# Osteoporosis: Etiology, Treatment and Biomarkers

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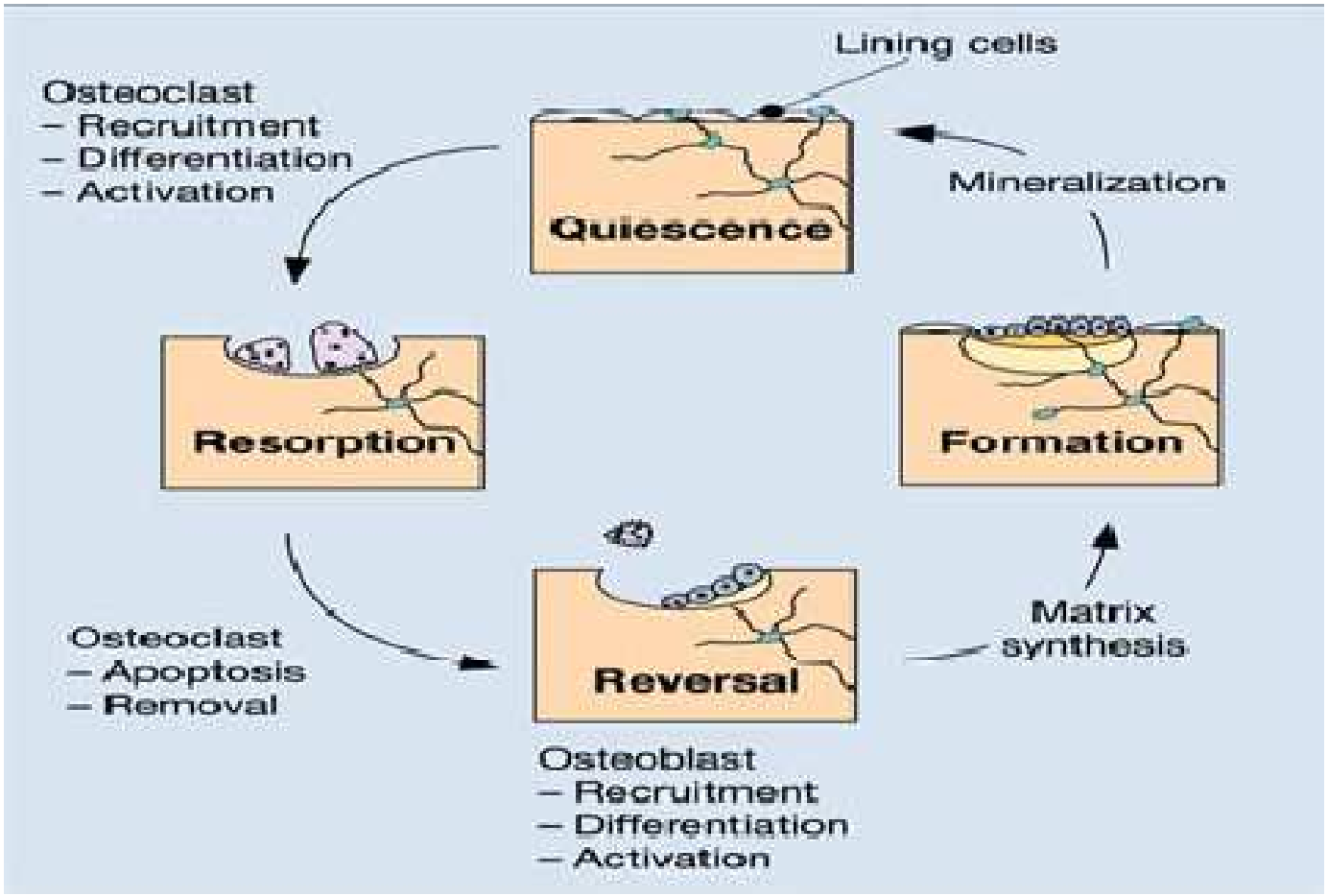
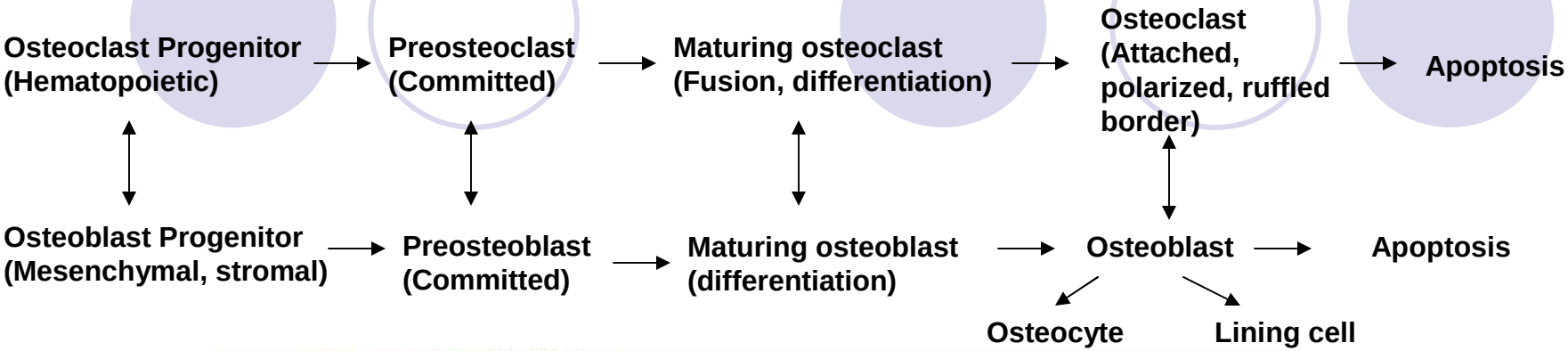
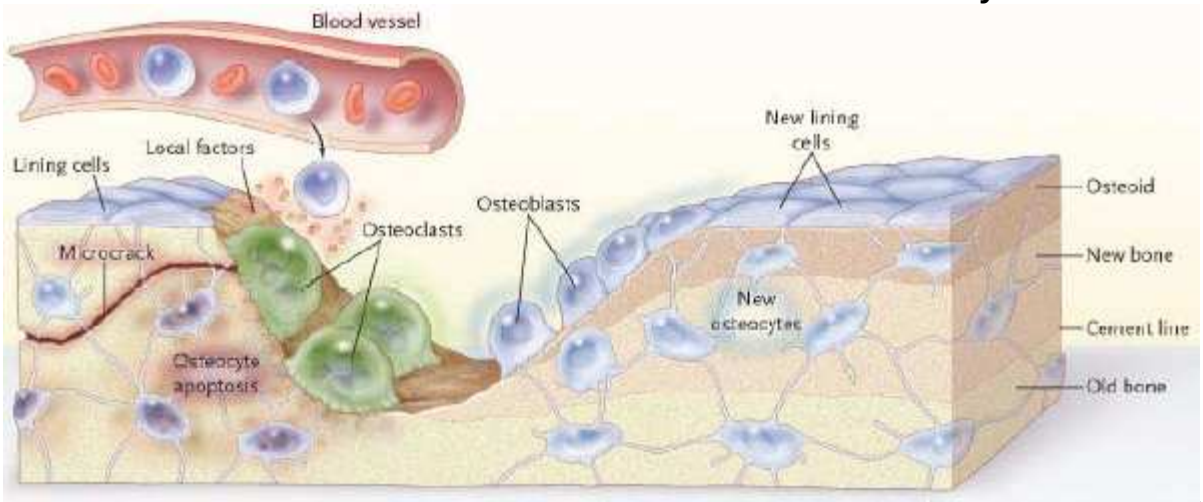
# The Remodeling Cycle on a Trabecula



