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# Osteoporosis for the Clinician 2008

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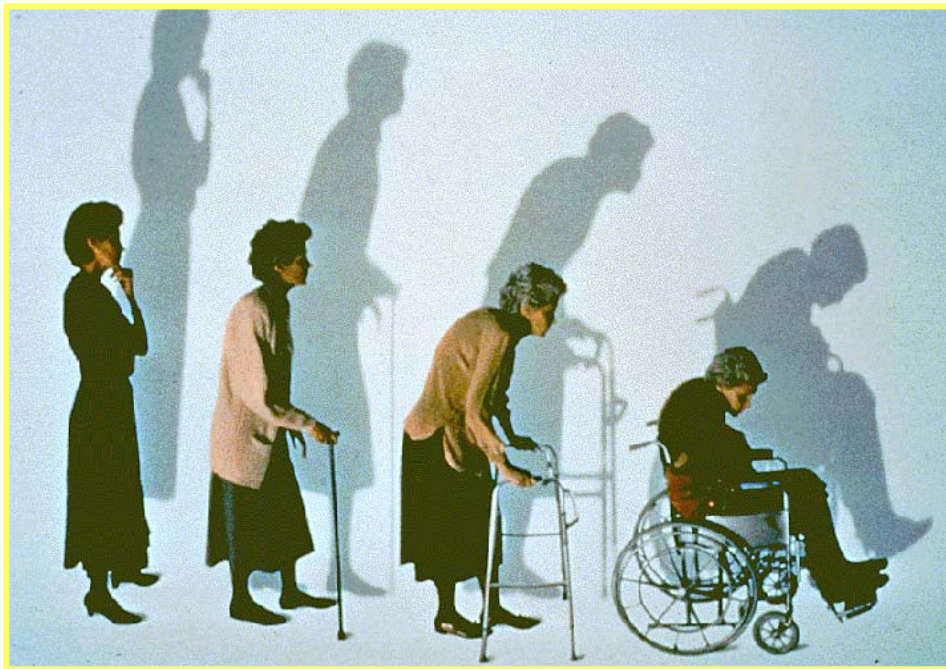
Joanne Valeriano-Marcet MD  
Associate Professor of Medicine  
University of South Florida

