The Bare Bones of Osteoporosis

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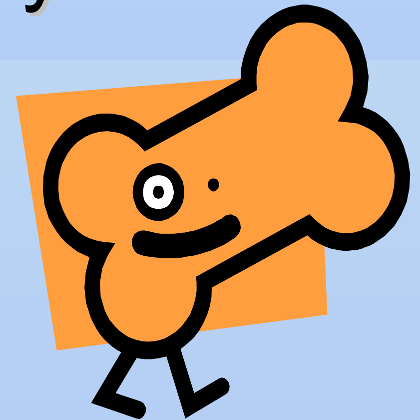
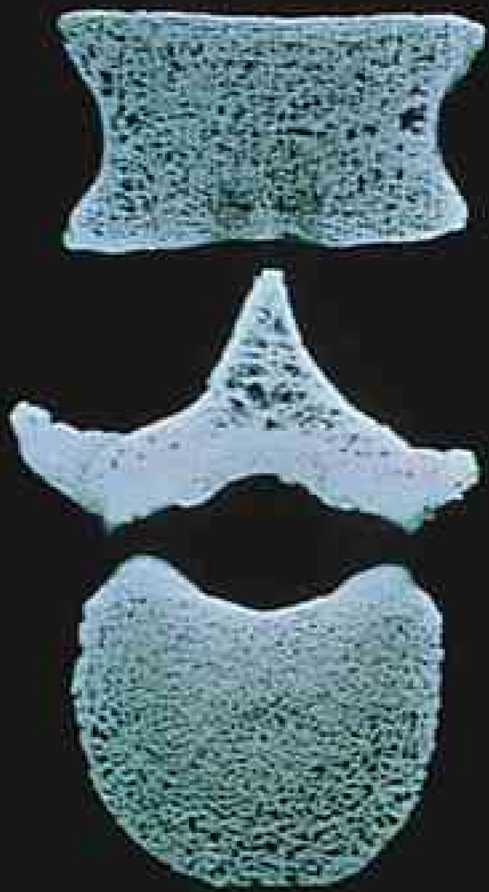
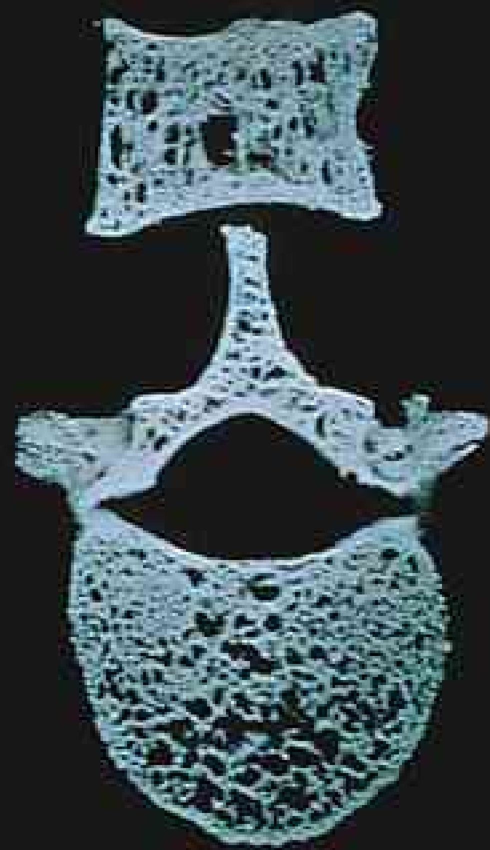
Definition