# Osteoclast and Osteoblast Lineages

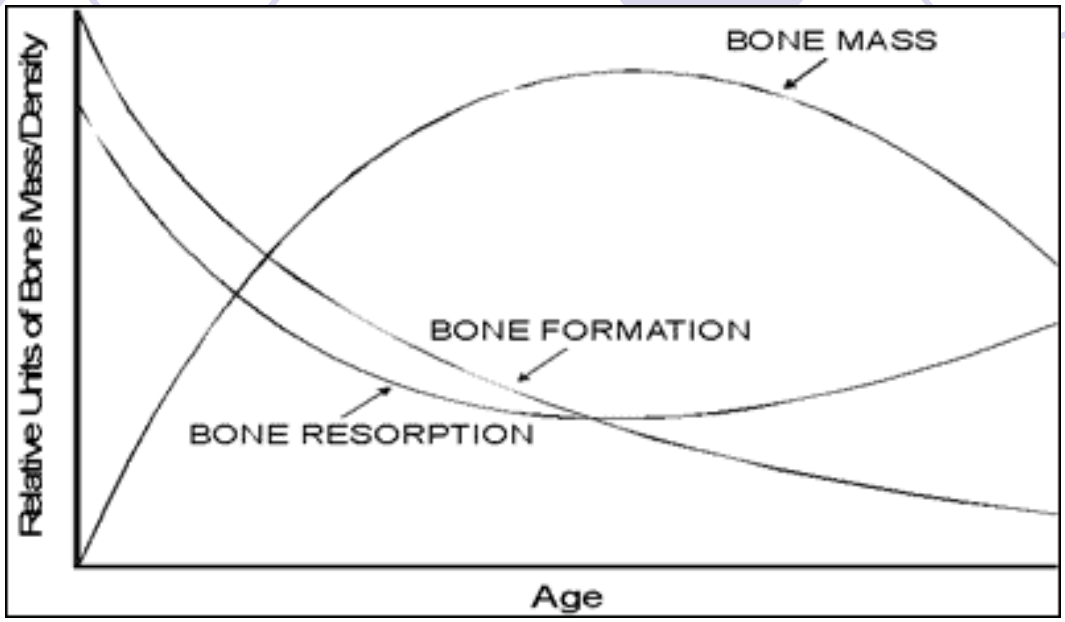



Osteoclasts originate from a hematopoietic stem cell that can also differentiate into a macrophage, granulocyte, erythrocyte, megakaryocyte, mast cell, B-cell, or T-cell.

Osteoblasts originate from a mesenchymal stem cell that can also differentiate into a chondrocyte, myocyte, fibroblast, or adipocyte. The terminology for these lineages is still evolving and is herein [over] simplified. Many intermediate steps and regulatory factors are involved in lineage development.

# Osteoporosis: A disorder of bone remodeling




First 3 decades of life, bone remodels (turnover) and peaks around 30 years of age. Peak bone mass determined by genetics, and modified by calcium intake, smoking, and others.
The crossover of formation/resorption occurs during the fourth decade. With aging, the rate of bone loss eventually exceeds therate of bone growth. Bone becomes more porous, thin and fragile, osteoporosis occurs.

# Osteoporosis: Definitions

National Osteoporosis Foundation:

- “a disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures.”

World Health Organization (1994) :

- “bone mineral density T-score greater than –2.5 standard deviations from the mean peak adult bone mass (ie. a woman in her 30’s).”