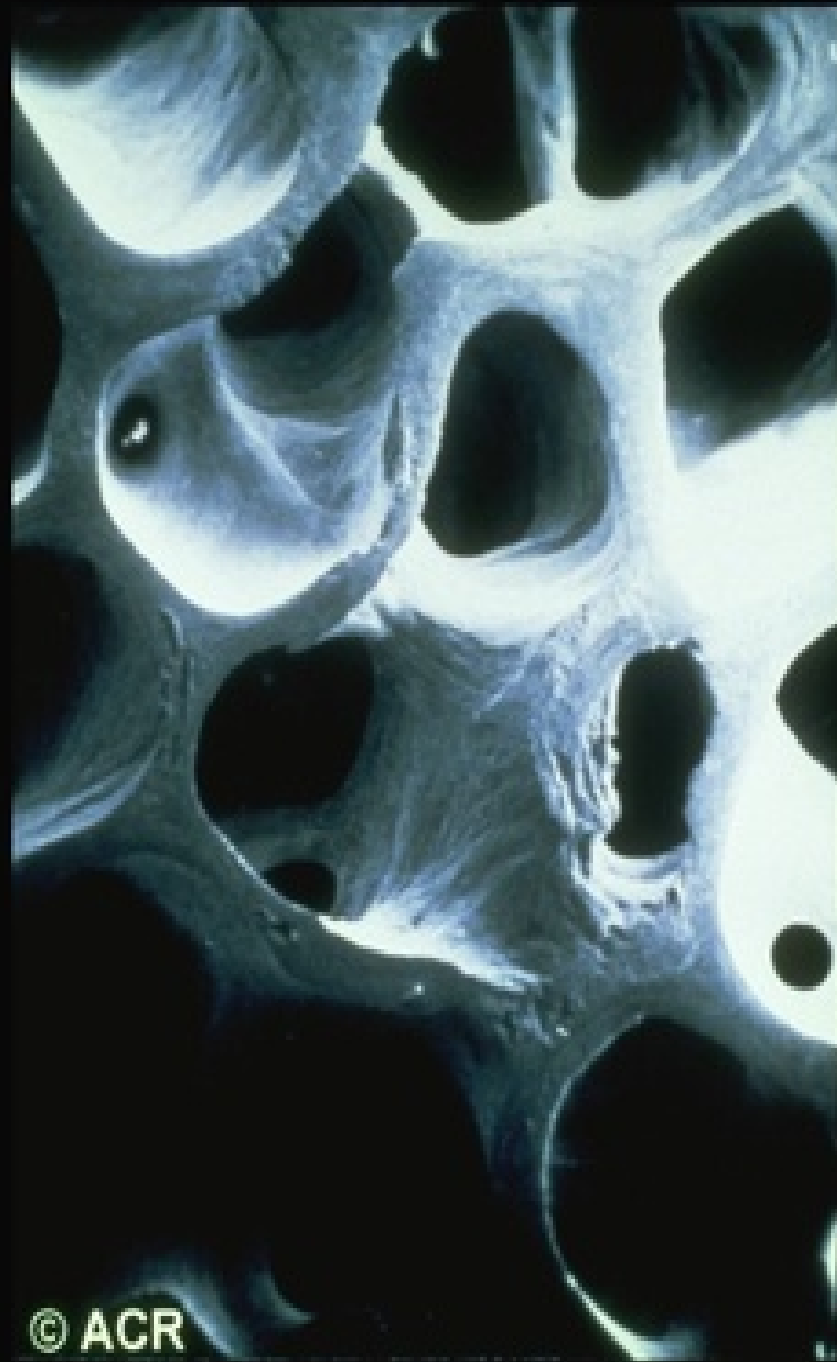
# Goals and Objectives

- Define Osteoporosis, the clinical features, and risk factors
- Understand the epidemiological impact of osteoporosis
- Apply the 2008 NOF Clinician's Guide in the prevention and management of osteoporosis
- Describe the role of the WHO FRAX tool in helping to guide therapy in patients with low bone mass
- Outline the FDA approved therapies for osteoporosis, the indications, contraindications and efficacy in treating osteoporosis

# Osteoporosis: Definition

A skeletal disorder characterized by compromised bone strength that leads to an increased risk of fracture





# Prevalence of Osteoporosis

Postmenopausal Caucasian females over 50 yo:

- hip osteoporosis 20%
- osteopenia 52%(1)

Men over 50 yo

( using male cut off):

- osteoporosis 4-6%
- osteopenia 33-47%(2)



# Lifetime Risk of fracture

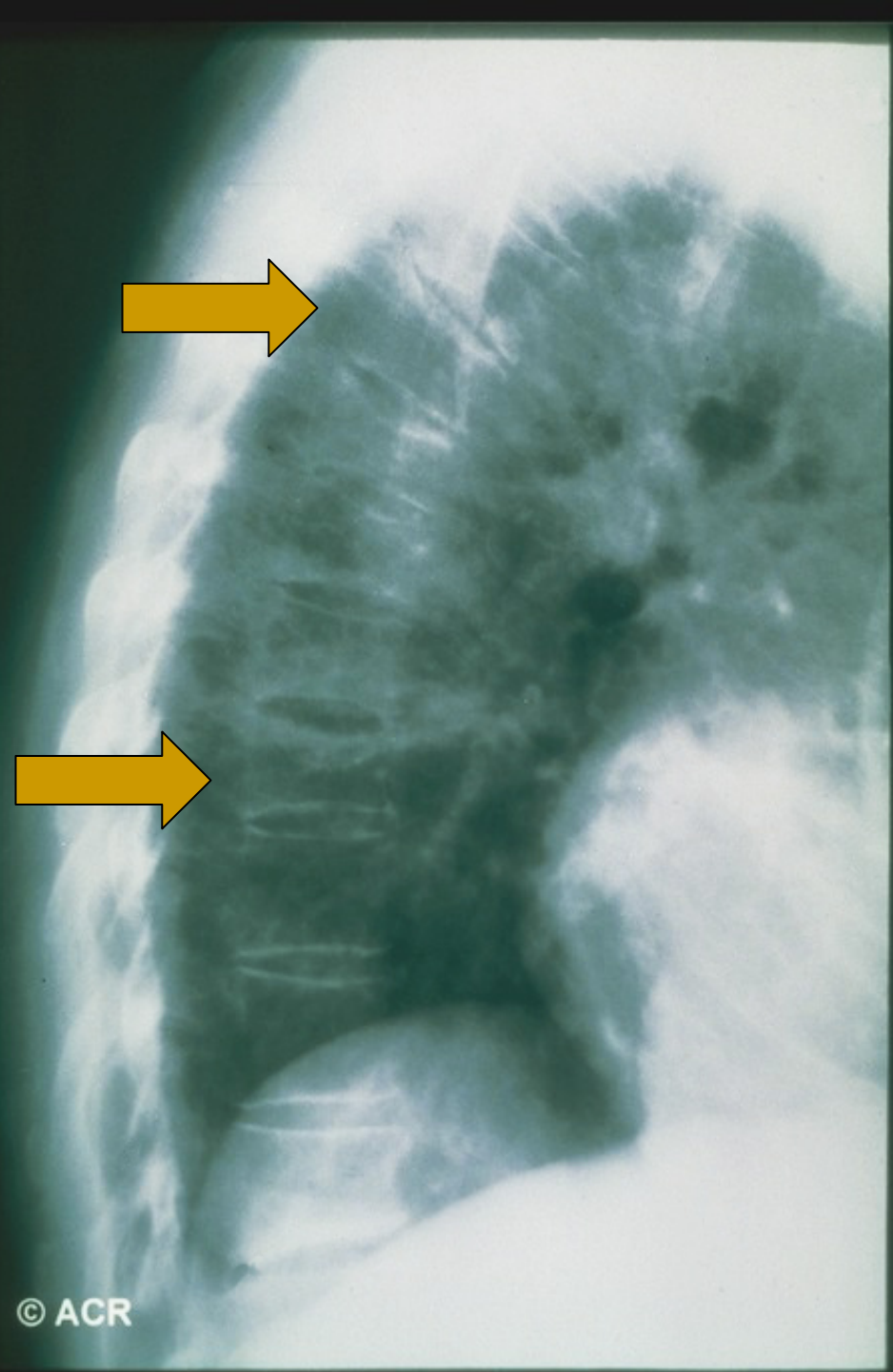
	<b>Hip</b>	<b>Vertebral</b>	<b>Any</b>
<b>Women</b>	15.6%	17.5%	39.7%
<b>Men</b>	5.0%	6.0%	13.1%

