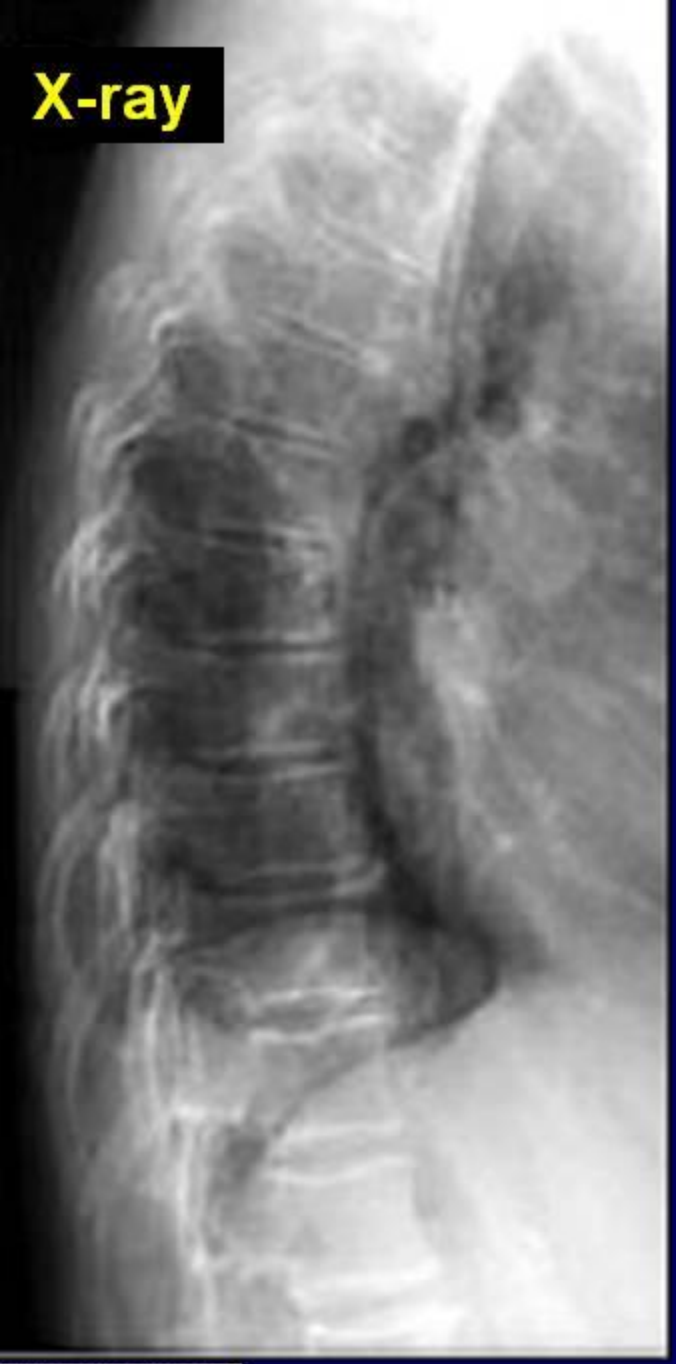


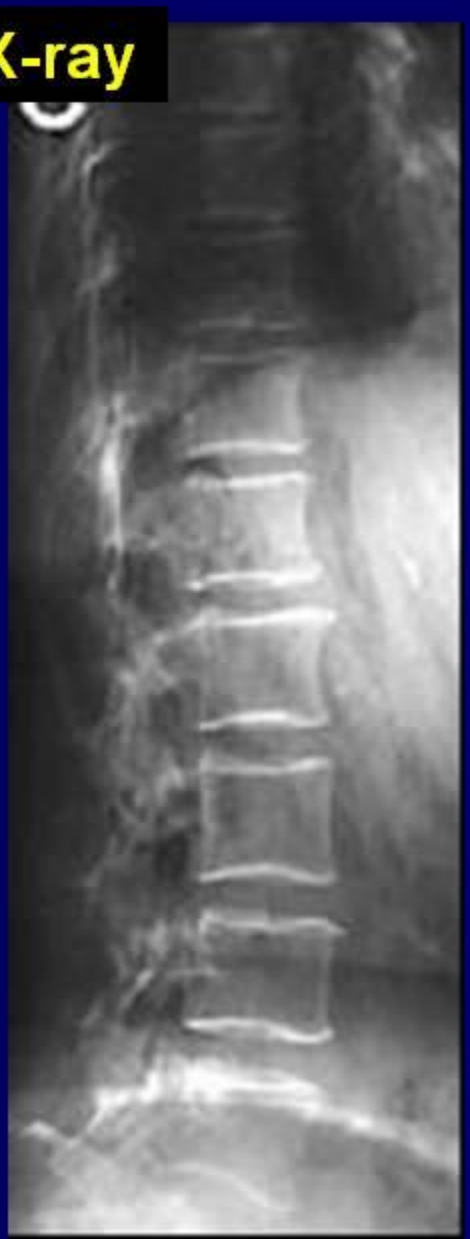


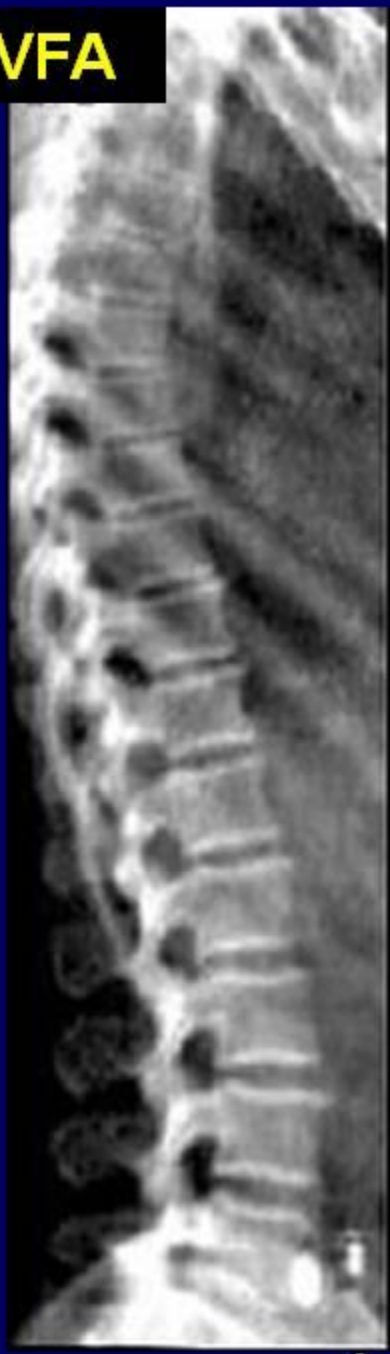
## FRATTURE VERTEBRE

- rilevazione problematica e spesso non clinicamente evidente, ma con notevole rilevanza diagnostica, prognostica e terapeutica

# Normal




ISCD

# Comparison of X-ray and VFA

| | X-ray | VFA |
|---|---|---|
| Radiation dose | 800μSv | 2-8 μSv |
| Access | Separate visit | Point of service |
| Cost | Higher ($92*) | Lower ($40*) |
| Resolution | Higher | Lower |
| Visualization | Superior above T7 | May be superior in LS |
| Obliquity | Common in LS | Less parallax effect |
| Automated morphometry | No | Yes |

ISCD

*Medicare reimbursement

# La diagnosi di osteoporosi

- Valutazione clinica
- Valutazione strumentale
- **Valutazione metabolica**

# Serum Markers of Bone Turnover

| | *Abbreviation* |
|---|---|
| ***Formation*** | |
| Bone alkaline phosphatase | ALP (BSAP) |
| Osteocalcin | OC |
| Procollagen type I C-propeptide | PICP |
| Procollagen type I N-propeptide | PINP |
| ***Resorption*** | |
| N-terminal cross-linking telopeptide of type I collagen | NTX |
| C-terminal cross-linking telopeptide of type I collagen | CTX |
| Tartrate-resistant acid phosphatase | TRAP |

Delmas PD. *J Bone Miner Res* 16:2370, 2001

# Urinary Markers of Bone Resorption

| *Marker* | *Abbreviation* |
|---|---|
| Hydroxyproline | HYP |
| Pyridinoline | PYD |
| Deoxypyridinoline | DPD |
| N-terminal cross-linking telopeptide of type I collagen | NTX |
| C-terminal cross-linking telopeptide of type I collagen | CTX |