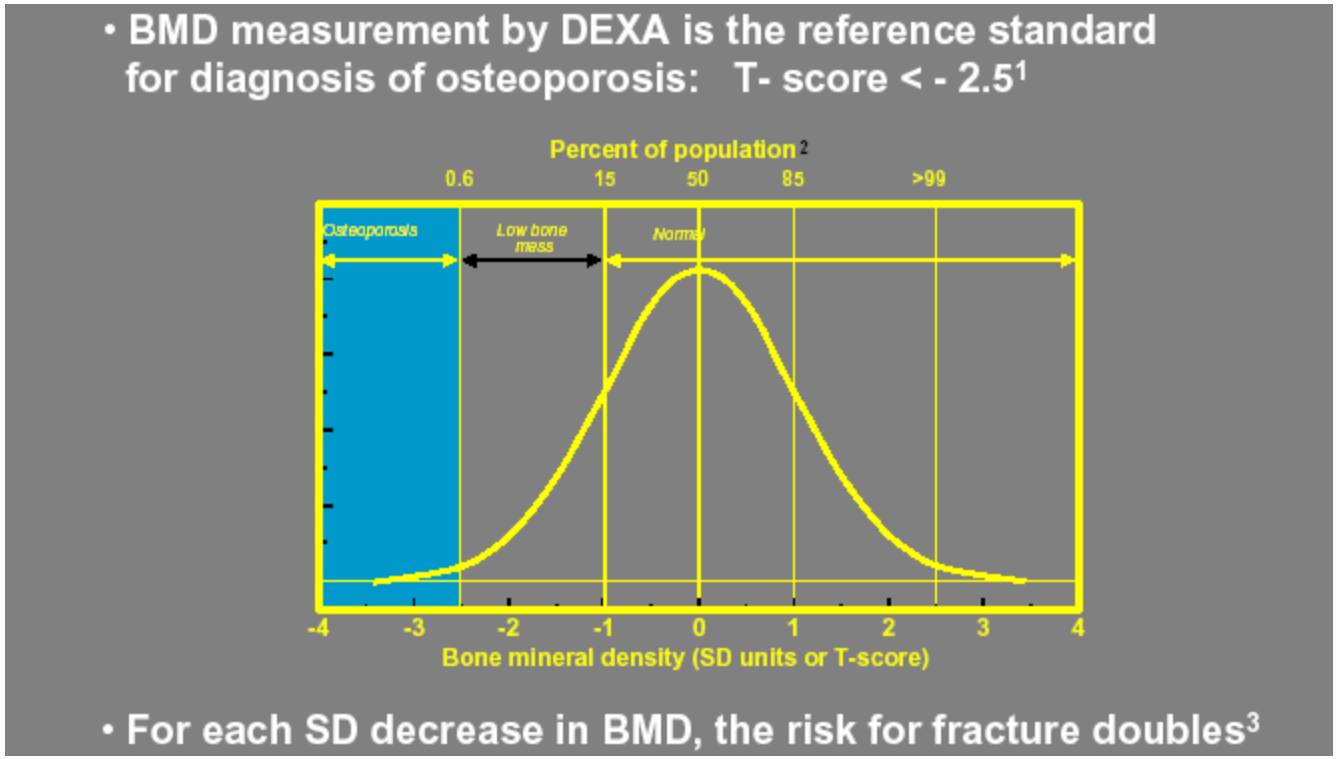
# Bone Mineral Density (BMD)

T-score = Standard Deviation (SD) to "young normal mean"

- compares BMD to optimal or peak density of a 30-year old healthy adult

Z-score = SD to "age-matched mean"

- compares BMD to what is expected in particular age and body size.




- -1 SD equals a 10-12% decrease in bone density.

- -2.5SD is roughly 25% decrease in normal bone density

# Classification

- **Normal.**

Bone Density is within 1 SD (+1 or -1) of the young adult mean.

- **Low Bone Mass (Osteopenia)**

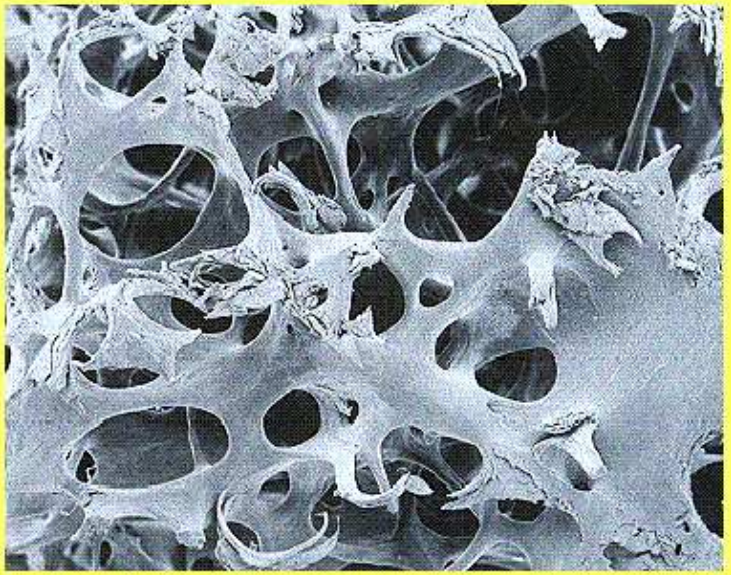
Bone density is 1 to 2.5 SD below the young adult mean (-1 to -2.5SD).

- **Osteoporosis.**

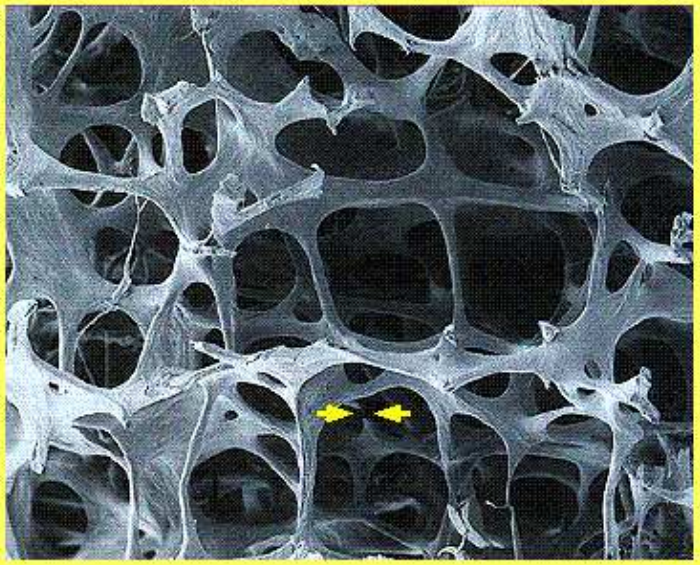
Bone density is 2.5 SD or more below the young adult mean (> -2.5SD).

- **Severe (established) osteoporosis.**

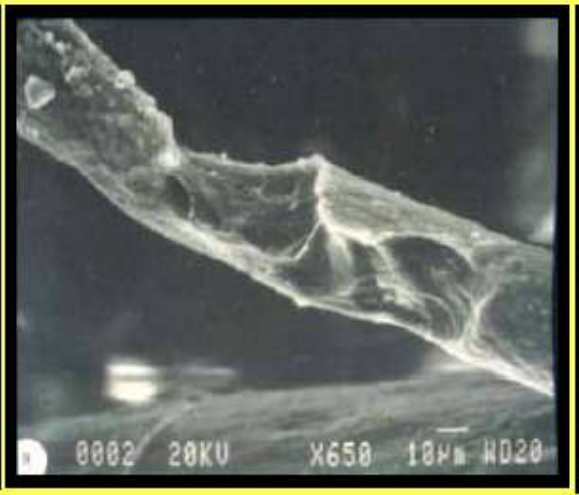
Bone density is more than 2.5 SD below the young adult mean and there has been one or more osteoporotic fractures.