# Osteoporosis

## Clinical features

- Asymptomatic (decreased density, possible fracture, no height loss)
- Asymptomatic with loss of height
- Thoracic/ Lumbar pain due to fracture
- Femoral neck fracture
- Distal radius fracture
- Sacral pain / sacral insufficiency fracture

# Vertebral Compression Fracture



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# Impact of Vertebral Fractures

- Pain
  - Possible permanent disfigurement
  - Possible loss of height
  - Loss of self esteem
  - Increased risk of hip fracture
  - Increased morbidity and mortality
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# Osteoporotic Hip Fractures

## Prevalence and outcomes in U.S.

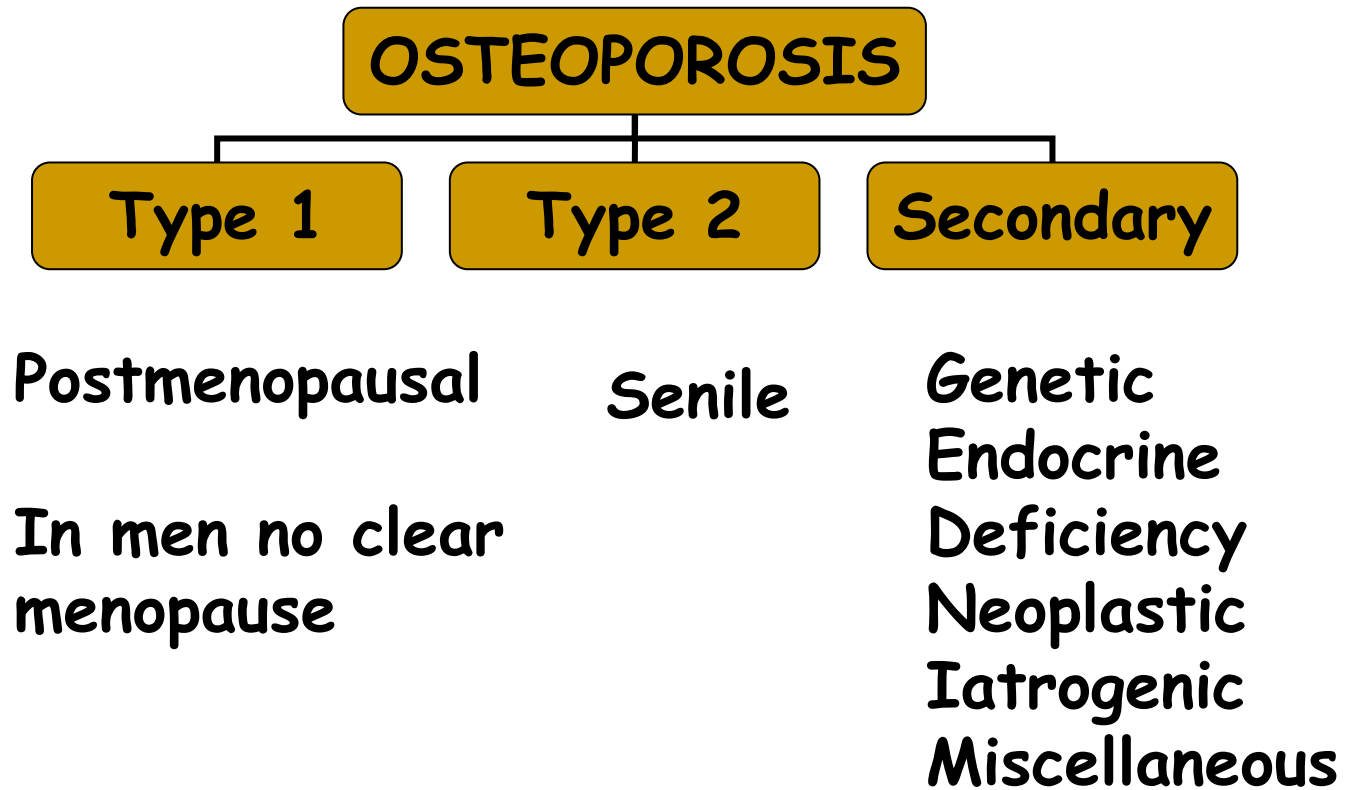
300,000 hip fractures annually

24% excess  
mortality in 1<sup>st</sup> year

50% never fully  
recover

25% require  
long term  
nursing home  
care

# OSTEOPOROSIS CLASSIFICATION



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A 65 year old postmenopausal  
caucasian female with osteoporosis

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What is the most common  
secondary cause of bone loss?  
And how do we assess for this?