- A systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture

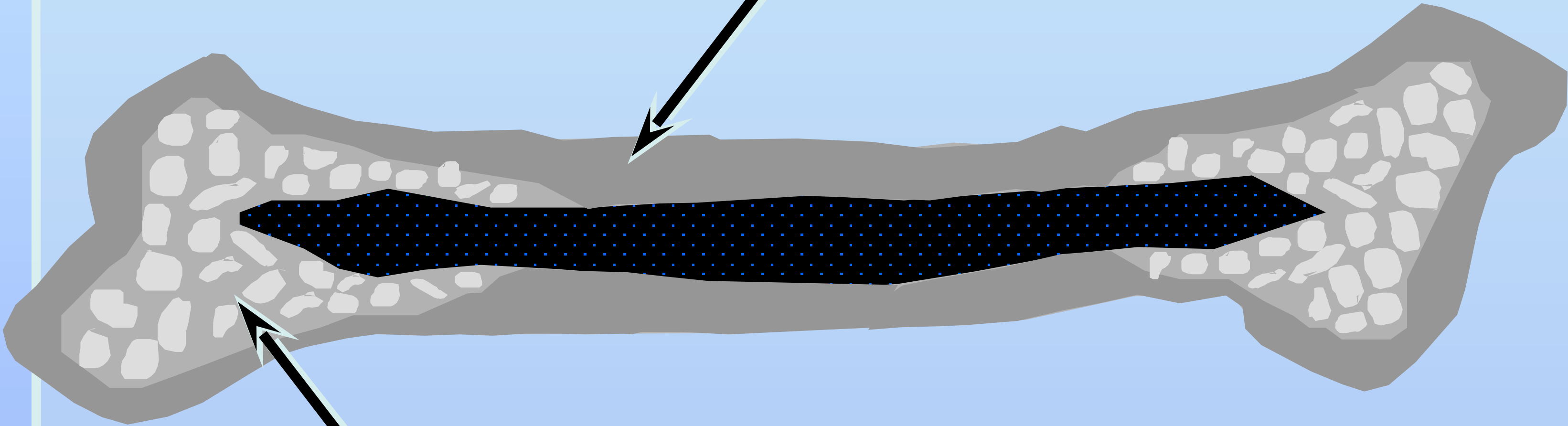



Normal


Osteoporotic

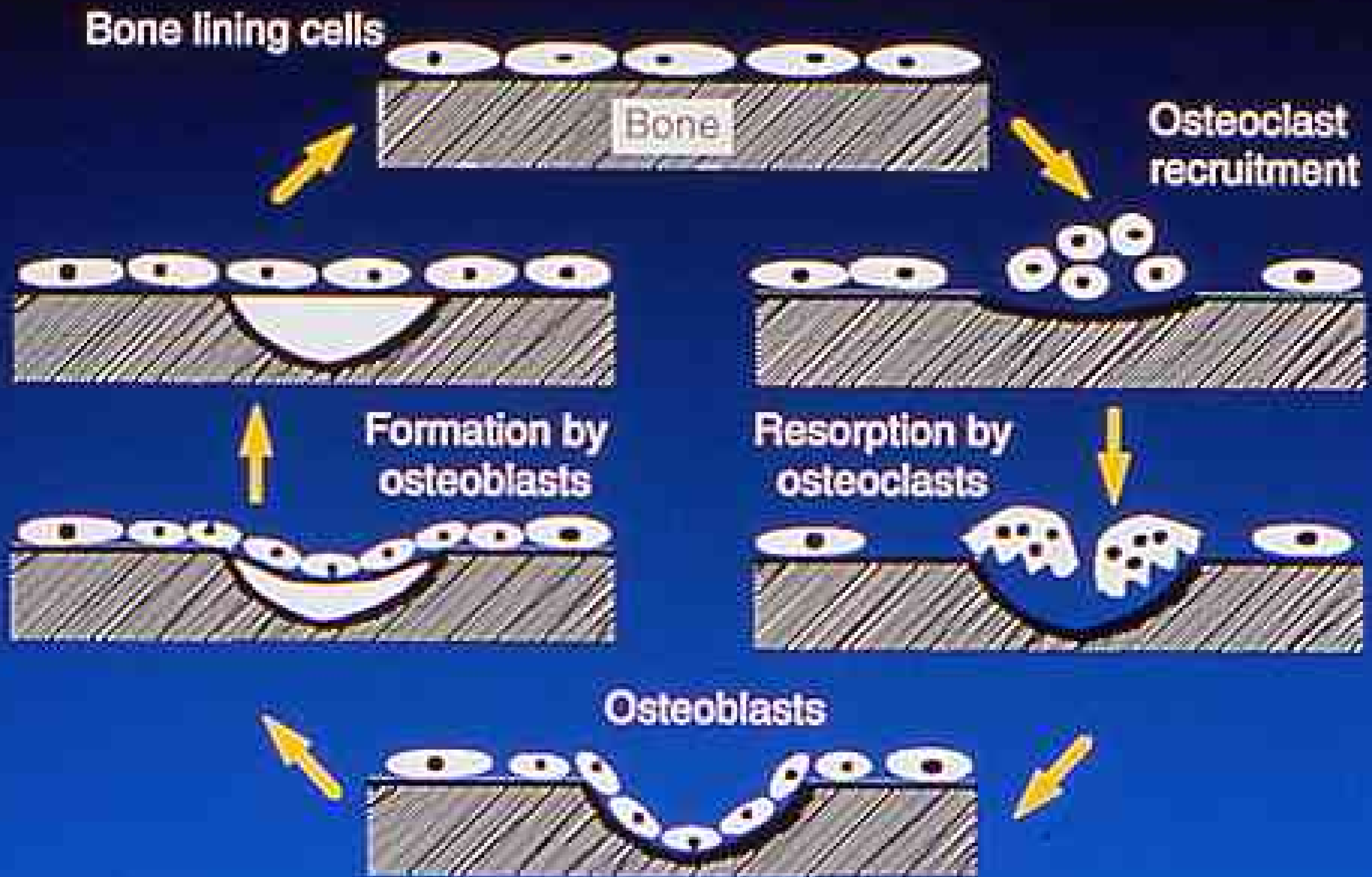
Prevalence

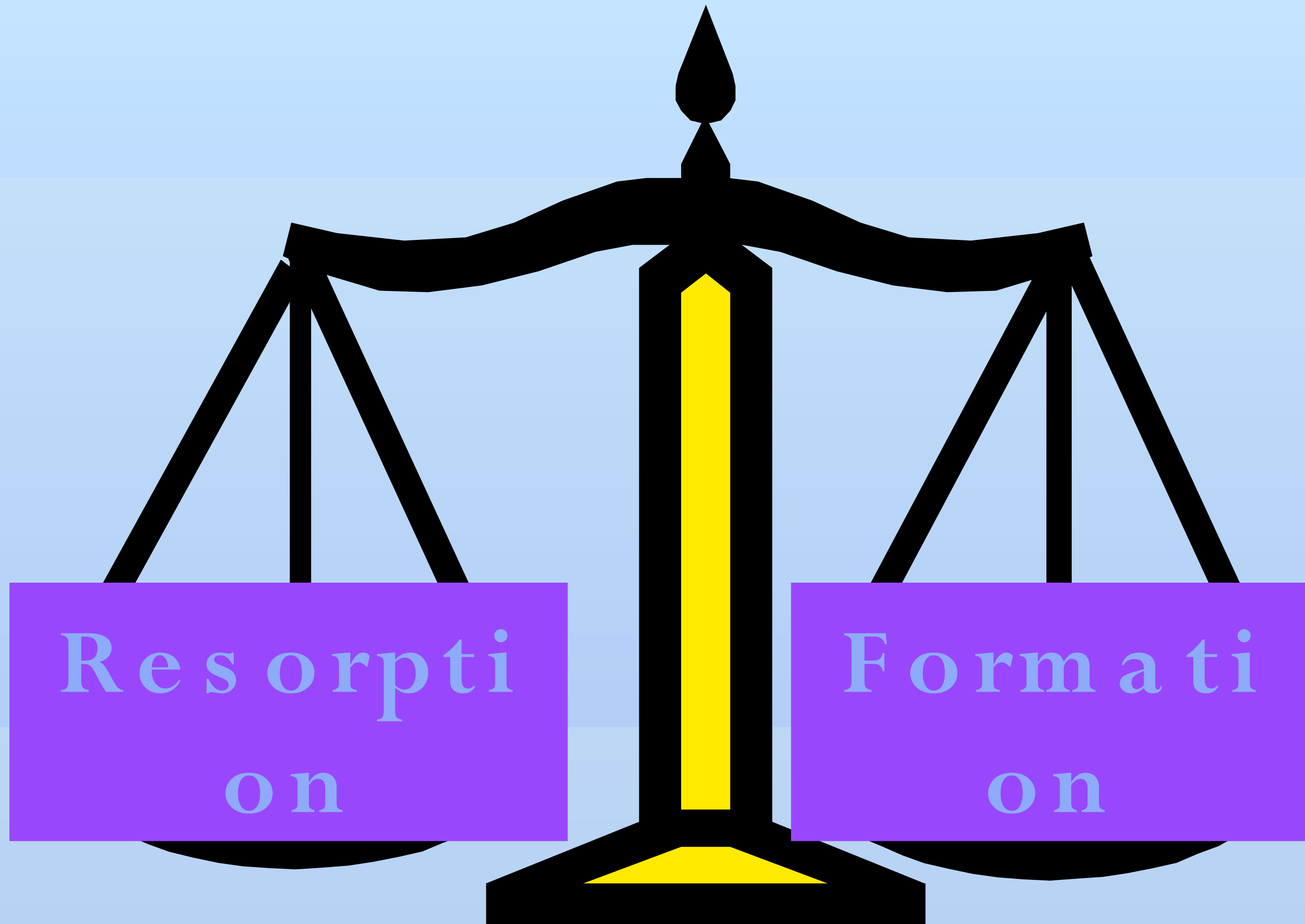
- Approximately 10 million people in the U.S. have osteoporosis
- 21% of postmenopausal white women in U.S. have osteoporosis
- 1 out of every 2 white women will experience an osteoporotic fracture during her life
- Less than 1/3 of cases of osteoporosis have been diagnosed; 1/7 of American women with osteoporosis receive treatment
- 50% of Americans over the age of 50 will be at risk of fracture by 2020 if nothing is done