Normal[2]



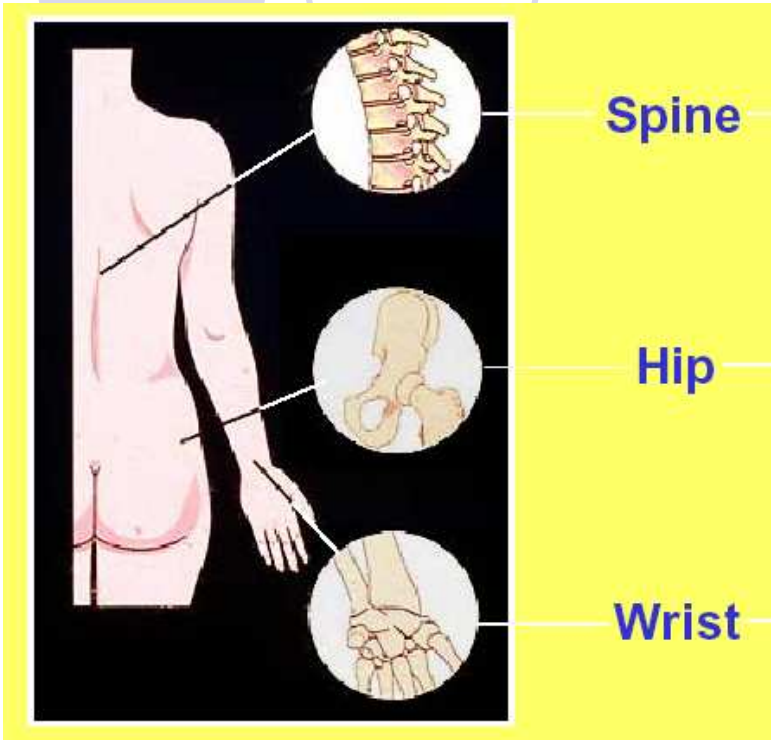
Osteoporosis[2]

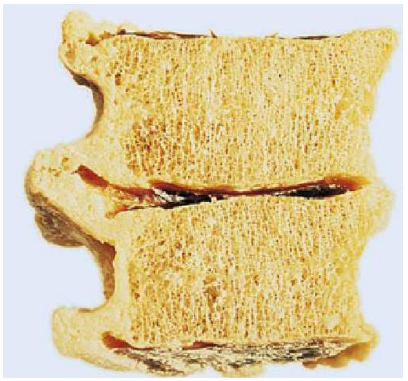

Normal[2]

Osteoporosis

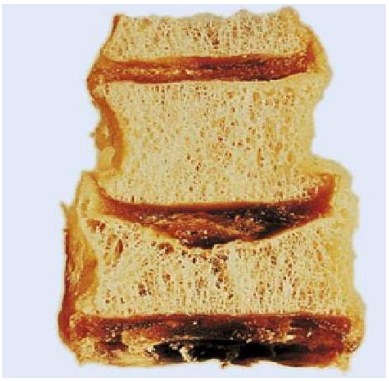
# Osteoporosis: Common Fracture Sites




Kyfosis
Height Loss
Fractures
Pain



Normal trabecular



Osteoporotic trabecular

# Risks and Consequences of Hip Fractures

- Result in permanent disability in 30% of patients
- 12%-20% die within 1 year after fracture
- >50% of survivors are unable to return to independent living and many require long term nursing home care

# Demographics

- Affects 75 million persons in the US, Europe and Japan.

- Affects half of all women, 1 in 8 men; however 30% of hip fx in persons > 65 occur in men.

- Results in 1.5 million fractures/year in US; estimated costs of $17 billion annually($14million/day)

- Over 50% of women aged 50 years or older and 20% of men will suffer an osteoporosis-related fracture within their remaining lifetime.

# Screening for Osteoporosis: Bone Density Testing Guidelines

| NOF[1] | AACE[2] | USPSTF[3] |
|---|---|---|
| BMD testing for:<br>▪ All women ≥65 years<br>▪ Younger postmenopausal women with one or more risk factors<br>▪ Postmenopausal women who present with fractures | BMD testing for:<br>▪ All women ≥65 years<br>▪ Pre- and postmenopausal women who have risk factors for fracture<br>▪ All women ≥40 years who have sustained a fracture<br>▪ Women beginning or receiving long-term glucocorticoid therapy | Screening for:<br>▪ All women ≥65 years<br>▪ For women at increased risk for fractures, begin screening at age 60 |

# Bone Mineral Density (BMD) Testing







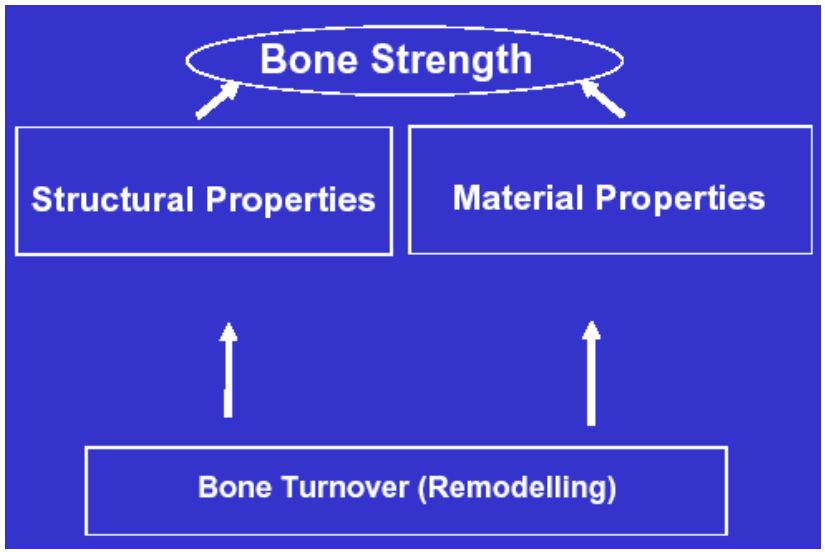
- Dual energy x-ray absorptiometry (DEXA) is most accurate and gold standard. Also is noninvasive.
- DEXA of hip is best predictor of hip fx (cost $125-200) but DEXA of wrist, hand, forearm and heel can also be measured to detect risk (cost $38-75).

