

# **Hot Topics in Osteoporosis: Atypical Fractures & How Long to Treat with Bisphosphonates**

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**Intercoastal Medical Group**

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**No Disclosures**

# Outline



- **Case**
- **Osteoporosis review**
- **Bisphosphonates review**
- **Atypical fractures**
  - **Clinical and radiologic features**
  - **Epidemiology**
  - **Pathogenesis**
- **Conclusions**
- **Recommendations**

# Case

- **HPI:** 41 y.o. WF with rheumatoid arthritis, constrictive bronchiolitis – steroid dependent, & osteoporosis – on alendronate x 8 yrs
  - 4 mos prior to visit, suffered left subtrochanteric femur fracture after tripping over speed bump in parking lot
  - Reported a snapping sound, pain & deformity before even hitting the pavement
  - Left hip pain for 4 wks prior to the fracture, but had negative imaging studies
- **Labs:** ca 9.4, alk phos 79, iPTH 33.1, 25-OH vit D 57, TSH 1.36, Free T4 0.8, 24-hr urine calcium 135

- **Dexa:**

	T-Score
L1-L4	-2.5
R femoral neck	-1.7
R total hip	-2.2

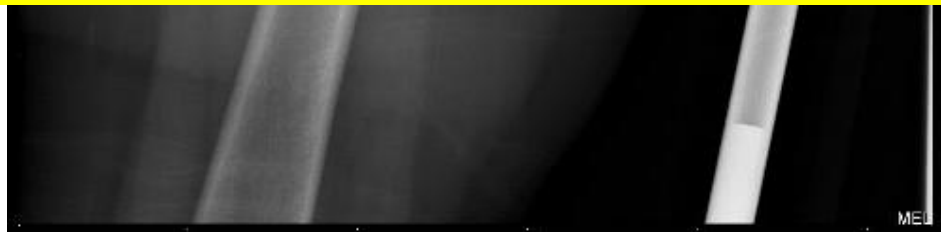
JAWN Lossy UVA  
Cano  
Nov



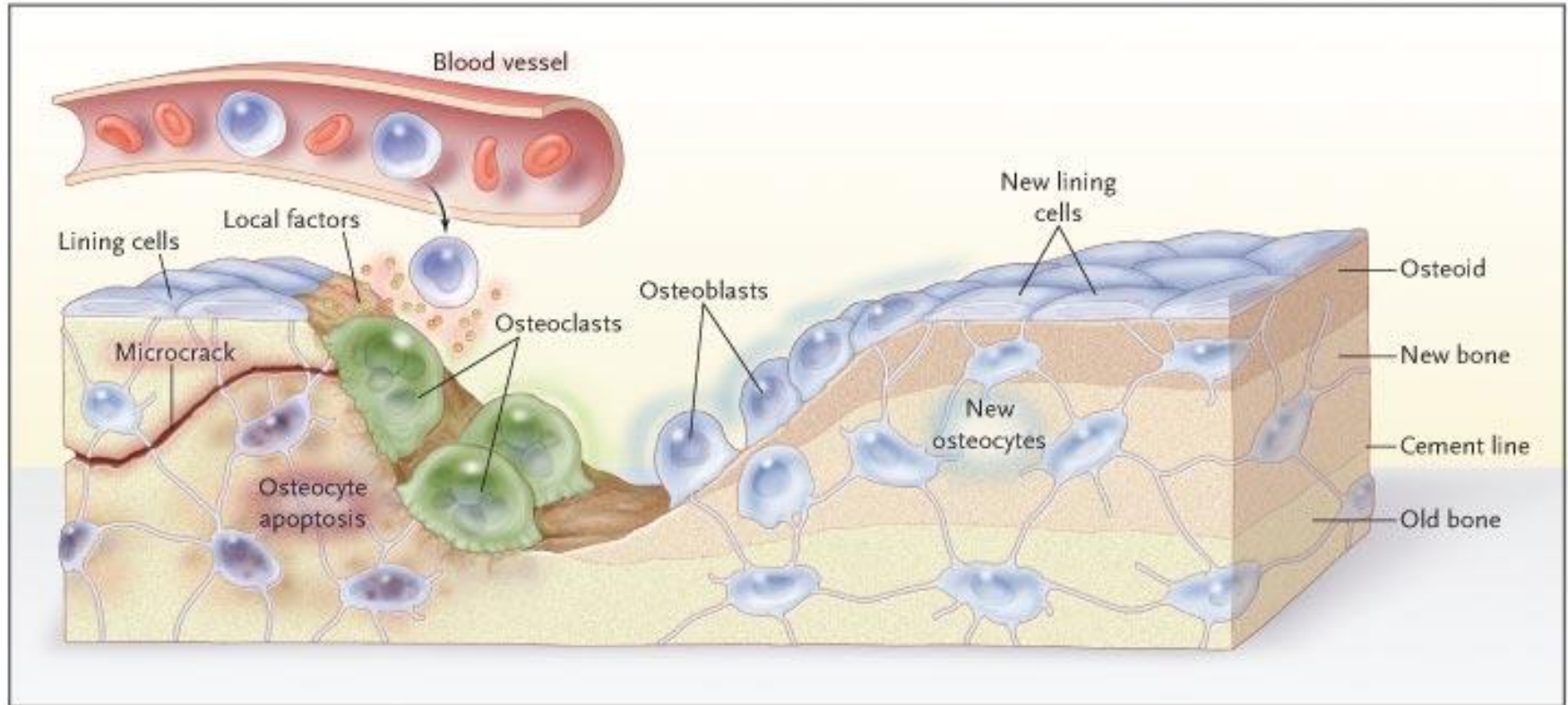
# Bisphosphonate failure???