# Secondary Causes of Osteoporosis

- Identified in 40 to 60% men with osteoporotic fracture(1,2,3)
  - Hypogonadism
  - GCO
  - GI disease
  - Anticonvulsant
  - Alcohol Abuse
- 40% of Women with unsuspected disorders of metabolism(4)
  - Vit D Deficiency 20%
  - Hyperparathyroidism primary or secondary 3%
  - Malabsorption 7%
  - Hypercalciuria 10%

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## Evaluation of patient with bone loss to exclude secondary causes

- Serum Ca, Alk phos, PO<sub>4</sub>, BUN Cr, LFTS
  - CBC, SPEP (over age 50)
  - 24 hr urine Ca, intact PTH, 25 OH Vit D level
  - Testosterone, free T4 TSH
  - Further evaluation should be guided by symptoms and presentation
-

# DXA Scanner



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# Sites of measurement

- Lumbar spine
  - Hip: Total hip and femoral neck
  - Radius: 33% radius (one third radius)
-

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# Bone Mass Measurement Data

- Absolute value ( $\text{g}/\text{cm}^2$ ) for patient
  - Comparison to age and sex matched reference values (Z score)
  - Comparison to sex matched mean peak reference values (T score)
-

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# Bone Mass Measurement Diagnostic Categories

- **Normal:** No more than 1 STD below the young reference mean peak value
  - **Low Bone Mass:** >1 but <2.5 STD below young reference mean peak value
  - **Osteoporosis:**  $\geq 2.5$  STD below young reference mean peak value
-

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# Who should have BMD testing?

## *NOF New Clinicians Guidelines*

- Women age 65 and men age 70 and older
  - Postmenopausal women and men age 50-69,
    - when risk factor profile raises concern
  - Patients with fracture
    - determine degree of severity
  - Follow up DXA
    - Monitor bone loss q 2 years, unless clinically warranted
-

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# Monitoring Treatment

- Discuss compliance with therapy
  - Review risk factors and encourage appropriate Ca, Vit D, exercise, fall prevention and other lifestyle measures
  - Serial DXA should be in accordance with medical necessity, expected response, and consider local regulatory requirements
  - NOF recommends q 2 years
  - More frequent testing based on clinical situation
-

# Impact of Osteoporosis

- Ageing population will lead to increasing fractures and associated increasing costs
- In US, by 2010 (NOF estimate)
  - 12 million Osteoporosis
  - 40 million low bone mass
- Decision for instituting pharmacotherapy
  - Established Osteoporosis: *little controversy*
  - Low Bone Mass
    - *need to determine those at high risk for fracture*
    - *maximize benefit while limiting risks and cost of therapy*

# How many of you


1. Have heard of the WHO FRAX tool for the evaluation of fracture risk?
2. Have used the WHO FRAX tool in your practice?
3. Understand when to use the WHO FRAX tool?
4. Know the limitations of the WHO FRAX tool?

**FRAX™**

# WHO FRAX [www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)

- Goal was to predict fracture risk in men and women world wide
- Integrates BMD( Tscore fem neck) and clinical risk factors
- Algorithm for assessing 10 year risk of fracture
  - *Hip*
  - *Major osteoporotic fracture*
    - *(clinical spine, forearm, hip or humerus fracture)*
- Clinical risk factors: validated in
  - *60,000 men and women from 12 prospective, population based cohorts*
  - *confirmed in other studies, including the Study of Osteoporotic Fractures in the Women's health initiative*

# 60 year old female with femoral neck T score -1.8, and LS spine T score -2.0

Country : **US(Caucasian)** Name / ID :  [About the risk factors](#) 

### 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) 100 lb

4. Height (cm) 65 inches

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

**BMI 16.6** 

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

**with BMD**

■ Major osteoporotic	<b>21</b>
■ Hip fracture	<b>3.4</b>

# Implementation FRAX in US

- FRAX algorithm uses National Health and Nutrition Examination Survey( NHANES III) caucasian female reference value( updated 1998)
- "FRAX™ Patch" calculates the T-score to use with FRAX™ from DXA BMD results
  - computes the appropriate femoral neck T-score to use in the FRAX™ calculator for men and women regardless of ethnicity.
  - GE-Lunar, Hologic or Norland DXA machines

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# FRAX patch [www.NOF.org](http://www.NOF.org)

- To use FRAX patch select the
    - brand of DXA machine
    - femoral neck BMD value in units of  $\text{g}/\text{cm}^2$ .
    - T-score to use for the FRAX™ calculator provided
-

## Use of WHO FRAX in the US

- Calibrated to US fracture and mortality rates
- Economic modeling
  - identified the 10 year hip fracture risk above which it is cost effective, from societal perspective to treat with pharmacological agents
- Use in postmenopausal women and men age 50 and older
- Applies only to previously untreated patients
- In the absence of femoral neck BMD, may use total hip BMD
- Use FRAX patch for any patient ( male or female) prior to entering T score into FRAX \*

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\* *Entering unconverted T scores will overestimate risk in many individuals*

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# Limitations of the WHO FRAX

- Not validated for the use of spine BMD
    - Requires special consideration with low spine and normal hip DXA
  - FRAX does not account for all important clinical RF
    - GCO used defined as ever/never, whereas amount and duration differentially affects risk
  - Algorithm cannot replace clinical judgement and patient preference
-

# Limitations of the NOF economic analysis

- Identified treatment thresholds on an overall drug efficacy of 35% not taking into account
  - Efficacy at specific skeletal sites, (ie spine)
  - Variability in treatment tolerability and adherence
  - Potential added benefit (ie breast cancer risk reduction with raloxifene)