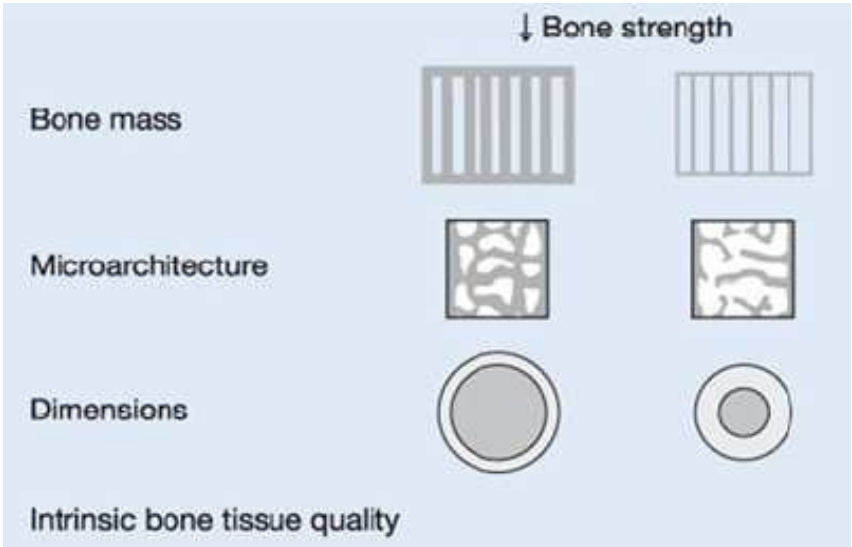
**Is mineral content alone, as measured by BMD, sufficient to assess fracture risk?**

– BMD by DXA measures the mineral content of the bone mass per projected area (g/cm2), providing an estimate of bone mass based on X ray absorption.

Bone Strength= Bone Density +Bone Quality

- Bone Quality = 20-30%???
- With treatment 20% women decreased fractures even without increase in T-score
- Treat the patient and the fracture risk, not just the T-score



# Clinical Evaluation

- **Medical history** including **risk factor assessment**
- **Physical exam**, including **consecutive height** assessments
- **Lab tests**, as indicated to rule out secondary causes of osteoporosis
- Bone mineral density (**BMD**) testing-spine and hip preferred for baseline and serial measurement—better for showing response to treatment
- Bone scan if possibility of metastatic disease
- MRI if + neurologic s/s

# Risk Factors for Postmenopausal Osteoporosis and Fracture

## Major Risk Factors

- Personal history of fracture as an adult
- History of fracture in first-degree relative
- Low body weight (<127 lb)
- Cigarette smoking
- Long-term glucocorticoid therapy (>3 months)

## Additional Risk Factors

- Impaired vision
- Estrogen deficiency at an early age (<45 years)
- Dementia
- Poor health/frailty
- Recent falls
- Low calcium intake (lifelong)
- Low physical activity
- Alcohol >2 drinks per day

# Causes of Osteoporosis

Failure to develop normal skeletal mass during growth and development because of poor nutrition or inadequate exercise

Endocrine deficiency or excess
- Estrogen or testosterone deficiency: related to aging, or $2^{o}$ to other diseases
- Cushing's syndrome: increase resorption and decrease formation
- Hyperthyroidism: increase resorption more than formation
- Hyperparathyroidism: increase resorption

Gastrointestinal diseases: $Ca^{++}$ absorption and VitD absorption and metabolism

Malignancy: humoral hypercalcemia of malignancy through PTHrP, local osteolysis

Chronic renal failure: secondary hyperparathyroidism due to hypocalcemia with hyperphosphatemia and 1.25 VitD deficiency

Medications: glucocorticoids, anticonvulsants, heparin, releasing hormone agonists, lithium, cytotoxic drugs, premenopausal tamoxifen, various chemotherapy agents

Genetic syndromes: hypophosphatasia, osteogenesis imperfecta

Cigarette smoking

# Labs to R/O Secondary Osteoporosis

Chemistry: creatinine, calcium, LFT's, phosphorus, alk phospatase, testoserone, estrogen, LH/FSH, TSH,T4, parathyroid hormone, albumin, ESR, CBC, 24 hour urine for calcium and/or free cortisol, serum iron and ferritin

# Non-Pharmacologic Treatment Options

- Aerobic and resistance exercises 3X/wk
- Calcium, vit D
- Weight loss
- Moderation of alcohol
- Decrease caffeine intake
- Bone density screening
- Decrease or d/c causative agents
- Fall prevention program (ie. Remove throw rugs)

Low impact aerobic exercise (swimming, walking) is better for CV fitness and does not provide enough stress to improve BMD. Brief, high intensity periods of loading that generate diverse strain patterns on the bones improve BMD: Weight-training, stairclimbing, field sports, racquet sports, court sports and dancing.