# Bisphosphonate induced???



# The Bone Remodeling Cycle



Seeman E and Delmas P. N Engl J Med 2006;354:2250-2261

# What is Osteoporosis?

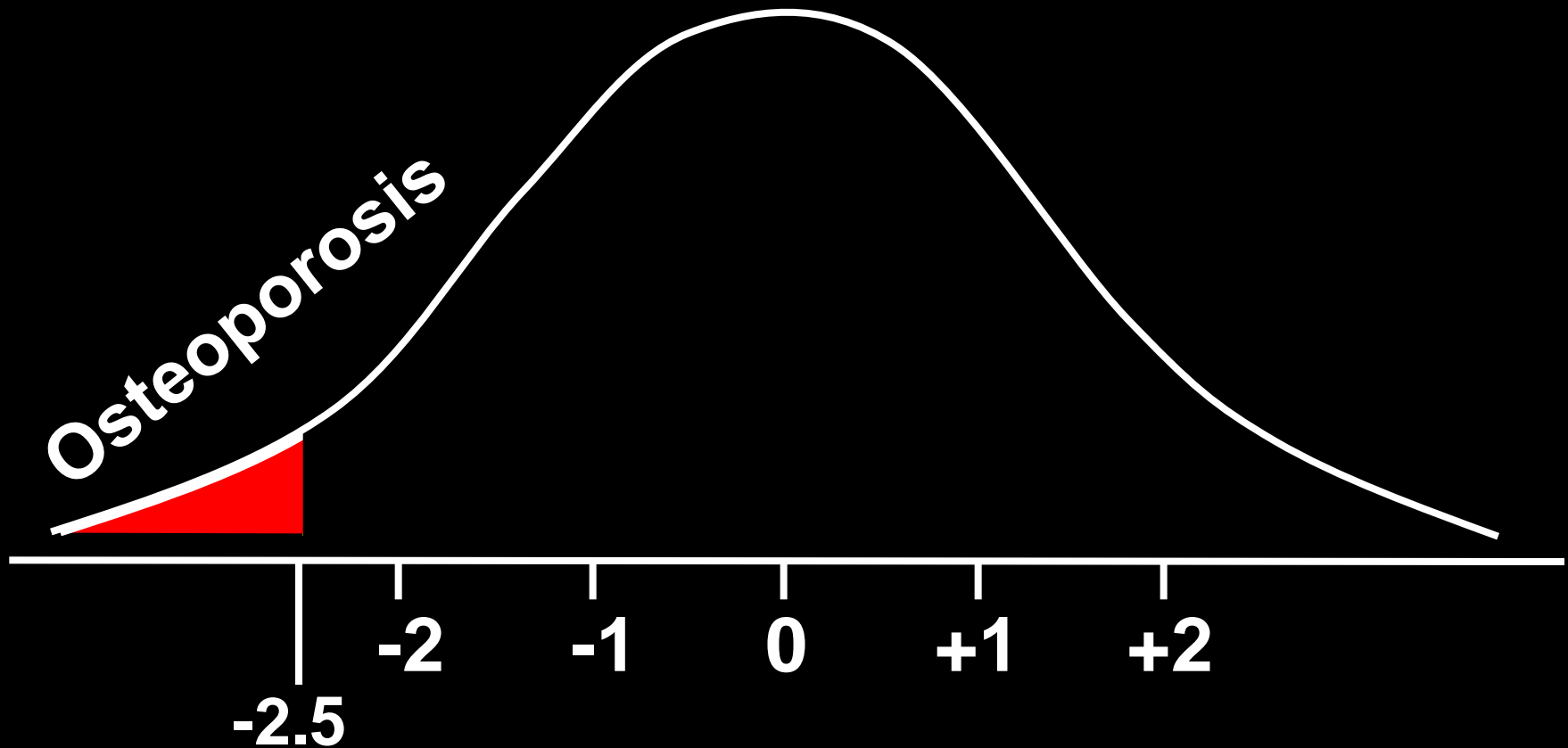
- BMD at the hip or spine that is  $\leq 2.5$  SD below the young normal mean reference population.

World Health Organization, 2004.

- A disease characterized by low bone mass & structural deterioration of bone tissue, leading to bone fragility & increased susceptibility to fracture.

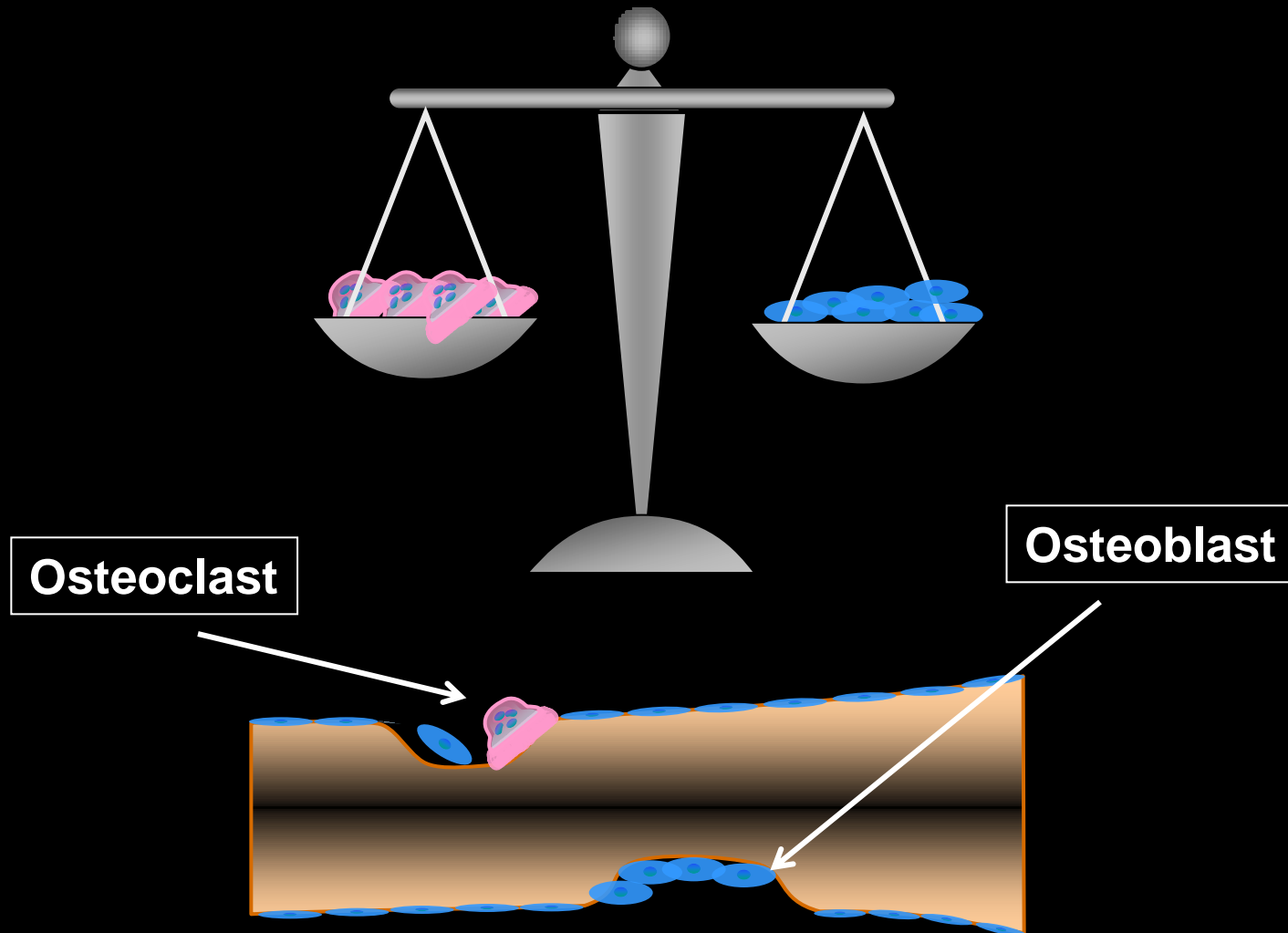
National Osteoporosis Foundation; Clinician's Guide to Prevention and Treatment of Osteoporosis, 2008.