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# New NOF Clinician Guidelines

- Women and men of all races/ethnicities:  
*age 50 year and older, not currently on a pharmacological agent*
- Reference point, not rigid standard
- Clinicians recommendations **must be tailored by**
  - *clinical judgment*
  - *estimated prospective risk*
  - *patient preferences*

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# New Clinicians Guidelines: *recommendations for men and postmenopausal women age 50 yr and older*

- Counsel on the risk of osteoporotic fractures
  - Evaluate for secondary causes
  - Advise
    - Ca (1200mg daily)
    - Vit D (800-1000 IU daily)
  - Regular weight bearing and strengthening
  - Avoid
    - Tobacco smoking
    - excessive alcohol intake
-

# General Rules for Treatment

- Fracture history
  - Hip
  - Vertebral (clinical or morphometric)
- Osteoporosis by DXA
  - Tscore  $\leq -2.5$  (fem neck, T hip, spine)
  - after exclude secondary causes


# General Rules for treatment

- Low bone mass by DXA in postmenopausal women and men age 50 yr and older
  - T score between -1.0 and -2.5 (fem neck, spine), if 10 year fracture probability
    - hip fracture probability  $\geq 3\%$
    - any major osteoporotic fracture probability  $\geq 20\%$  \*

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\* Based on the US adapted WHO absolute fracture risk model [www.NOI.org](http://www.NOI.org)

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

**with BMD**

Major osteoporotic	<b>21</b>
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# Pharmacologic Management of Osteoporosis

## TREATMENT and PREVENTION

- Alendronate  
Risedronate  
Ibandronate
- SERM: Raloxifene

## TREATMENT ONLY

- Salmon calcitonin nasal spray
- Teriparatide  
osteoblast stimulator
- Zoledronate

## PREVENTION ONLY

- Estrogen and/or Hormone Replacement Therapy

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# Bisphosphonates

- Alendronate: oral daily, weekly
  - Risedronate: oral daily, weekly or monthly
  - Ibandronate: oral monthly and **IV quarterly**
  - Zoledronate: **IV yearly**
-

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# Alendronate

- Prevention of postmenopausal osteoporosis
    - 5 mg daily, 35 mg weekly
  - Treatment of postmenopausal osteoporosis
    - 10 mg daily, 70mg tablet or liquid weekly
    - 70 mg weekly tablet with 2800, or 5600 IU Vit D
  - Treatment to increase bone mass in men with osteoporosis
  - Treatment of osteoporosis in men and women taking GCO
-

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# Alendronate

- Fracture reduction
  - In patients with prior vertebral fracture: 50% reduction spine and hip fracture over 3 years
  - In patients without prior fracture: 48% reduction spine fracture over 3 years \*

# Ibandronate

- Treatment( oral and IV) of postmenopausal osteoporosis
- Prevention (oral) of postmenopausal osteoporosis
- 2.5 mg daily, 150 mg monthly, 3 mg IV q 3months
- Vertebral fracture reduction 50% over 3 years \*

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# Risedronate

- FDA approved
    - Prevention and treatment of postmenopausal osteoporosis
    - increase bone mass in men with osteoporosis
    - Prevention and treatment of osteoporosis in men and women who are taking or initiating GCO.
  - 5 mg daily, 35mg weekly, 75 mg on 2 consecutive days every month, and 150 mg monthly
-

# Risedronate

- Fracture reduction
  - Reduces vertebral fracture 41 to 49% (1,2)
  - Reduces non-vertebral fractures by 39% (1) over 3 years, significant reduction within 1 year with patients with prior vertebral fracture.
  - Reduces hip fracture 30%-40%(3)

1. Harris et al A randomized controlled trial. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *JAMA* 282:1344-1352

2. Reginster et al VERT Study Group *Osteop Int* 11:83-91

3. Mcclung et al. Hip Intervention Study Group. *N Eng J Med* 344:333-40

# Zoledronate

- 5 mg IV infusion over 15 to 30 minutes once yearly
- Approved by the FDA for the treatment of PMO
- Approved for prevention of new clinical fractures in patients( male, female) who have recently had a low trauma hip fracture
- Over 3 years, reduces risk of
  - vertebral fractures by 70%( with sig reduction by one year)
  - Hip fractures by 41%
  - Nonvertebral fractures by 25% \*

*\*Black et al N Engl J Med. 2007 May 3;356(18):1809-22.*

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# Oral bisphosphonates: side effects and administration

- Similar side effects for all
    - Difficulty swallowing
    - Esophageal inflammation
    - Gastric ulcer
  - Directions:
    - Take on an empty stomach with 8 oz water
    - 30-60 minutes prior to breakfast, or other meds
    - DO not lie down for at least 60 minutes
-

# OSTEONECROSIS OF THE JAW



Exposed area of bone in the mandible, maxilla, or palate that heals poorly, or does not heal over 6 weeks

# Estrogen /Hormone Therapy(HT) \*

- **Indication:** Prevention of Postmenopausal osteoporosis (*use lowest dose for shortest duration to meet treatment goals*)
- **Benefit:** HT Decreases hip and spine fractures during 5years treatment (WHI)
- **Risk:**
  - HT: increased MI, stroke, invasive breast CA, DVT, PE (WHI)
  - Additional analysis, no increase CVD in women starting treatment within 10 years of menopause
  - Estrogen only:** No increased breast CA( 7 years), increased stroke