# Pharmacologic Treatment

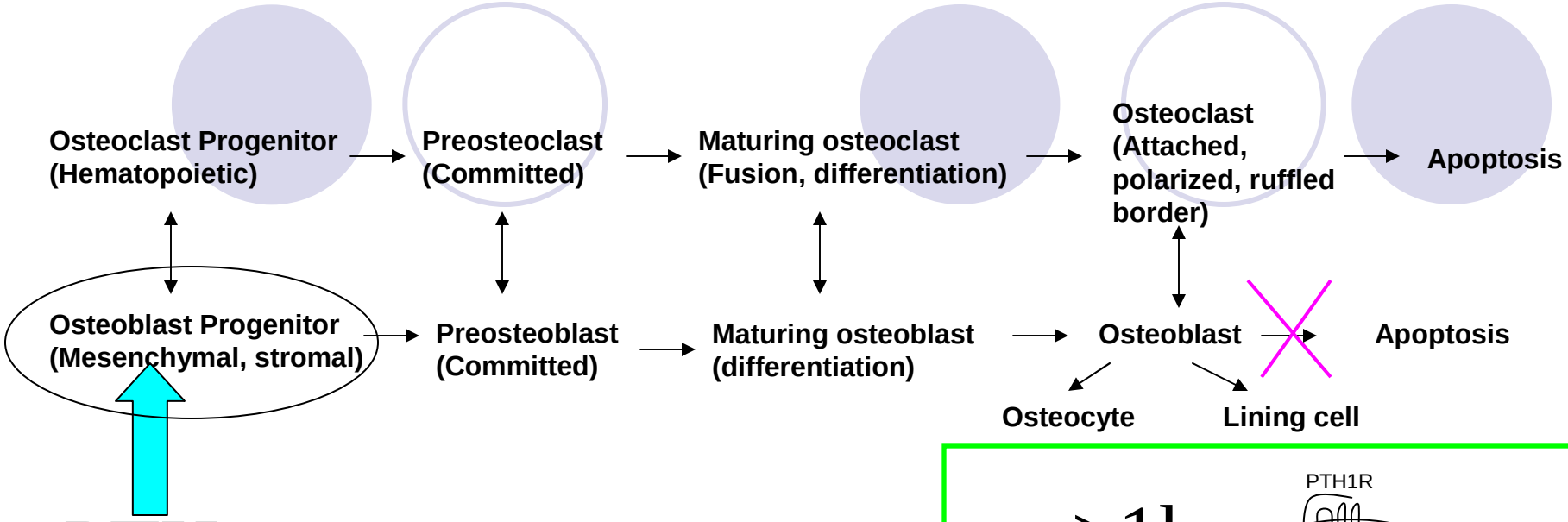
• Should be considered when a patient has a T score of less than -2.0, or less than -1.5 w/ risk factors

• Goal: to prevent fractures by utilizing a therapy that quickly reverses osteoporosis and offers long term protection against fractures.

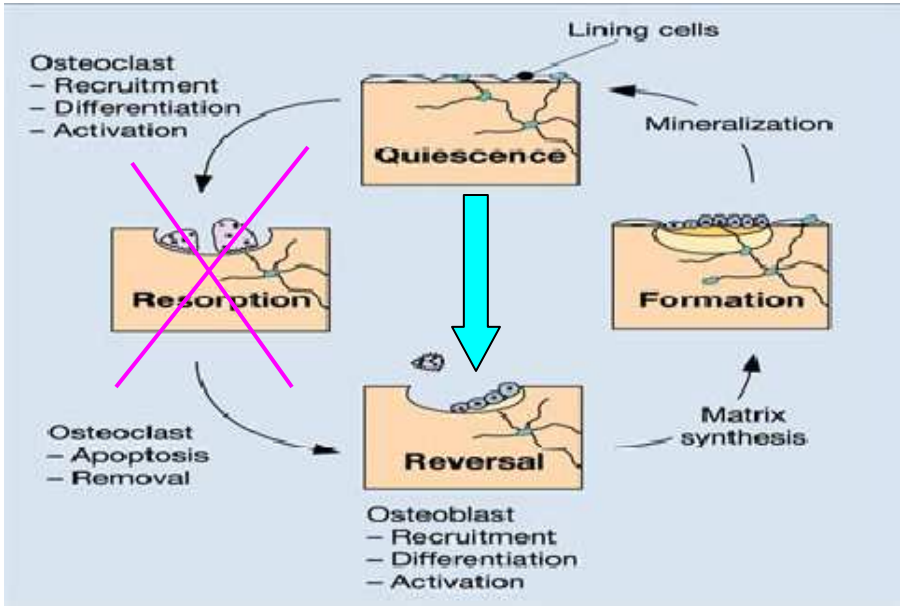
• Drugs currently used for treatment work to decrease osteoclastic activity and reduce bone breakdown, thus maintaining BMD. The ultimate impact of these drugs on fracture reduction varies.