# Defining Osteoporosis By BMD: World Health Organization

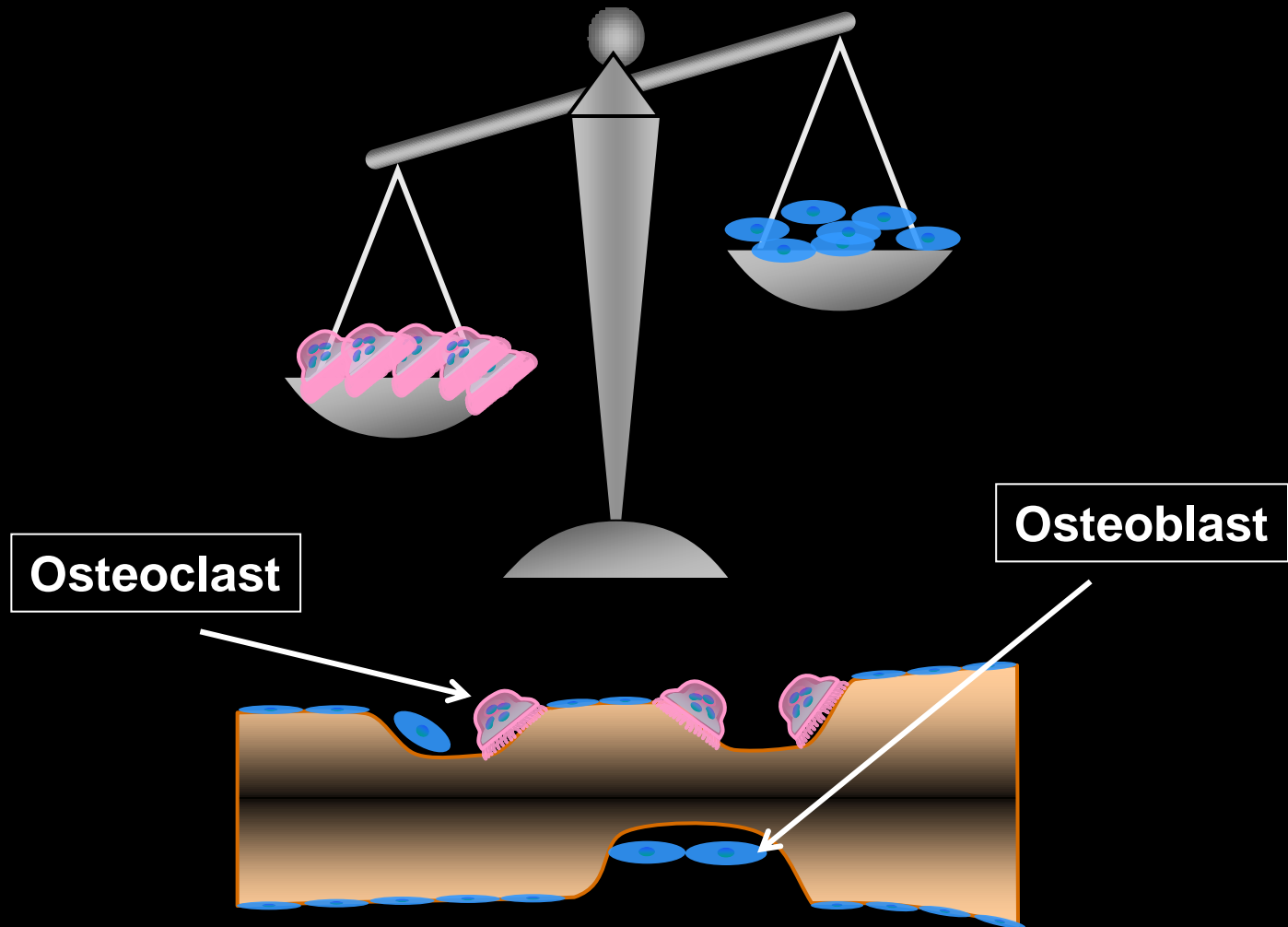


**T-score:** Standard Deviation from Peak Bone Mass

# Normal: Balanced Rate of Bone Resorption & Formation

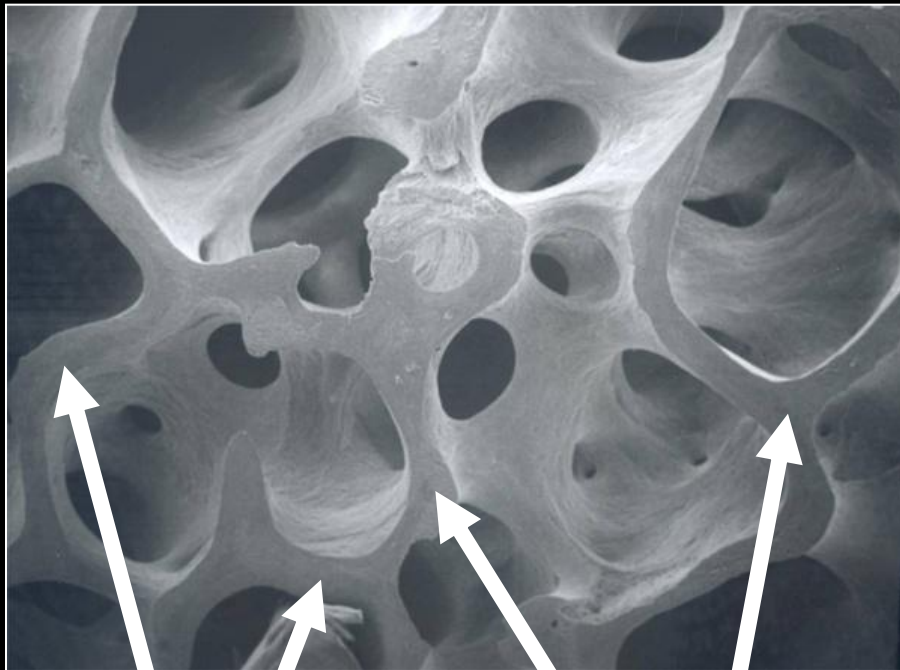


# Pathologic: Increased Bone Resorption +/- Impaired Bone Formation



# Trabecular Bone

## Normal



Uniform  
thickness &  
separation

Interconnected  
trabecular  
plates

## Osteoporosis



Poor  
Bone  
Quality

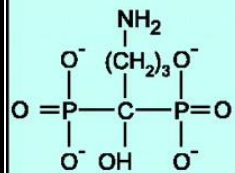
Disconnected  
trabecula

Thin  
trabecular  
rods

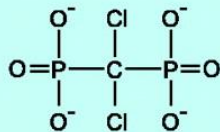
Enlarged  
trabecular  
spaces

<b>1 in 2</b>	<b>Lifetime incidence of osteoporosis-related fracture in postmenopausal white women</b>
<b>1 in 5</b>	<b>Lifetime incidence of osteoporosis-related fracture in white men <math>\geq</math> age 50</b>
<b>24%</b>	<b>% of pts <math>\geq</math> age 50 that will die w/in 12 months of hip fracture</b>
<b>20%</b>	<b>% of pts who were ambulatory pre-fracture that will require placement in a long-term care facility</b>
<b>15%</b>	<b>% of hip fracture pts that will be able to walk across a room unassisted 6 months after fracture</b>