Cortical
Trabecular

Bone Composition

BONE	% Cortical	% Trabecular
Midradius	95	5
Heel	10 - 25	75 - 90
Femur neck	75	25
Finger	60	40
Lumbar spine	40	60


Bone Remodeling Cycle
Bone lining cells
Bone
Osteoclast recruitment
Formation by osteoblasts
Resorption by osteoclasts
Osteoblasts


Resorption
Formation

Age-Related Bone Loss

- **Protracted slow phase**
  - Starts around age 35
  - Lose bone at a rate of 0.5-1% per year
  - Due to ↓ osteoblastic activity and ↓ GI calcium absorption
- **Transient, accelerated phase (women)**
  - Occurs after menopause
  - Lose bone at a rate of 2-5% per year for 5-10 years
  - Due to ↑ osteoclastic activity

Phases of Bone Loss

- **Normal Bone** : 90-100% of peak bone mass
- **Osteopenia** : 75-90% of peak bone mass
  - Thinning bone
  - Microarchitecture intact
  - Slightly higher risk of fracture
- **Osteoporosis** : <75% of peak bone mass
  - Thinning bone
  - Microarchitecture disrupted
  - High risk of fracture

Risk Factors for Osteoporosis and Fracture

Who has the most risk factors for osteoporosis? Greatest risk for fracture?

- 35 yo Hispanic Female
  - Problem list: asthma, h/o anorexia
  - Weight: 120 lb
  - Family history: Grandmother had osteoporosis
- 55 yo White Female
  - Problem list: HTN, smokes
  - Weight: 135 lb
- 65 yo Black Female
  - Problem list: h/o vertebral fracture
  - Weight: 145 lb

35 yo Hispanic Female

- Problem list: asthma, h/o anorexia
- Weight: 122 lb
- Family history: Grandmother had osteoporosis

55 yo White Female

- Problem list: HTN, smokes
- Weight: 135 lb

65 yo Black Female

- Problem list: h/o vertebral fracture
- Weight: 145 lb

Osteoporotic Fractures

- **Wrist**
  - > 250,000 annually
  - Results from trying to break a fall
  - Warning of cortical bone loss
- **Vertebral**
  - >700,000 annually
  - Most likely to occur between 50 – 70 yo
  - Associated with pain and deformity
- **Hip**
  - >250,000 annually
  - Median age of first hip fracture is 82 yo
  - Primary cause of morbidity, mortality and cost
- **Other**
  - >300,000 annually