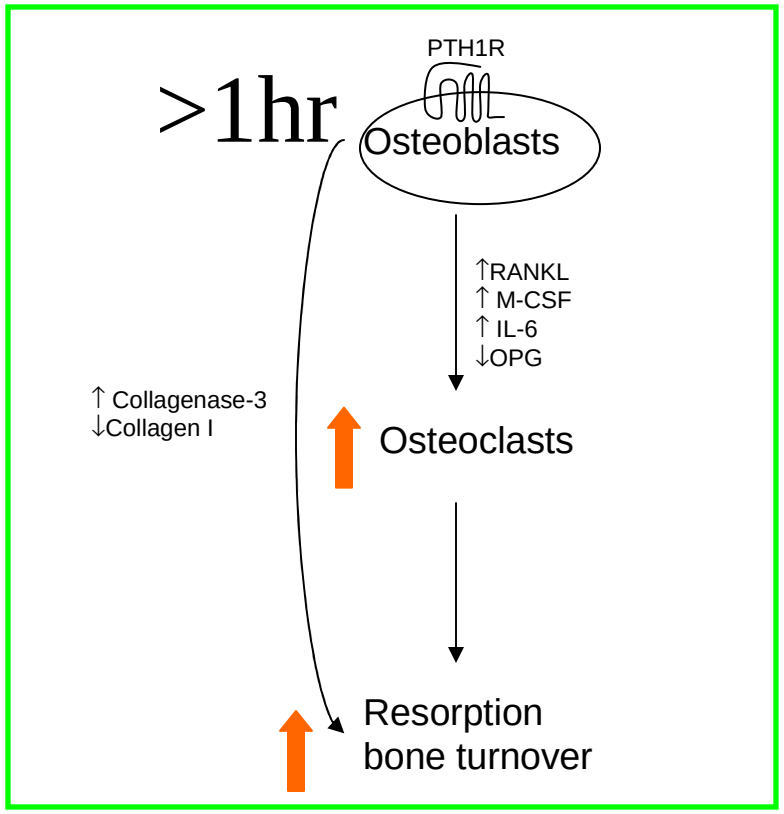
# Approved Therapies

| Drug | Mechanisms |
|---|---|
| Biphosphonates:<br>Actonel (risedronate)<br>Fosamax (alendrontate)<br>Boniva (Ibandronate)<br>Zoledronic acid (once/year) | Inhibit resorption<br>Bind strongly onto bone mineral, inhibit calcium phosphate crystal formation and dissolution, inhibit normal and ectopic mineralization (probably through a physicochemical inhibition of crystal growth). |
| Hormone therapy:<br>Premarin (CEE)<br>Estraderm (estradiol) | Inhibit osteoclast activity (resorption)<br>Downregulate pro-inflammatory cytokines which increase osteoclast activity. Increases BMD, has adverse effects on breast or uterus. |
| SERM: (Selective Estrogen Receptor Modulator)<br>Evista (Raloxifene) | Inhibit osteoclast activity (resorption)<br>Mimics estrogen's effects on bone w/o adverse effects on breast or uterus, Increases in venous thromboembolic disease threefold |
| Calcitonin | Inhibits osteoclast activity (resorption)<br>Binds to high-affinity G protein–coupled receptors on the osteoclast |
| PTH1-34<br>Forteo (teriparatide) | Stimulates osteoblast when used intermittently (brief boluses)<br>Induce osteosarcoma in lab rats, human??? |

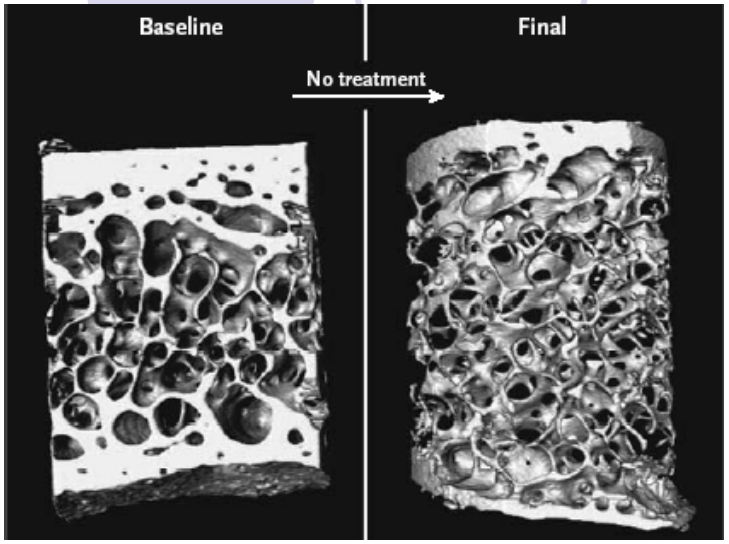



PTH once daily or infused <1hr

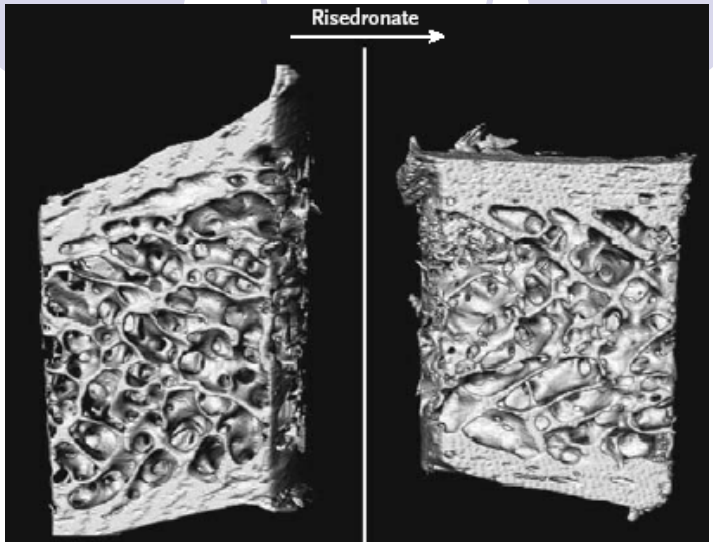


# Effects of Treatment with Anti-resorptive or Anabolic Agents

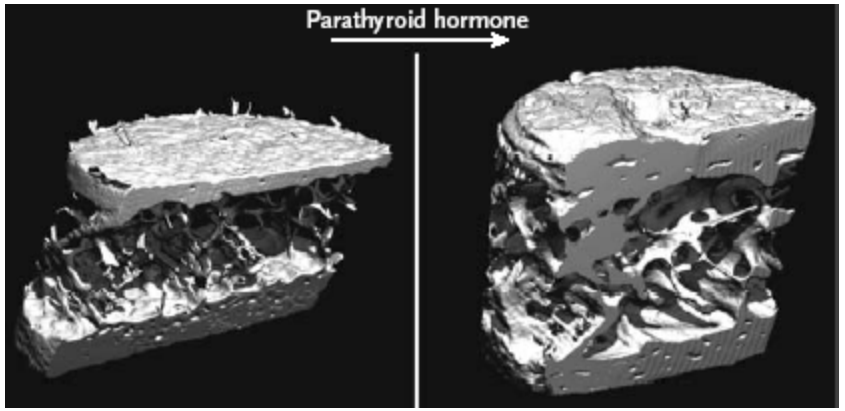



Microcomputed tomography of biopsy specimens of the iliac crest at baseline and after 3 years in an untreated control subject shows cortical and trabecular thinning and a loss of connectivity.