Delmas PD. *J Bone Miner Res* 16:2370; 2001

# FRAX WHO Fracture Risk Assessment Tool

HOME | CALCULATION TOOL | FAQ | REFERENCE

Your Country : UK  Name / ID :  About the risk factors

**Weight Conversion:**

pound:  convert

1 pound = 0.453592 kg

**Height Conversion:**

inch :  convert

1 inch = 2.54 cm

## Questionnaire:

1. Age (between 40-90 years) or Date of birth

   Age:  Date of birth: Y: M: D:

2. Sex  ○ Male ● Female

3. Weight (kg)

4. Height (cm)

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

    T-score

Clear  Calculate

**BMI:** 24

**The ten year probability of fracture (%) with BMD**

| | |
|---|---|
| Major osteoporotic fracture | 23.9 |
| Hip fracture: | 8.0 |

La diagnosi di osteoporosi e l'eventuale terapia non possono derivare solo dal risultato densitometrico, ma devono scaturire da una valutazione clinica complessiva…

Linee guida SIOMMMS

# Livelli di Prevenzione dell'Osteoporosi

## PREVENZIONE PRIMARIA

Include tutte le misure adottate a livello della popolazione generale senza che venga analizzato il rischio del singolo soggetto

## PREVENZIONE SECONDARIA

Mira ad una diagnosi precoce della malattia utilizzando apparecchiature oppure algoritmi in grado di stimare il rischio di andare incontro a fratture

## PREVENZIONE TERZIARIA

Si rivolge ai pazienti che hanno già subito una frattura e hanno pertanto manifestato clinicamente i segni della fragilità scheletrica

# General management - nutrition

**Recommendations men, women 50+:**

- Dietary intake (RNI)
  - Calcium: 1,000 mg/day
  - Vitamin D: 800 IU/day
  - Protein: 1 g/kg body weight