<b>\$17 Billion</b>	<b>Cost of fracture-related health-care in 2005</b>

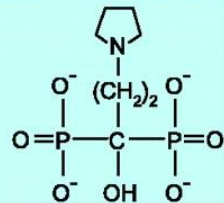
# **Brief Review of Bisphosphonates**



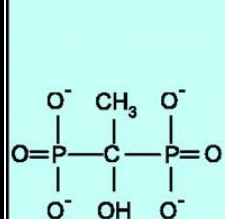
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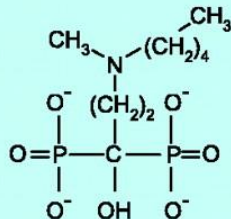
clodronate



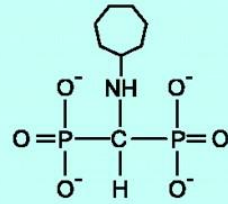
EB-1053



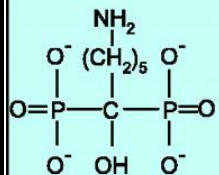
etidronate



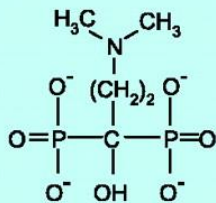
ibandronate\*



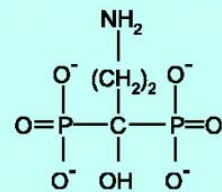
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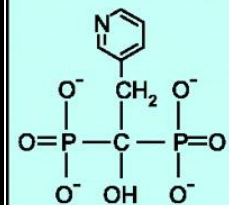
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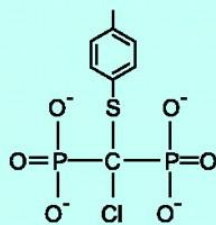
olpadronate



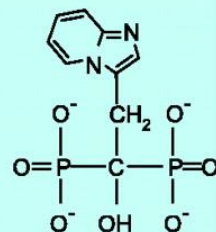
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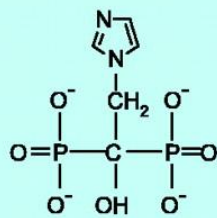
risedronate



tiludronate



YH 529



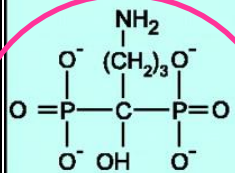
zoledronate

## Bisphosphonates (BPs):

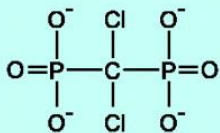
- Pyrophosphate backbone acts as a hook to avidly bind to hydroxyapatite crystals on bone surfaces, particularly at sites of active bone remodeling