JAMA 2002 288;(3)321-333

JAMA 2004:291(14) 1701-12

\*Women with intact uterus require HT which contains progestin to protect uterine lining

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# Selective Estrogen Receptor Modulator

- Bind estrogen receptors
  - Produce estrogen effects in some tissues
  - Produce estrogen blocking effects in other tissues
-

# Raloxifene

- **Indication:** Prevention and treatment of postmenopausal osteoporosis
- **Benefit:** Decreases spine fracture 30-50% \*, **No proven effect on non vertebral or hip fracture rates**  
Decreases risk of invasive breast CA 76%  
Decreases Total and LDL cholesterol
- **Risk:** Increases risk of DVT by 3x
- **Route of administration:** oral

*\*Ettinger et al MORE Study JAMA 1999; 282:637-645*

# Calcitonin

- **Indication:** Treatment of Osteoporosis in women who are at least 5 years postmenopause
- **Benefit:**  
36 % reduction in the risk of new vertebral fracture \*
- **Adverse Effects:**  
*Rhinitis*  
*Nasal symptoms: crusting, itching, soreness*  
*Arthralgia*  
*Headache*  
*Backache*
- **Route of Administration:** intranasal,  
injectable

\*Chestnut et al The prevent Recurrence of Osteoporotic Fractures Study AM J Med 109:267-276

# Teriparatide

- Approved for treatment
  - PMO in patients at high risk of fracture
  - Increase bone mass in men with primary or hypogonadal osteoporosis at high risk of fracture
- Decrease vertebral fractures by 65% and nonvertebral fractures by 53% \*
  - Osteoporotic patients
  - 18 months therapy
- Dose 20 mcg subcutaneous daily

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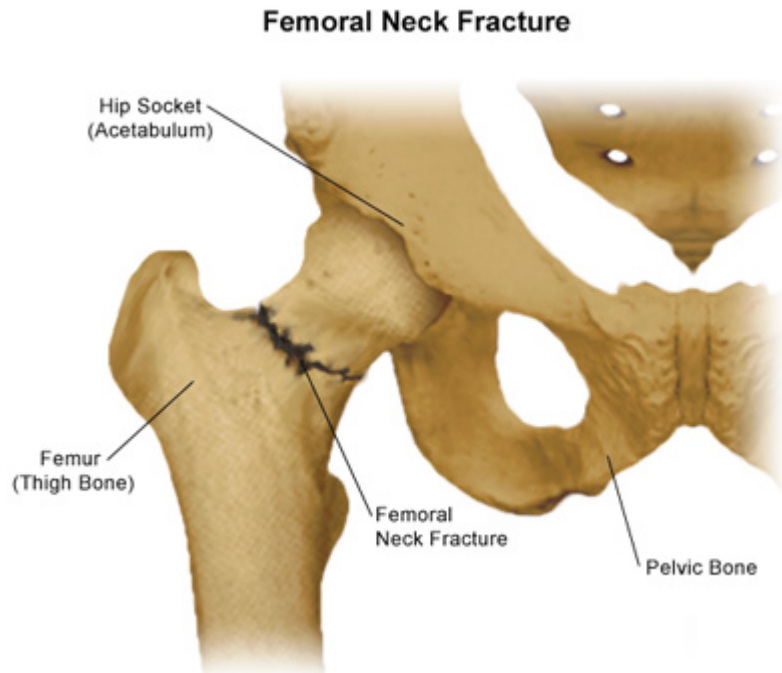
\*Neer et al. *N Engl J Med* 2001; 344:1434-41

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# Teriparatide

- Side effects: leg cramps, dizziness
  - Osteosarcoma in rats
  - Avoid in the following patients
    - Pagets disease of bone
    - Prior skeletal RT
    - Bone Metastases
    - Hypercalcemia
    - History of skeletal malignancy
-

An 80 year old male is referred to you following a femoral neck fracture.



DXA T score L fem neck -2.0  
DXA T score L T hip -1.8  
DXA T score spine +0.5

What pharmacologic therapy would you recommend?

# Zoledronic Acid post hip fracture

- Randomized, double-blind, placebo-controlled trial,
  - 1065 patients were assigned to receive yearly intravenous zoledronic acid (at a dose of 5 mg), and 1062 patients were assigned to receive placebo.
  - The infusions were first administered within 90 days after surgical repair of a hip fracture.
  - All patients received supplemental vitamin D and calcium.
  - The median follow-up was 1.9 years.
  - The primary end point was a new clinical fracture.

# RESULTS

## ■ Fracture Rates

### □ Any new clinical fracture

- 8.6% in the zoledronic acid group and 13.9% in the placebo group, a 35% risk reduction ( $P = 0.001$ );

### □ respective rates of a new clinical vertebral fracture were 1.7% and 3.8% ( $P = 0.02$ ),

### □ respective rates of new nonvertebral fractures were 7.6% and 10.7% ( $P = 0.03$ ).

# Results

- In the safety analysis
  - 101 of 1054 patients in the zoledronic acid group (9.6%) and 141 of 1057 patients in the placebo group (13.3%) died
  - reduction of 28% in deaths from any cause in the zoledronic-acid group ( $P = 0.01$ ).