Drug Therapy Management of Osteoporosis

Treatment Guidelines

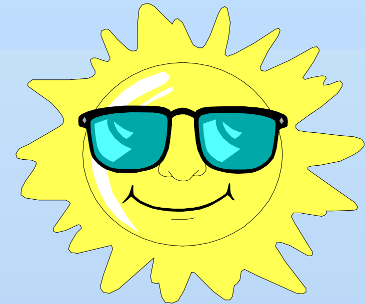
- N. American Menopause Society 2006 Position Statement on Management of Osteoporosis in Postmenopausal Women (Menopause 2006;13:340-367)
- Bone Health & Osteoporosis: A Report of the Surgeon General (2004 http://surgeongeneral.gov/library/bonehealth/content.h)
- NOF Physician's Guide to Prevention & Treatment of Osteoporosis (2003 www.nof.org)
- AACE Medical Guidelines for Clinical Practice for Prevention & Management of Postmenopausal Osteoporosis (Endo Prac 2003;9:545-564. www.aace.com/clin/guidelines)

Adequate Daily Calcium Intake

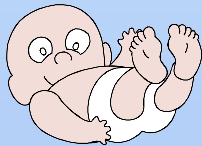
- No universal standard
- NOF: All individuals should intake at least 1200 mg of elemental calcium daily

Adequate Daily Vitamin D

- **Sun exposure**
  - 5 – 15 minutes 2 – 3 times/week

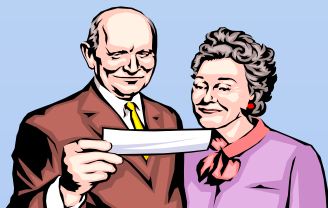


- **Oral intake**



  - Birth to 50 years = 200 IU/d

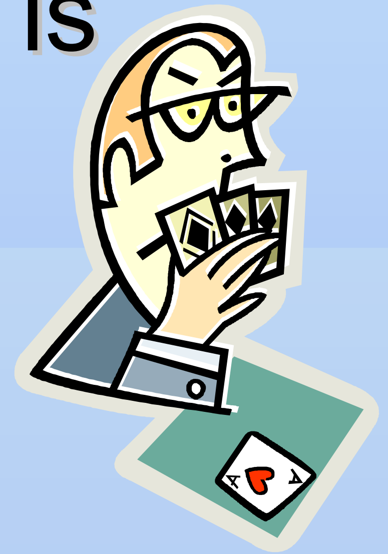
  - 51-70 years = 400 IU/d



  - >70 years = 600 IU/d

“Calcium with vitamin D supplementation is akin to the ante for a poker game: it is where everyone starts.”

JS Finklestein N Engl J Med 2006;354:750-1



Drug Therapy for Osteoporosis

Antiresorptive Agents

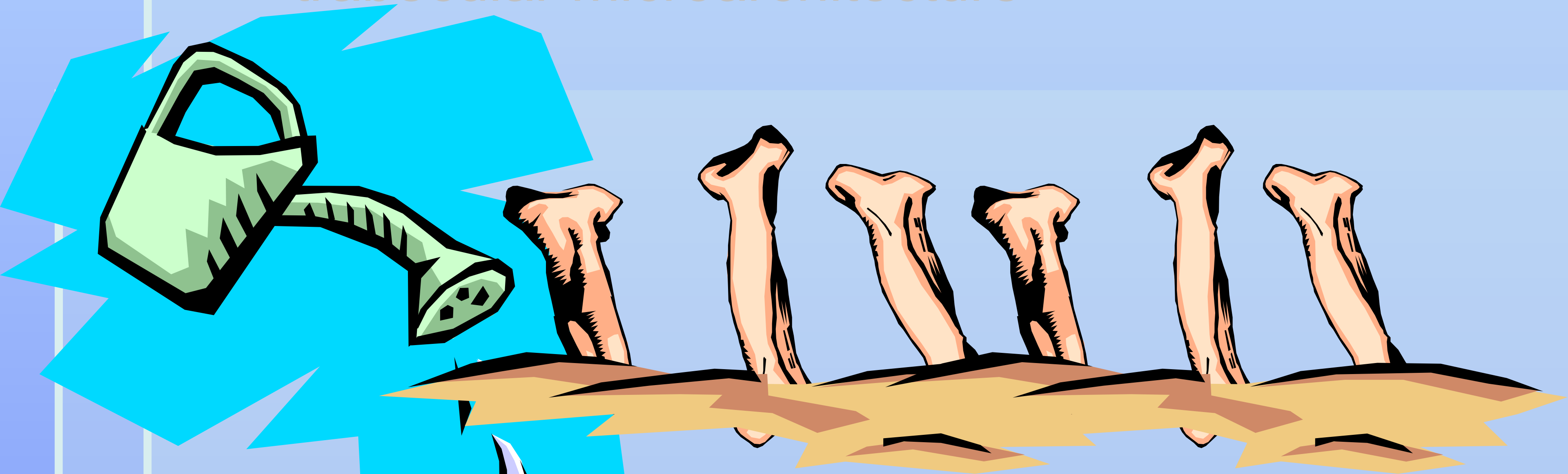
- Major Action: suppress bone resorption preventing further bone loss
  - Decrease in number or depth of resorptive sites
  - Stops further architectural loss
  - Slower turnover allows better mineralization
- Resulting increase in BMD due to more complete mineralization, not increased synthesis of bone
  - May increase BMD by 2-8%