- BPs released from bone, enter the osteoclast & cause loss of resorptive function & accelerated apoptosis

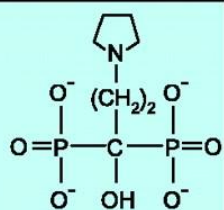
- Inhibit an enzyme called farnesyl pyrophosphate synthase



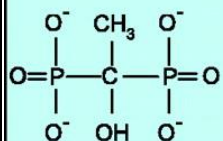
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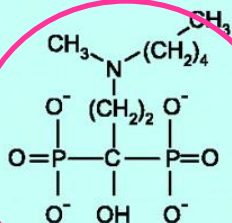
clodronate



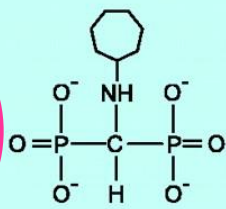
EB-1053



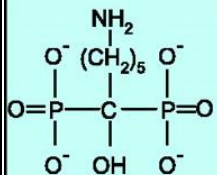
etidronate



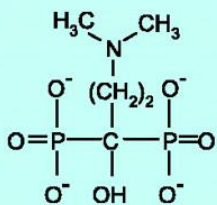
ibandronate\*



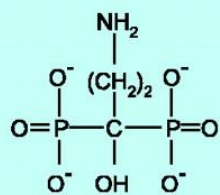
incadronate



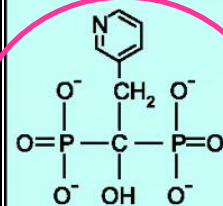
neridronate



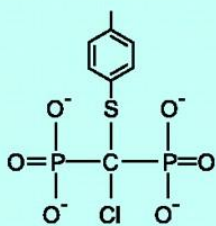
olpadronate



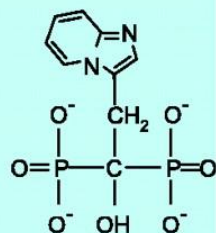
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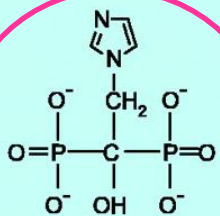
risedronate



tiludronate



YH 529



zoledronate

**FDA-approved for the prevention and treatment of osteoporosis**

<b>Alendronate</b>	<b>1995</b>
<b>Risedronate</b>	<b>2000</b>
<b>Ibandronate</b>	<b>2005</b>
<b>Zoledronate</b>	<b>2007</b>

# BPs Reduce Bone Remodeling

- Prevent loss of bone & deterioration of microarchitecture
- Increase BMD
- Increase bone mineralization
- Increase bone strength & stiffness

# FDA-Approved Indications for BPs

	Postmenopausal Osteoporosis		Glucocorticoid-Induced Osteoporosis		Men
	Prevention	Treatment	Prevention	Treatment	
<b>Alendronate</b>	✓	✓		✓	✓
<b>Ibandronate</b>	✓	✓			
<b>Risedronate</b>	✓	✓	✓	✓	✓
<b>Zoledronate</b>	✓	✓	✓	✓	✓

# Fracture Efficacy

	Vertebral	Non-vertebral	Hip
<b>Alendronate</b>	√	√	√
<b>Ibandronate</b>	√		
<b>Risedronate</b>	√	√	√
<b>Zolendronate</b>	√	√	√

# Are BPs Effective in the Long-Term?

- Typical fracture efficacy trial: 3 years
- Long-term studies exist
  - Alendronate (ALN) 10 years
  - Risedronate 7 years
  - Zoledronic Acid 5+ years

# ALN Trials: FIT & FLEX

- **FIT**: RCT of ALN use in postmenopausal women (PMW) for mean of 4.2 years
- **FLEX**: Extension Trial of FIT
  - All previously randomized to receive ALN in FIT for an average of 5 yrs
  - RCT of 1099 PMW to ALN or placebo for 5 yrs
  - Mean age 73 yrs old; 34% vertebral fractures; mean femoral neck T-score: -2.2