- Supplemental calcium & vitamin D combined
  - Fortified dairy foods (calcium: 400 mg/serving; vitamin D: 200 IU/serving)
  - Supplements (calcium: 0.5-1.2 g/day; vitamin D: 800 IU/day)

- Supplemental vitamin D alone
  - 800 IU/day

# OSTEOPOROSIS
## Treatment Options

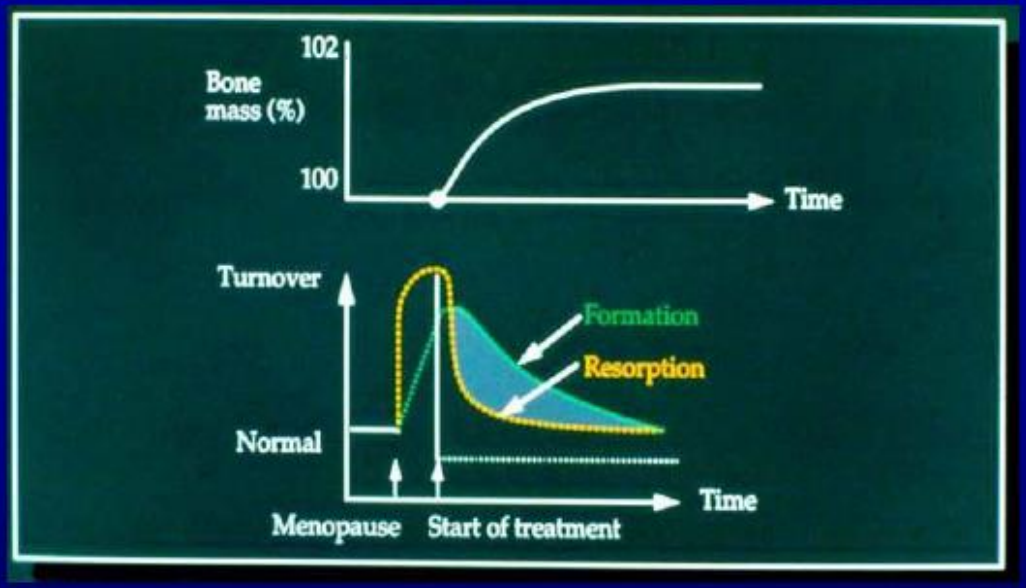
1. Optimize Mineralization
   - Restore vitamin D status
2. Reduce deep excavations by osteoclasts
   - Prevent merging of clusters into composite osteons
   - Prevent fenestration of trabeculae
3. Increase bending resistance
   - Trabeculae: make them thicker and if possible more connected
   - Tubular bones: add bone on the *periosteal* surface

# Osteoporosis Drugs: Mechanisms of Action on Bone Remodelling

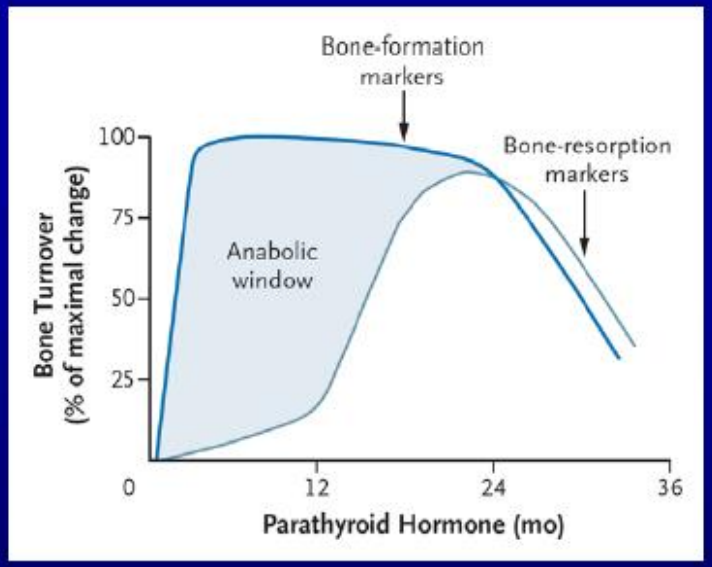
| | Compounds | Resorption | Formation | Final result |
|---|---|---|---|---|
| ANTIRESORPTIVES | Bisphosphonates | ↓↓ | ↓ | Inhibited |
| | Denosumab | ↓↓ | ↓ | Inhibited |
| | SERMs | ↓ | ↓ | Inhibited |
| ANABOLICS | Teriparatide | ↑ | ↑↑ | Increased |
| | Strontium Ranelate | ↓ | ↑↑ | Unchanged |

# Therapeutical Windows

## Antiresorptives




## Anabolics



1990:no approved medications for osteoporosis!