Antiresorptive Agents

- ERT/HRT
- Bisphosphonates
  - Alendronate (Fosamax®)
  - Risedronate (Actonel®)
  - Ibandronate (Boniva®)
  - Zoledronic acid (Reclast ®)
- Salmon-calcitonin (Fortical® Miacalcin®)
- Raloxifene (Evista®)

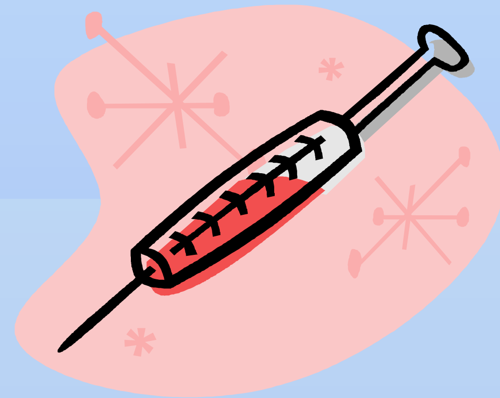
Formation-Stimulating Drugs

- Major Action: stimulate formation of bone mass
  - May increase BMD by 10-20%
  - May increase cortical thickness & enhance trabecular microarchitecture



Formation-Stimulating Drugs

- Teriparatide (Forteo®)

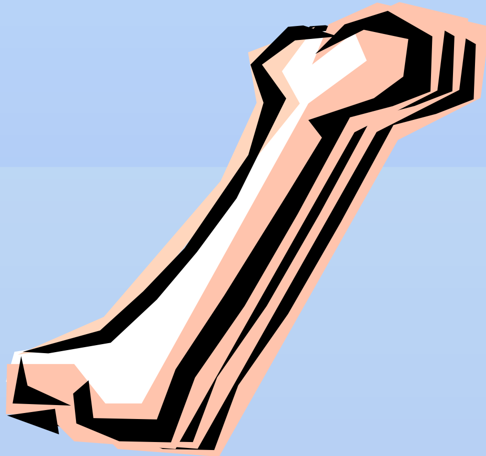


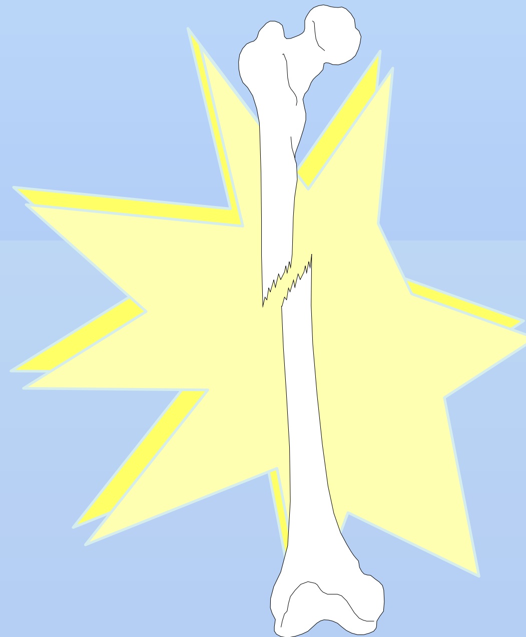
65 yo Black Female

- Problem list: h/o vertebral fracture
- Weight: 145 lb

Evaluation of Drug Therapy Effectiveness

- Effect on bone density
- Effect on fracture incidence





ERT/HRT

- US Preventive Services Task Force (Ann Intern Med 2005;142:855-860)
  - Recommends against the routine use of combined estrogen & progestin for the prevention of chronic conditions
- Am College of Ob Gyns & N Am Menopause Society
  - Recommend caution in using HRT solely to prevent osteoporosis & suggest alternative therapies should be considered
- Labeling update for estrogen products (Wyeth):
  - Women taking estrogen only for osteoporosis prevention should consider alternative therapies
  - Take HRT for shortest time possible at lowest dose

Hip & Non-spine Fracture Risk Reductions Differ Among Antiresorptive Agents: Evidence From Randomized Controlled Trials Int J Clin Prac 60(11):1394-1400,2006.

- Fracture reduction rates
  - Alendronate: 45 – 55%
  - Risedronate: 26 – 27%
  - Ibandronate, Calcitonin & Raloxifene: insufficient and/or inconsistent evidence

Bisphosphonates

Indications	Alendronate	**Risedronate**	**Ibandronate**	**Zoledronic acid**
Prevention PMW*	Yes	Yes	Yes	
Treatment PMW	Yes	Yes	Yes	Yes
Treatment Males	Yes	Yes		

PMW* = Postmenopausal Women

Bisphosphonates

Administration Issues

- Poor oral absorption
  - Only 1-5% is absorbed
  - Reduced further with the presence of food or calcium
- GI irritation
  - May cause local irritation of the upper GI mucosa if not taken precisely as directed