# BMD Change in FLEX Participants

## Femoral Neck

FIT

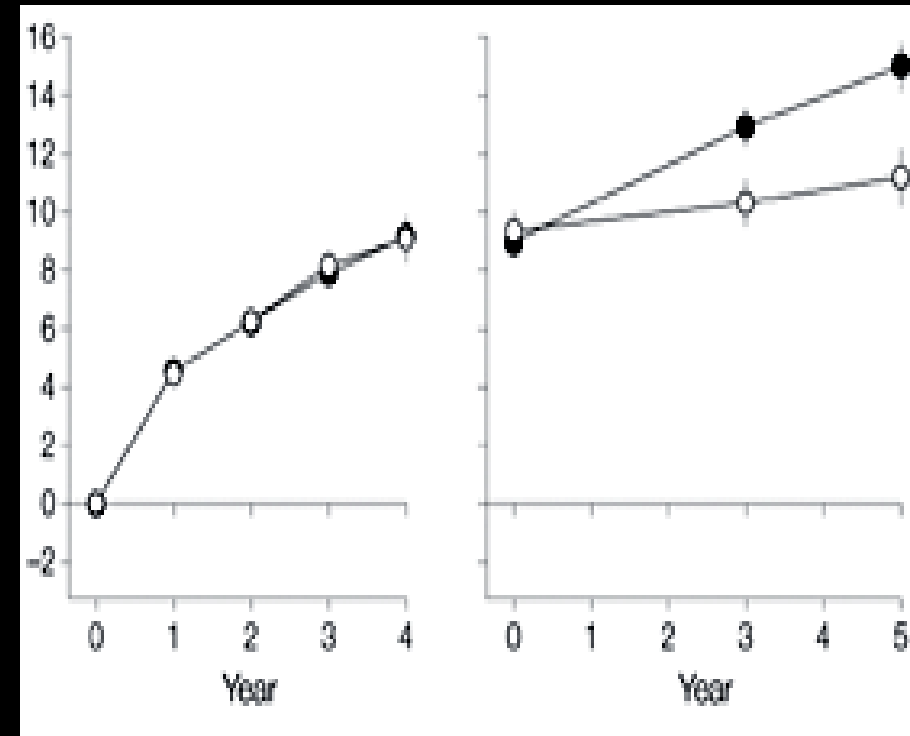
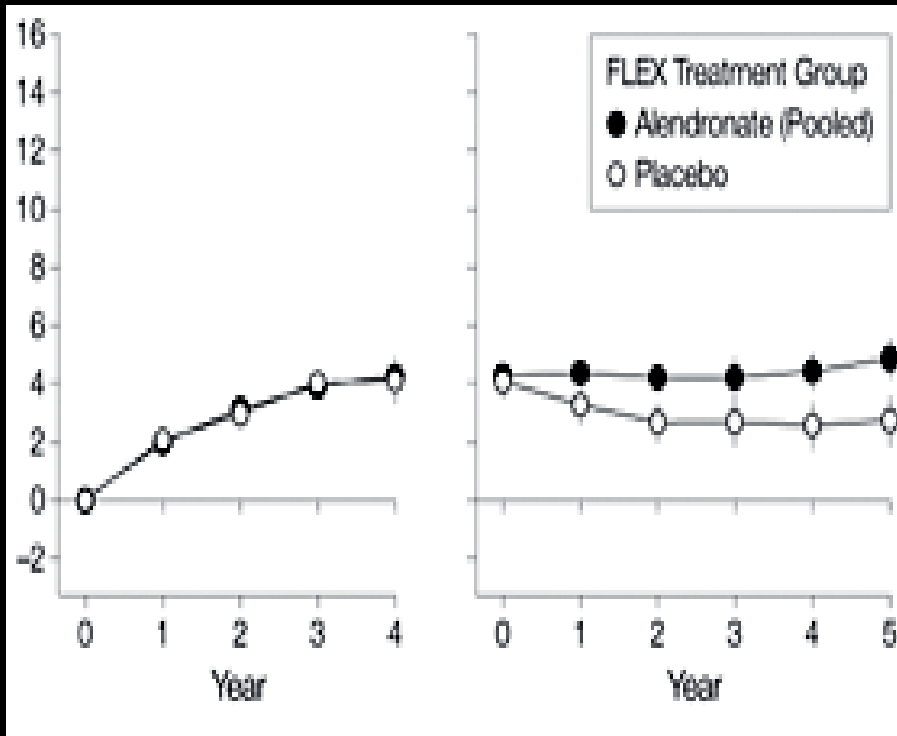
FLEX

## Lumbar Spine

FIT

FLEX

BMD Change from FIT Baseline (%)



# Incidence of Fracture by Treatment Group: FLEX Trial

**Table 3.** Incidence of Fracture by Treatment Group

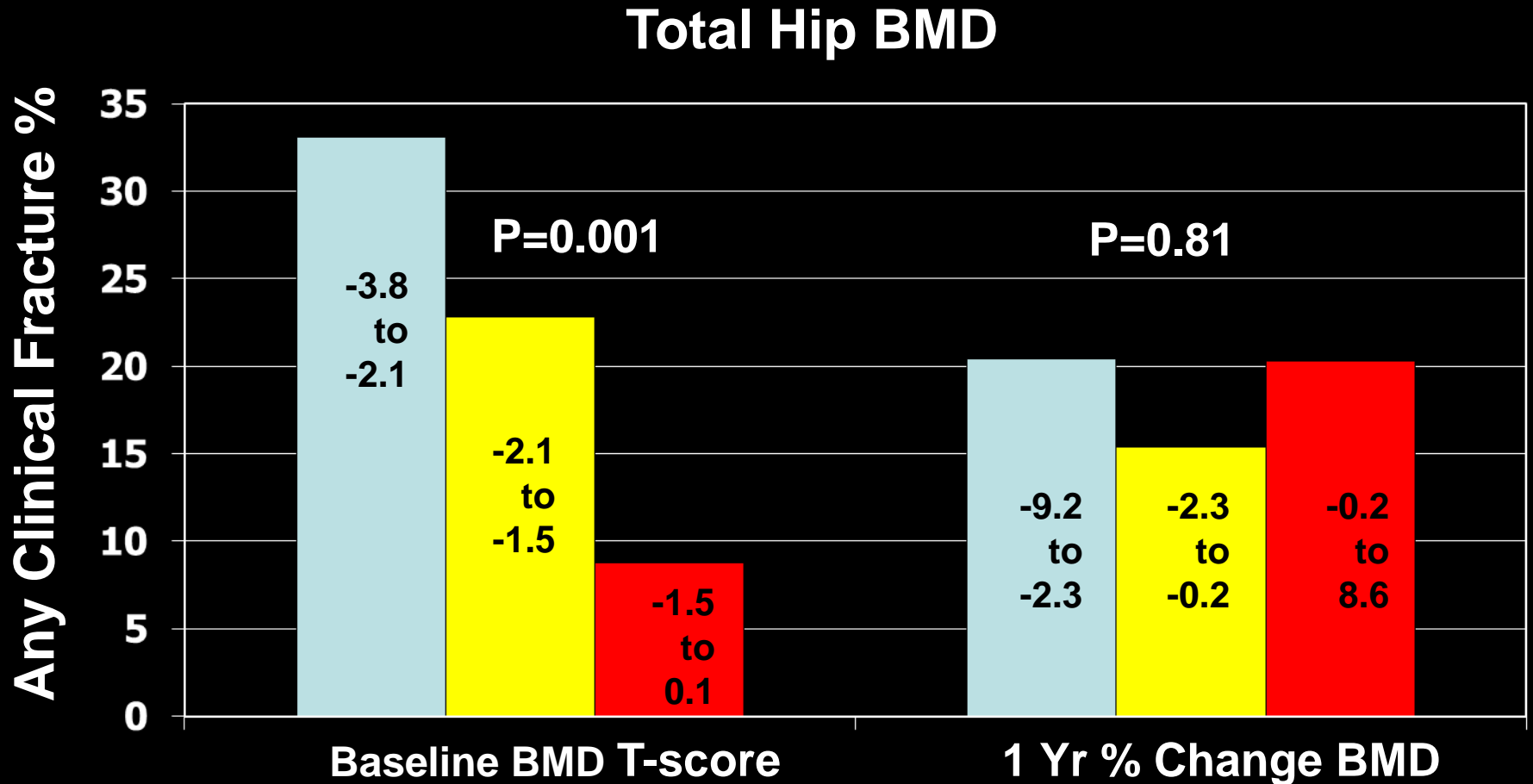
Fractures	Placebo, No. (%) (n = 437)	Pooled Alendronate, No. (%) (n = 662)	Relative Risk (95% Confidence Interval)*
Vertebral			
Clinical	23 (5.3)	16 (2.4)	0.45 (0.24-0.85)
Morphometric	46 (11.3)	60 (9.8)	0.86 (0.60-1.22)
Clinical			
Any	93 (21.3)	132 (19.9)	0.93 (0.71-1.21)
Nonspine	83 (19.0)	125 (18.9)	1.00 (0.76-1.32)
Hip	13 (3.0)	20 (3.0)	1.02 (0.51-2.10)
Forearm	19 (4.3)	31 (4.7)	1.09 (0.62-1.96)