# Antifracture efficacy of major interventions for postmenopausal osteoporosis

| | Vertebral fracture risk | | Non-vertebral fracture risk | |
|---|---|---|---|---|
| | Osteoporosis | Established osteoporosis | Osteoporosis | Established osteoporosis |
| Alendronate | + | + | NA | +[hip] |
| Risedronate | + | + | NA | +[hip] |
| Ibandronate | NA | + | NA | +[1] |
| Zoledronic acid | + | + | NA | + |
| HRT | + | + | + | +[hip] |
| Raloxifene | + | + | NA | NA |
| Bazedoxifene | + | + | + | +[1] |
| Teriparatide/PTH | NA | + | NA | +[2] |
| Strontium ranelate | + | + | +[1, hip] | +[1, hip] |
| Denosumab | + | + | +[hip] | + |

+ effective drug; [1] post-hoc analysis; [2] for teriparatide only, [hip] including hip fracture

*JA Kanis, EV McCloskey, H Johansson, C Cooper, R Rizzoli, J-Y Reginster (2013) Osteoporosis Int 24: 23-57*

# Are These Drugs Efficacious?

**They have all been shown to reduce risk of vertebral fractures. Some have also shown to reduce the risk of non-vertebral fractures, and in some cases, agents have been shown specifically to decrease risk at the hip**

**Range of potency: 30-70%**

All seems fine for fragility fractures prevention, but…

question, doubts, uncertainties mine the enormous work done in the past two decades

# QUESTIONS (with answers)

For howlong?

In sequence?

Is safety a concern?

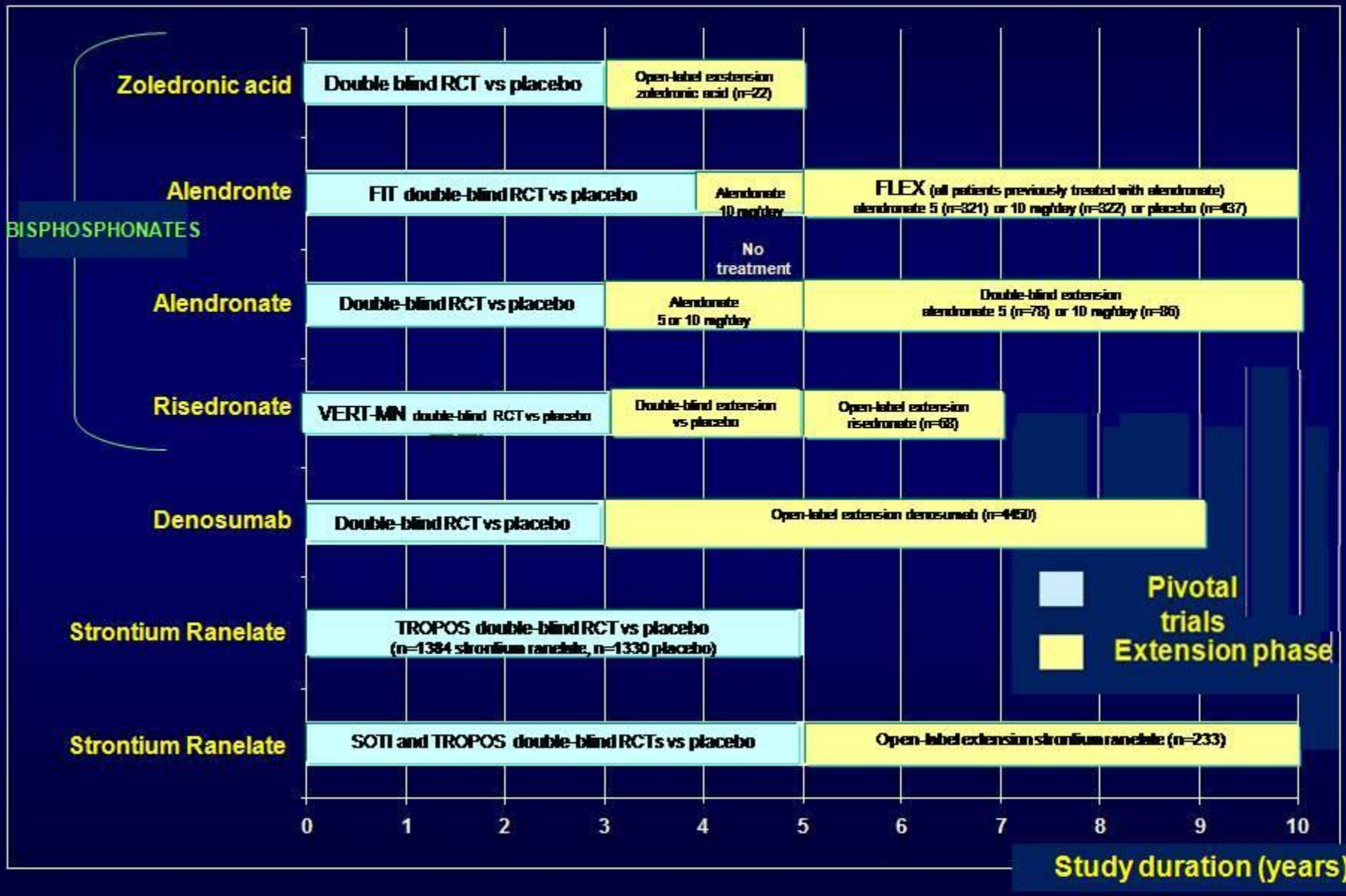
How to select the patient?

Should the patient be monitored?