# Adverse Events

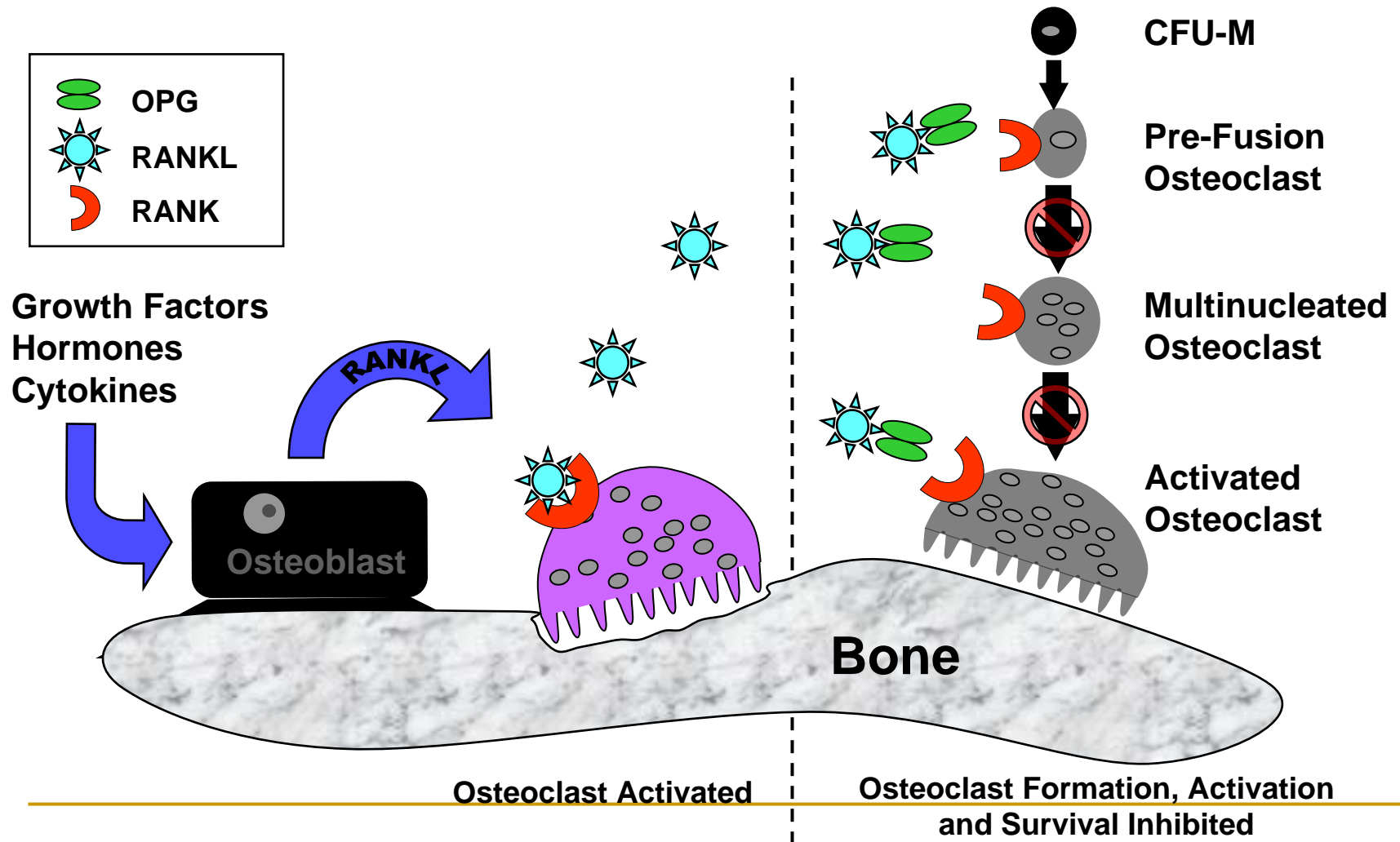
- Most frequent adverse events in patients receiving zoledronic acid
  - pyrexia, myalgia, and bone and musculoskeletal pain.
- No cases of osteonecrosis of the jaw were reported
- no adverse effects on the healing of fractures were noted.
- The rates of renal and cardiovascular adverse events, including atrial fibrillation and stroke, were similar in the two groups.

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# CONCLUSIONS

- An annual infusion of zoledronic acid within 90 days after repair of a low-trauma hip fracture was associated with
    - reduction in the rate of new clinical fractures
    - improved survival.
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# Osteoclast Regulation by RANK Ligand and Osteoprotegerin (OPG)



CFU-M = colony forming unit macrophage

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# Denosumab

- Investigational fully human monoclonal AB
  - inhibits receptor activator of nuclear factor- $\kappa$ B ligand(RANKL), an essential mediator of osteoclast formation, function, and survival
-

# Comparison of the Effect of Denosumab and Alendronate on Bone Mineral Density and Biochemical Markers of Bone Turnover in Postmenopausal Women With Low Bone Mass

- Phase 3, multi-center, double-blind study
- 1189 postmenopausal women
  - T score  $\leq -2.0$  at the lumbar spine or total hip were randomized 1:1 to receive subcutaneous denosumab injections (60 mg every 6 months [Q6M]) plus oral placebo weekly (n=594) or
  - oral alendronate weekly (70 mg) plus subcutaneous placebo injections Q6M (n=595).
- Changes in BMD and bone turnover markers
  - total hip, femoral neck, trochanter, lumbar spine, and 1/3 radius at 6 and 12 months,
  - and in bone turnover markers at months 1, 3, 6, 9, and 12.