\*Adjusted for clinic and stratum.

# What Happened to the Placebo Group in FLEX Trial?

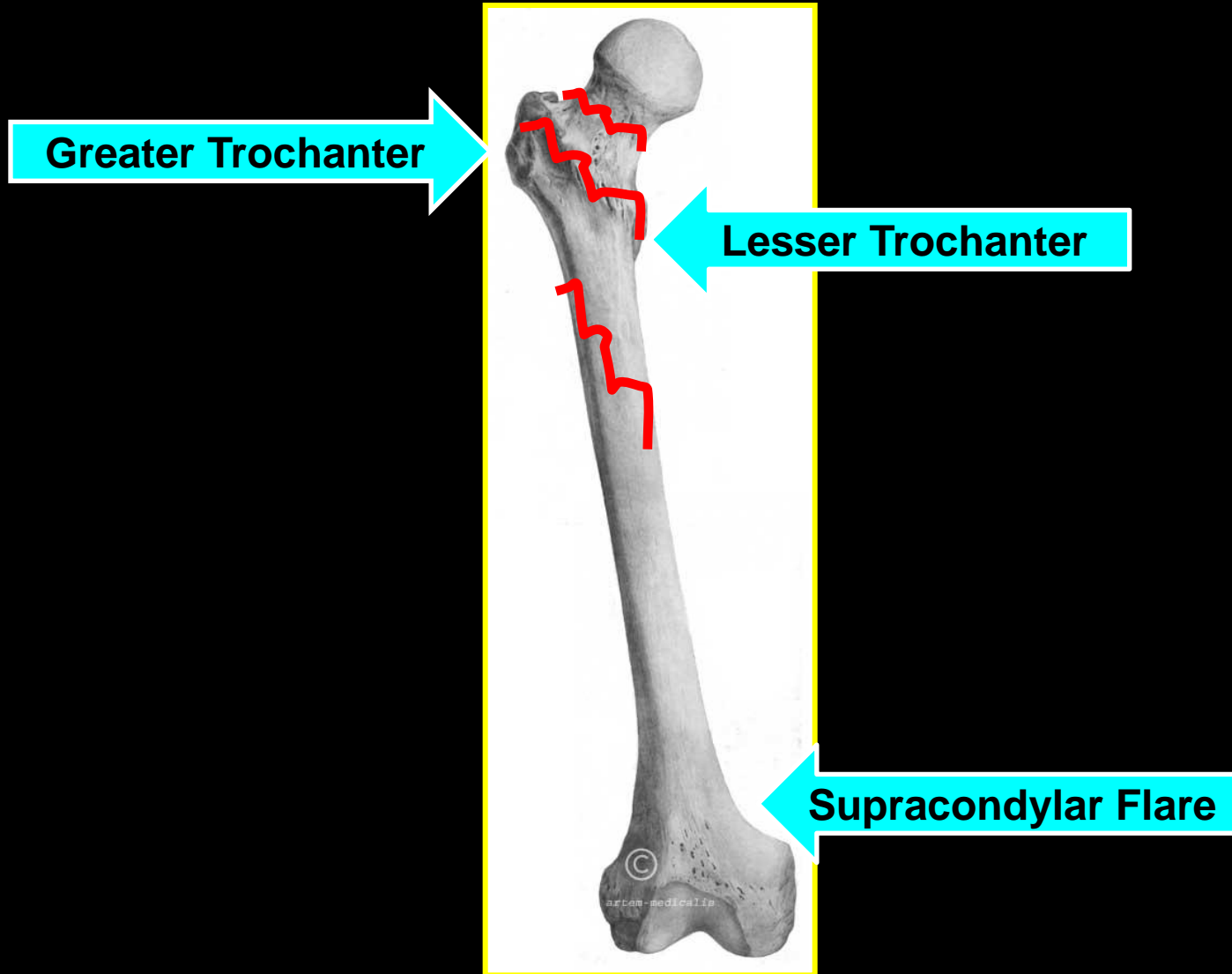
- 21% of PMW fractured in the 5 yrs after stopping ALN
- Fracture after discontinuation was:
  - Strongly related to total hip BMD at baseline
  - May not be related to change in total hip BMD at 1 yr and 2 yr

# FLEX: Predicting Fractures in the 5 Years After Discontinuing ALN



**Are Atypical Femur Fractures a  
Risk of Long-Term BP Therapy?**

# Anatomy of the Femur



# Subtrochanteric/Diaphyseal Region of the Femur

- One of the strongest parts of the femur
- Unlikely to fail in low-energy trauma unless extreme osteoporosis present
- 10-34% of fractures of the hip are in this region
- ~75% are associated with major trauma
- In older pts, femoral shaft fractures occur after total hip replacement just below the prosthesis
- Stress fractures can occur in this region in athletes