# For Howlong?

# Summary of published STUDY DESIGN FOR THE LONG TERM TRIALS

## *with osteoporosis treatments with fracture related end-points*




Cooper C, et al. Current Medical Research & Opinion Vol. 28, No. 3, 2012, 1–17

# Side-effect of established treatments for osteoporosis

| Type of therapy | Drugs | Side effects |
|---|---|---|
| Antiresorptive | Bisphosphonates | Osteonecrosis of the jaw<br>Subtrocanteric fractures<br>Possible risk of atrial fibrillation<br>Esophageal irritation<br>Hypocalcemia<br>Potential renal toxic effects |
| | Denosumab | Osteonecrosis of the jaw<br>Subtrocanteric fractures<br>Hypocalcemia |
| | SERMs | Thromboembolic disease |
| Anabolic | Strontium Ranelate | Thromboembolic disease<br>Dress syndrome<br>Myocardial infarction |
| | Teriparatide | Hypercalcaemia<br>Nausea and diarrhoea |

# Long-term treatment: Controversies and unresolved questions…Where to start?

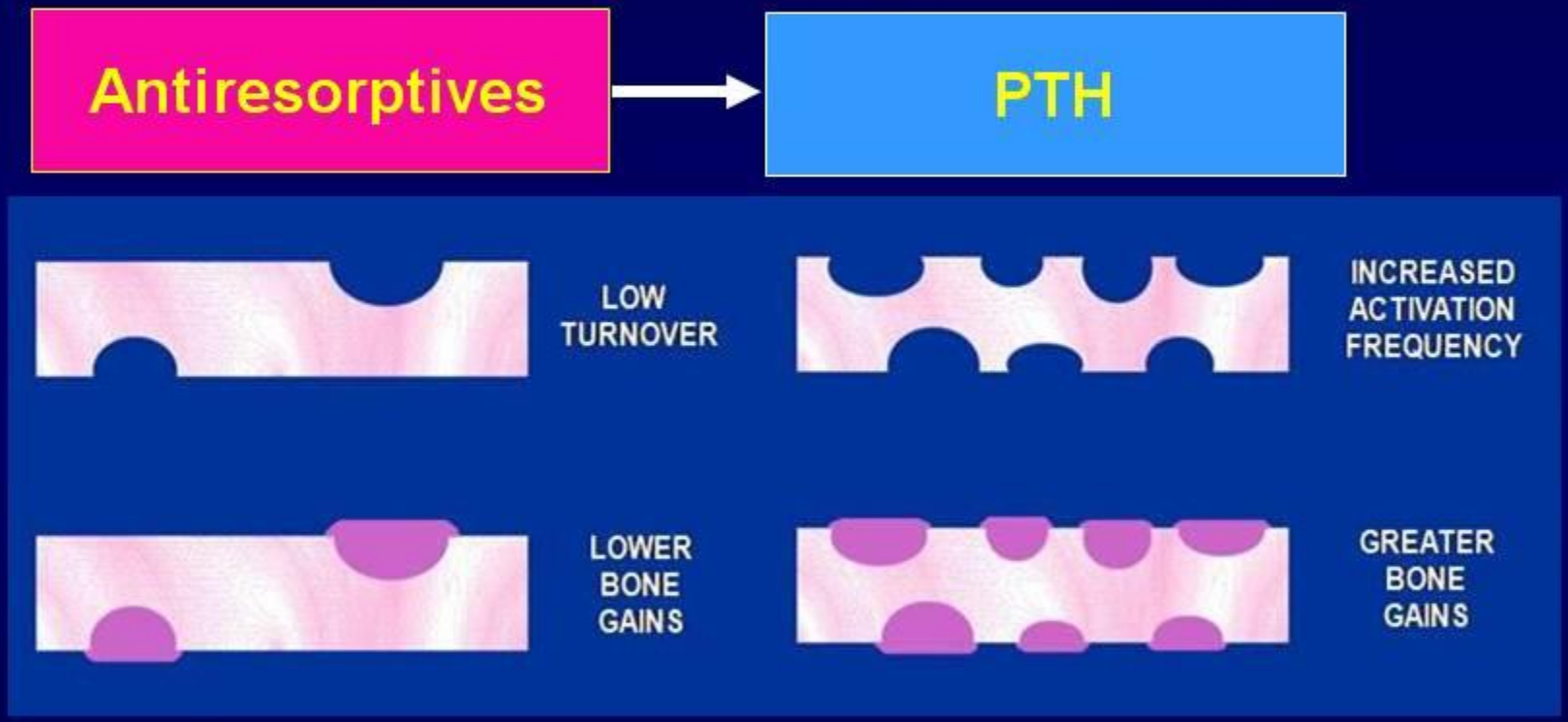
- Benefits of long term use of bisphosphonates and other therapies
- Does treatment now prevent fractures in 20 years?
- Do A-R's cause AFFs? If so, how long and what is magnitude of risk?
- Can we predict risk of AFF? (very interesting)
  - Use prior AFF (or focal thickening), duration of treatment, time since therapy, gender, race (asian high?)
- Optimal sequential therapy (and combo)
- How to decide when to stop therapy and how long should drug holiday be? When to restart?