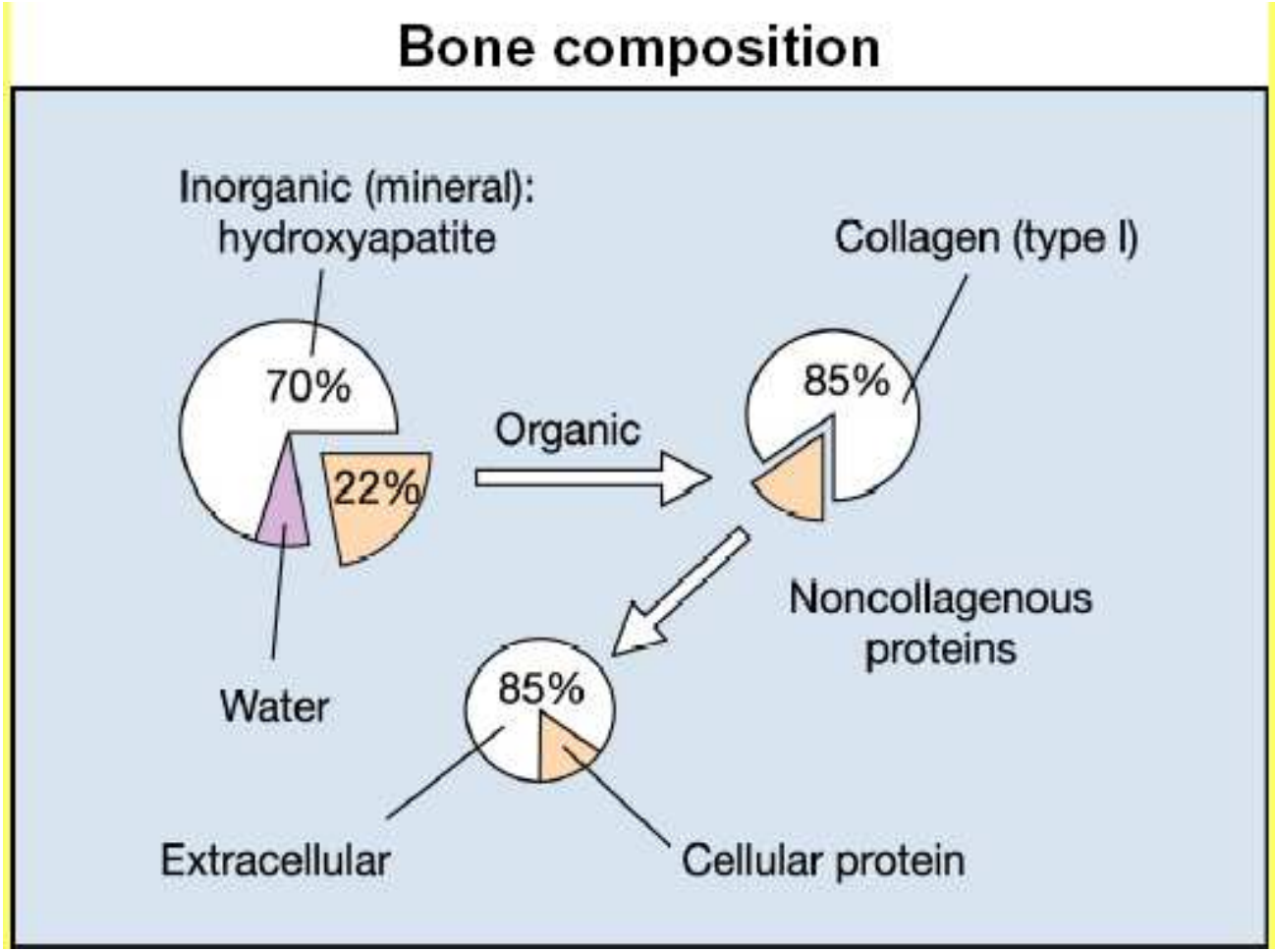

Treatment with the antiresorptive agent risedronate maintains structure.

Treatment with parathyroid hormone, an anabolic agent, promotes the deposition of bone and cortical and trabecular thickening after 18 months of treatment.




Seeman, E. et al. N Engl J Med 2006;354:2250-2261

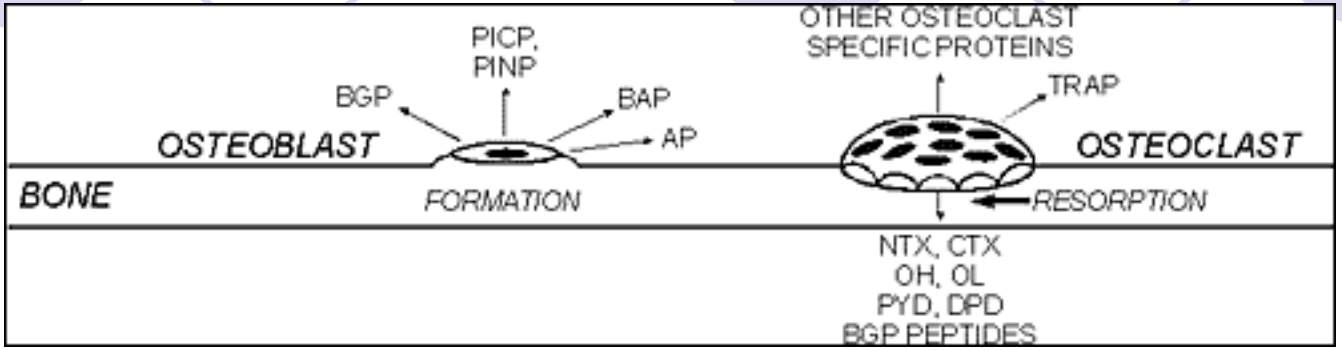
# Biochemical Markers of Bone Turnover (Markers of Bone Resorption/Formation)



# Biochemical Markers of Bone Turnover (Markers of Bone Resorption/Formation)

- Monitoring the effects of therapy
- Selection of patients for therapy
- Prediction of bone loss
- Prediction of fracture risk

# Schematic Representation of the Cellular and Skeletal Sources of Serum and/or Urinary Markers of Bone Formation and Bone Resorption




**Markers of Bone Resorption**

- **TRAP, Tartrate-resistant acid phosphatase**
- **NTx, N-terminal cross-linked telopeptide of type I collagen** (Osteomark NTx,Urine (Random),MSH)
- **CTx, C-terminal cross-linked telopeptide of type I collagen**
- **OH, hydroxyproline** (HPLC?, 24hr urine, Western)
- **OL, hydroxylysine**
- **Pridinium cross-links: PYD, pyridinoline(total, free)**
- **DPD, deoxypyridinoline (total, free).** (Randomurine, St Michael's Hospital)

**Markers of Bone Formation**

- **BAP, bone-specific alkaline phosphatase** (ELISA, MSH)
- **AP, alkaline phosphatase** (Enzymatic)
- **Osteocalcin, BGP, bone gamma carboxyglutamic acitd (GLA) protein** (IRMA, St Michael's Hospital)
- **PICP, procollagen type I C-terminal propeptide**
- **PINP, procollagen type I N-terminal propeptide**