Bisphosphonates

Administration Requirements

- Take with a full glass of water in morning
- Do NOT eat or drink anything for at least 30 minutes after taking *(Ibandronate: 60 min)*
- Do NOT lie down for at least 30 minutes after taking and until after eating *(Ibandronate: 60 min)*

Same for all oral dosage forms

Bisphosphonates

Dosing Options	Alendronate	**Risedronate**	**Ibandronate**	**Zoledronic acid**
Daily PO	5 & 10mg tab		2.5mg tab	
Weekly PO	35 & 70mg tab 70mg solution	5 & 35mg tab		
Monthly PO		75mg tab on 2 consecutive days	150mg tab once monthly	
Quarterly IV			3mg infusion	
Yearly IV				5mg infusion

Bisphosphonates

- Combination Products
  - Fosamax Plus D®
    - Alendronate 70mg / vitamin D 2800 IU
    - Alendronate 70mg / vitamin D 5600 IU
    - Once weekly tablet
  - Actonel® with Calcium
    - Co-packaged product contaning risedronate 35mg & calcium carbonate 1250mg
    - Risedronate day 1; calcium carbonate days 2 – 7

Bisphosphonates

Fracture Risk Reduction	Vertebral fractures	Non-spine fractures
Alendronate	47% reduction	51% reduction
Risedronate	41% reduction	36% reduction
Ibandronate	52% reduction	No significant reduction
Zoledronic acid	70% reduction	41% reduction

Bisphosphonates

Adverse Effects

- Esophageal irritation or erosion
- Bone, joint and/or muscle pain
- Hypocalcemia

Treatment with Once-Weekly Alendronate 70mg Compared to Once-Weekly Risedronate 35mg in Women with Postmenopausal Osteoporosis

JBMR 2004

- *Pt Pop:* 1053 postmenopausal women with low BMD in at least 1 of 4 sites
- *Therapy:* Randomized to once weekly alendronate 70mg or risedronate 35mg. All received 1000mg calcium & 400 IU vit D
- *Results:*
  - Sig greater gains in BMD with alendronate at all BMD sites
  - 12 month differences: total hip 1.0%, femoral neck 0.7%, lumbar spine 1.2%
  - Tolerability profiles similar

Teriparatide

- **Indication**
  - For the treatment of postmenopausal women with osteoporosis who are at high risk for fracture
  - To increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture

Teriparatide

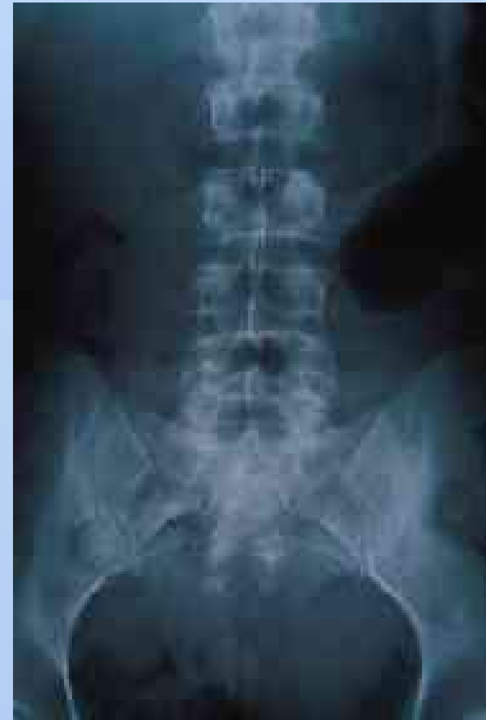
Dosage and Administration

- 20 mcg once daily administered as subcutaneous injection into thigh or abdominal wall
- Take at any time of the day
- Supplied a pre-assembled disposable pen device with 28 doses
  - www.forteo.com for instructions on use
- Use for longer than 2yr not recommended due to lack of safety & efficacy data

Teriparatide

Efficacy

- Reduced fracture rate at the spine by 65% and nonvertebral fractures by 53%



Teriparatide

Adverse Effects

- Dizziness
- Leg cramps
- Transient orthostatic hypotension
  - Infrequent event seen within first several doses
  - Begins within 4 hr of dosing and then resolves
- Transient increases serum calcium

Second Line Options

	Raloxifene	Calcitonin
Indication	Prevention & treatment in PMW	Treatment in PMW > 5 yr post menopause
Administration	60mg tab daily	200 IU spray to one nostril daily
Adverse Effects	Hot flashes Venous thromboembolic events Lowers risk of breast cancer	Rhinitis Nasal crusts, sores, bleeding Arthralgia

Efficacy

Calcitonin

- Reduced vertebral fractures 36%
- Has not been studied in nonvertebral fractures

Raloxifene

- Reduces rate of vertebral fractures about 40%
- No apparent effect on nonvertebral fractures

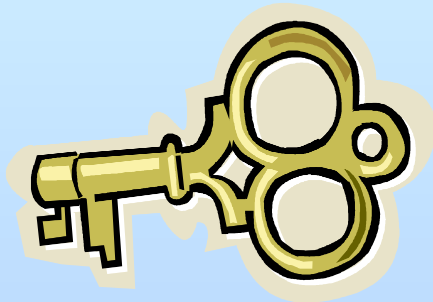
Combination Therapy

- Combo tx results in greater gains in BMD than monotherapy
- None of the trials examined impact on fracture rate
- Combo tx has cost implications & likely to be associated with increased ADRs, reduced tolerability & reduced adherence
- **Combining a bisphosphonate with PTH failed to provide additive effects. Bisphosphonates may reduce the anabolic effects of PTH**

65 yo Black Female

Drug therapy options

- Bisphosphonate
- Teriparatide



Key Point

- Adequate calcium and vitamin D supplementation are required adjunctive therapy with medications for osteoporosis

Summary

- **ERT/HRT**
  - Prevention indication
  - Should not be used for prevention of chronic disease
- **Alendronate, Risedronate, Ibandronate, Zoledronic acid**
  - Prevention & treatment indications
  - Decreases vertebral & nonvertebral fractures – ibandronate?
  - Generally considered first line therapy

Summary

- **Raloxifene**
  - Prevention & treatment indication
  - Decreases vertebral fractures; no effect on nonvertebral fractures
  - Role in therapy unclear
- **Calcitonin**
  - Treatment indication
  - Vertebral fracture data only
  - Considered safe but somewhat less effective
- **Teriparatide**
  - Treatment indication
  - Decreases vertebral & nonvertebral fractures
  - Use limited to high risk patients