# Clinical Question:
# 3 Ways to Use Anabolics with Antiresorptives

1. Antiresorptives + Anabolics
2. Anabolics → Antiresorptives
3. Antiresorptives → Anabolics

# Combination Regimen #3

- Pre-treatment with antiresorptives followed by anabolics




**Anabolic effect at the level of the individual bone remodelling unit causes an increase in the thickness of complete packets**

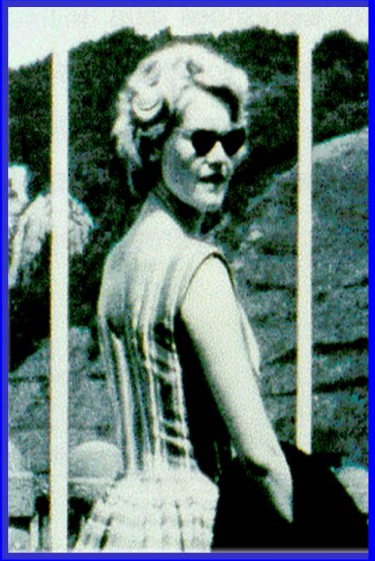
# Osteoporosis in Europe: Policy Developments 1998-2008


Achievements & Challenges for the Future

Challenges:

- Osteoporosis needs a higher political profile
- Most countries do not have fracture registries
- Reimbursement policies are too restrictive
- Many high-risk individuals are not being detected or treated

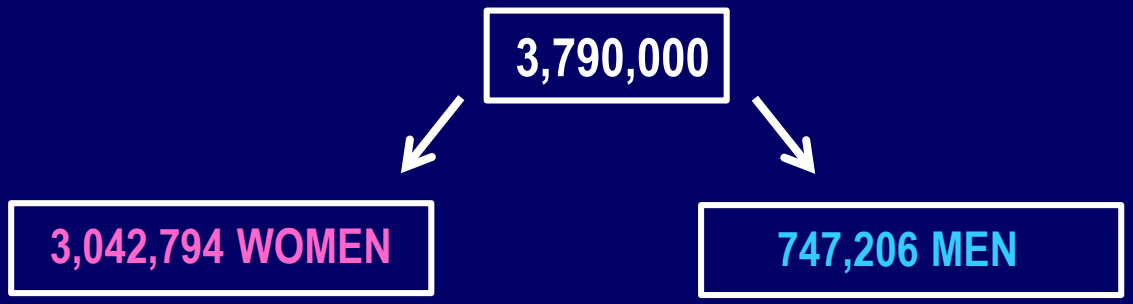
# VENUS



# MARS

# EPIDEMIOLOGY OF OSTEOPOROSIS IN ITALY IN 2010

- ESTIMATED OSTEOPOROSIS POPULATION IN THE OVER-50 YEARS




- ESTIMATED NUMBER OF INCIDENT FRACTURES (hip, vertebra, forearm, other)


- INCIDENCE (per 100,000) OF CAUSALLY RELATED DEATHS WITHIN A YEAR AFTER FRACTURE (hip, vertebral, other)

# BURDEN OF DISEASE (€)

- COST OF INPATIENT FRACTURES IN 2010 ( “first year cost”)

13,527 EACH

TOTAL 4,268,582,839

2,934,052,250 WOMEN

1,334,530,589 MEN

- COST (NURSING HOME) OF FRACTURES SUSTAINED PRIOR TO YEAR 2010 BUT WHICH STILL INCURRED COSTS IN 2010 (“long-terms costs”)

50,202 EACH

TOTAL 2,402,414,082

1,725,816,327 WOMEN

676,597,756 MEN

- ANNUAL COST FOR PREVENTION (visit, DXA scan, drug)