# Results at 12 months

- Total hip, denosumab significantly increased BMD compared with alendronate (3.5% versus 2.6%;  $p < 0.0001$ )
- Significantly greater increases in BMD were observed with denosumab
  - 0.6% femoral neck; 1.0% trochanter; 1.1% lumbar spine; 0.6% 1/3 radius;  $p \leq 0.0002$  all sites
- Denosumab significantly reduced bone turnover markers compared with alendronate therapy.
- Adverse events and laboratory values were similar for both groups

# Goals and Objectives

- Define Osteoporosis, the clinical features, and risk factors
- Understand the epidemiological impact of osteoporosis
- Apply the 2008 NOF Clinician's Guide in the prevention and management of osteoporosis
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- Outline the FDA approved therapies for osteoporosis, the indications, contraindications and efficacy in treating osteoporosis

# Estimating Daily Dietary Calcium Intake

- Step 1: Estimate calcium intake from calcium-rich foods\*

Milk (8 oz.) \_\_\_\_\_ x 300 = \_\_\_\_\_ Ca in mg/day

Yogurt (6 oz.) \_\_\_\_\_ x 300 = \_\_\_\_\_

Cheese (1 oz. or 1 cubic in.) \_\_\_\_\_ x 200 = \_\_\_\_\_

Fortified foods or juices \_\_\_\_\_ x 80 to 1,000\*\* = \_\_\_\_\_

STEP 2: Total from above + 250 mg for nondairy sources

= total dietary calcium \_\_\_\_\_ in mg

*\* About 75 to 80 percent of the calcium consumed in American diets is from dairy products.*

*\*\* Calcium content of fortified foods varies.*

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# Vitamin D

- Major role in Ca absorption, bone health, muscle performance, balance and risk of falling
  - Dietary sources
    - Vit D fortified milk: 400 IU per quart
    - Vit D fortified cereals 40-50 IU/serving
    - Egg yolk, salt water fish, and liver
  - Risk of Vit D deficiency
    - Elderly
    - Malabsorption ( celiac d)
    - Chronic renal insufficiency
  - Higher doses up to 2000 IU qd
-

# Bisphosphonate Holiday? Comparison of ALN for 5 verses 10 years

- 1099 postmenopausal women
  - who had been randomized to alendronate in FIT, with a mean of 5 years of prior alendronate treatment.
  - Randomized to
    - alendronate, 5 mg/d (n = 329) or 10 mg/d (n = 333),
    - or placebo (n = 437) for 5 years (1998-2003).

# Alendronate discontinuation

## ■ Outcome Measures

- The primary outcome measure was total hip bone mineral density (BMD);
- secondary measures were BMD at other sites and biochemical markers of bone remodeling.
- An exploratory outcome measure was fracture incidence.

Results: Compared with continuing alendronate, switching to placebo for 5 years resulted in

□ Declines in BMD

- total hip (-2.4%; 95% confidence interval [CI], -2.9% to -1.8%;  $P < .001$ ) and
- spine (-3.7%; 95% CI, -4.5% to -3.0%;  $P < .001$ )
- mean levels remained at or above pretreatment levels 10 years earlier.

# Results

- Cumulative risk of nonvertebral fractures : Not significant
  - placebo(18.9%) vs. ALN(19%) (RR, 1.00; 95% CI, 0.76-1.32)
- Clinically recognized vertebral fractures: Significant
  - placebo 5.3% vs. 2.4% ALN (RR, 0.45; 95% CI, 0.24-0.85)
- Morphometric vertebral fractures: Not significant
  - Placebo 11.3% vs. 9.8% ALN (RR, 0.86; 95% CI, 0.60-1.22).
- A small sample of 18 transilial bone biopsies did not show any qualitative abnormalities, with bone turnover

# Conclusions

- Women who discontinued alendronate after 5 years
  - showed a moderate decline in BMD
  - gradual rise in biochemical markers
  - no higher fracture risk other than for clinical vertebral fractures compared with those who continued alendronate.
- These results suggest that for many women, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk.
- women at very high risk of clinical vertebral fractures may benefit by continuing beyond 5 years.

## Risk of hip fracture after bisphosphonate discontinuation: implications for a drug holiday.

- Using administrative databases from a large U.S. healthcare organization
- Women initiating bisphosphonate therapy compliant for 2 years  
(Medication Possession Ratio, MPR  $\geq$  66%)
- Examined the rate of hip fracture among women who discontinued bisphosphonates versus those who remained on therapy.

# RESULTS:

- 9,063 women were eligible for analysis.
- Hip fracture incidence among women who discontinued bisphosphonates versus those who did not
  - 8.43 versus 4.67 per 1000 person years ( $p = 0.016$ ).
- For women with higher compliance at 2 years (MPR  $\geq$  80%) or compliant for 3 years,
  - there were no significant differences in risk associated with discontinuation.