TOTAL 360,810,039

316,392,635 WOMEN

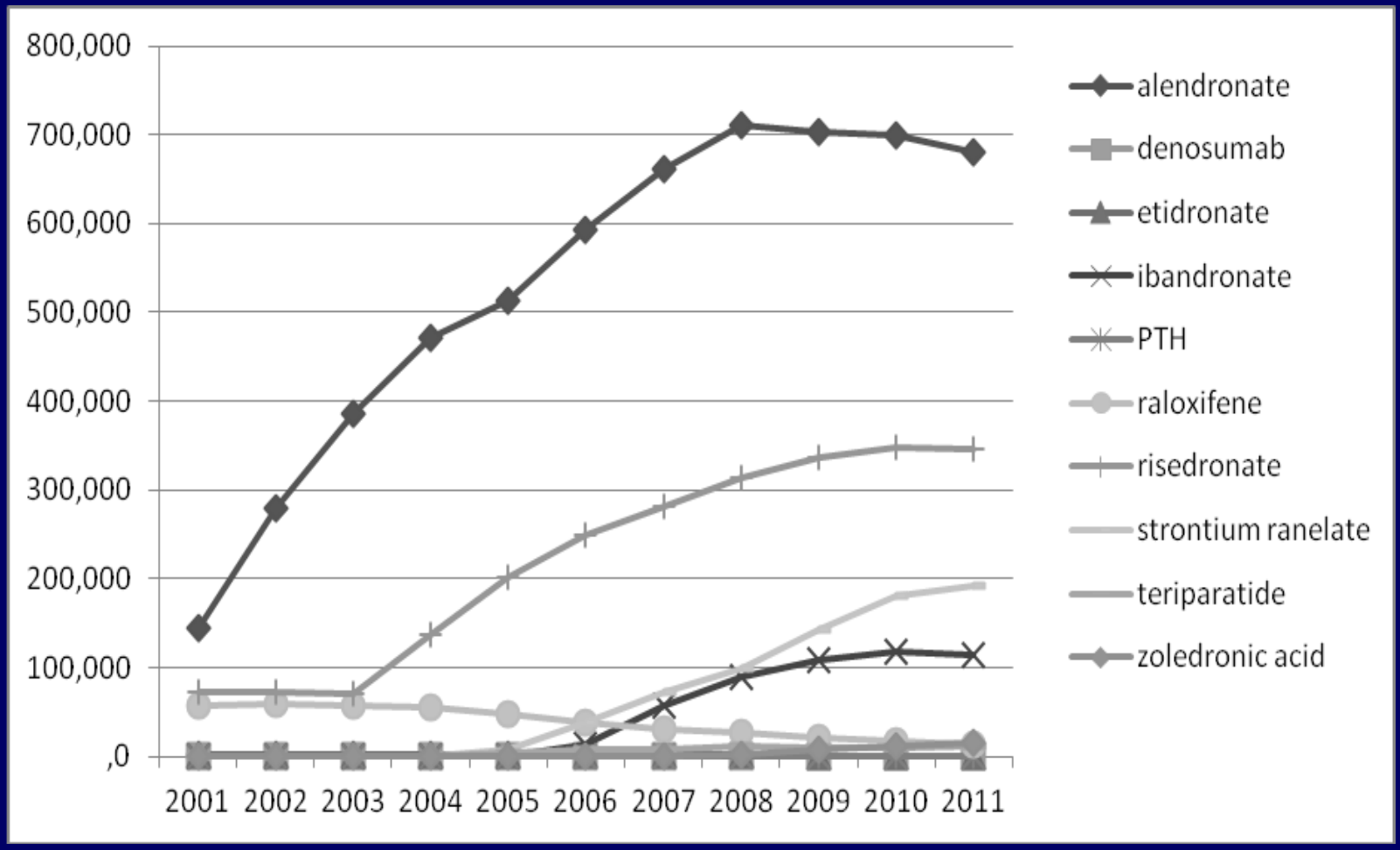
44,417,403 MEN

GRAND TOTAL 7,031,806,960

COST INCLUDING $QALY_S$, LOST ~ 15,800,000,000

| Incident fracture | Prior fracture | Prevention | $QALY_S$ lost |
|---|---|---|---|
| 27% | 15% | 2% | 56% |

# TREATMENT UPTAKE OF INDIVIDUAL OSTEOPOROSIS TREATMENT



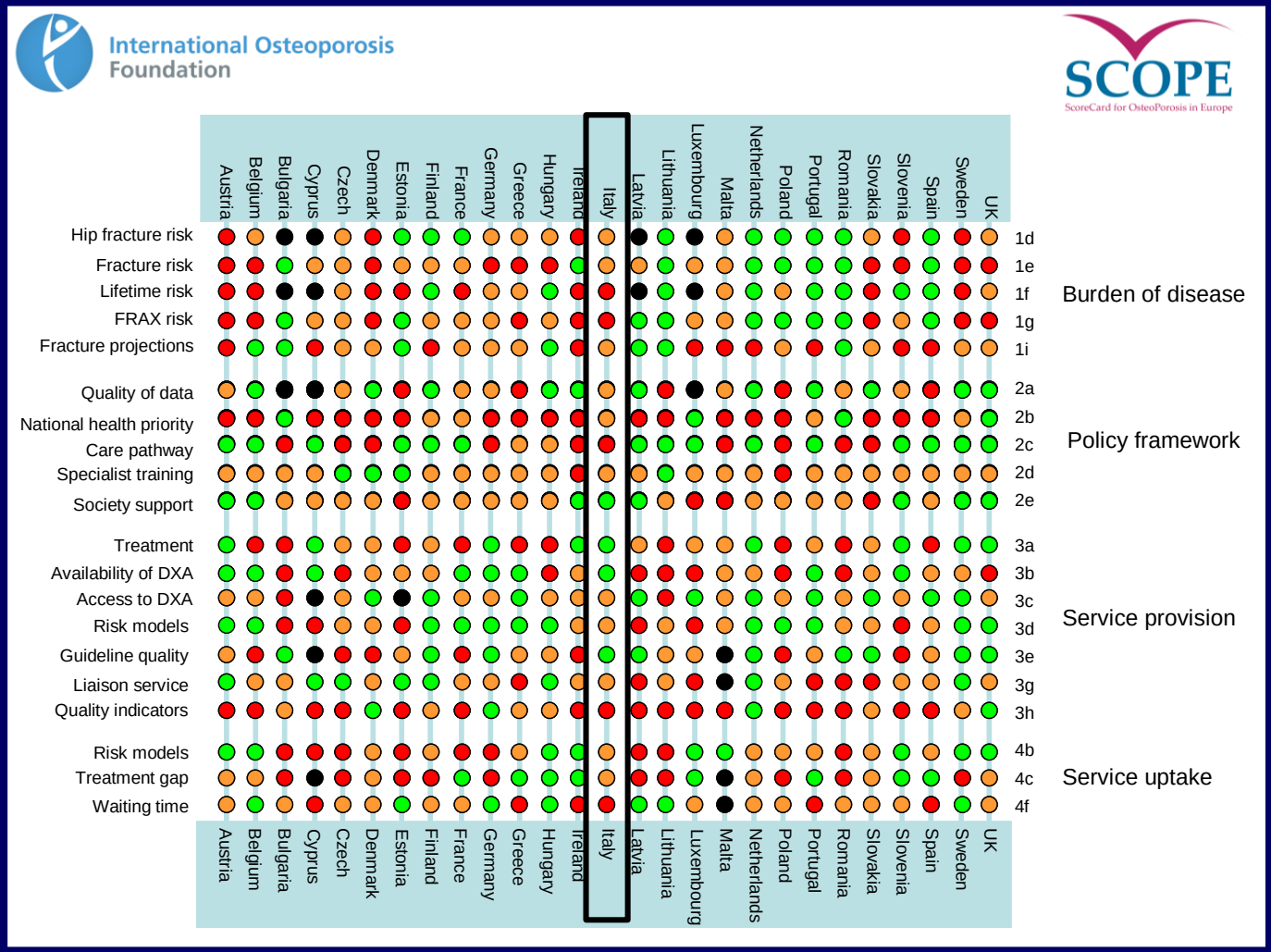

**INCREASE FROM 1.03% IN 2001 TO 5.2% IN 2010**
**(with a subsequent decrease to 5.14% in 2011)**

# TREATMENT GAPS CALCULATED BY FRAX



*Very conservative calculation as based on current use of treatments only directed to patients at high risk*

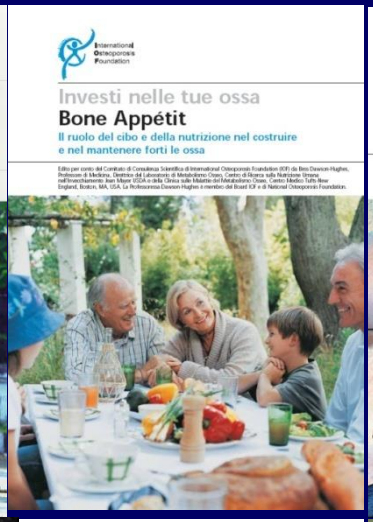
# SCOPE TOOL IN 27 EU COUNTRIES
## Italy Red Dots




## KEYS

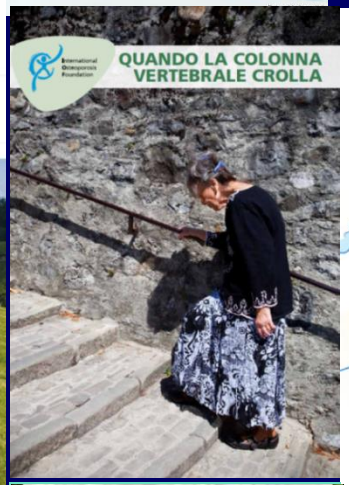
- Lifetime risk in women aged 50 years: >18%
- FRAX risk >10% in women aged 50-89 years: >25%
- Care pathway in primary care: multiple specialties
- Quality indicators: no systems in place
- Waiting time for hip surgery: >2 days

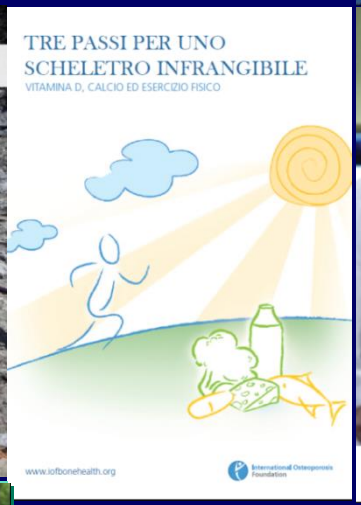


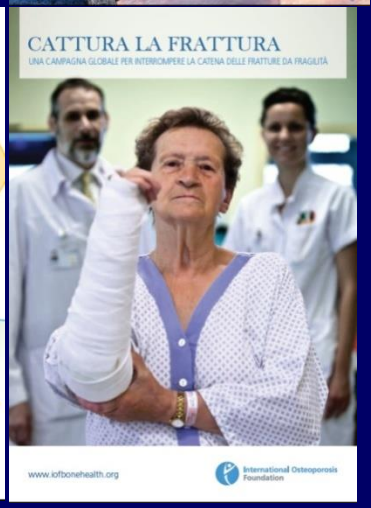



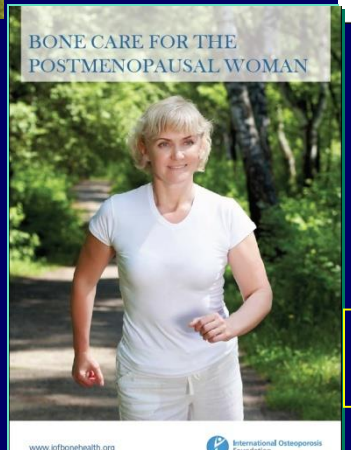




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