# Low-Energy Femur Fractures Associated with BP Use

Delayed healing

cortical thickening

No/minimal trauma

R

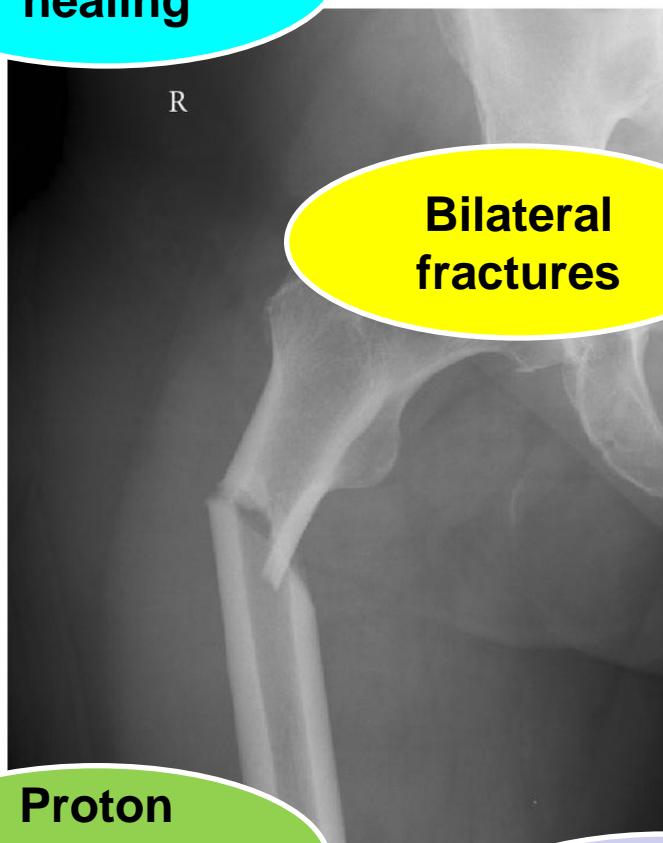
Bilateral fractures

short/oblique

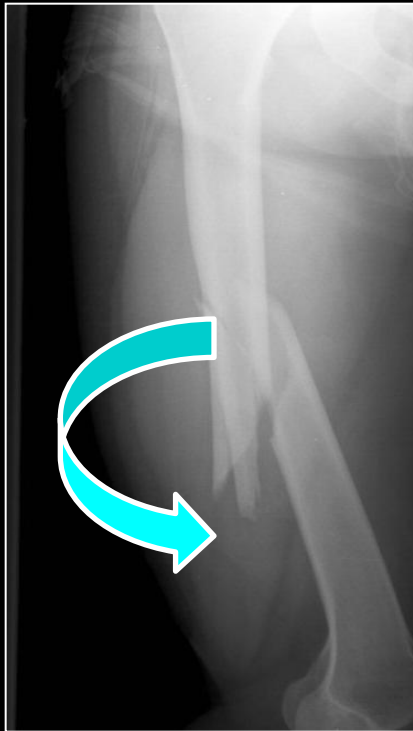
glucocorticoids

Proton pump inhibitors

prodromal pain



# Comparison of Subtrochanteric Hip Fracture Configurations



**Typical subtrochanteric fracture**

-Spiral pattern

# Comparison of Subtrochanteric Hip Fracture Configurations



## Typical subtrochanteric fracture

- Spiral pattern
- Substantial comminution

# Comparison of Subtrochanteric Hip Fracture Configurations



## Typical subtrochanteric fracture

- Spiral pattern
- Substantial comminution
- Cortical thinning

# Comparison of Subtrochanteric Hip Fracture Configurations



**Typical subtrochanteric fracture**

- Spiral pattern
- Substantial comminution
- Cortical thinning



**Atypical subtrochanteric fracture**

- Transverse or short oblique pattern

# Comparison of Subtrochanteric Hip Fracture Configurations



**Typical subtrochanteric fracture**

- Spiral pattern
- Substantial comminution
- Cortical thinning



**Atypical subtrochanteric fracture**

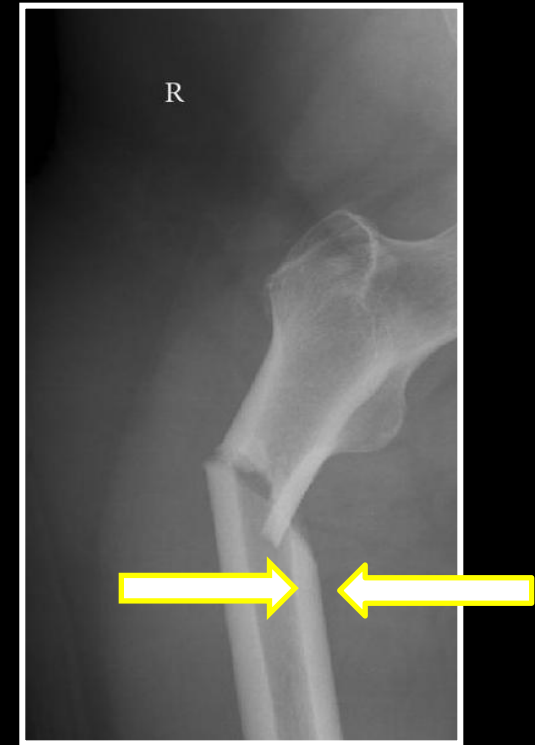
- Transverse or short oblique pattern
- No comminution

# Comparison of Subtrochanteric Hip Fracture Configurations



**Typical subtrochanteric fracture**

- Spiral pattern
- Substantial comminution
- Cortical thinning



**Atypical subtrochanteric fracture**

- Transverse or short oblique pattern
- No comminution
- Cortical thickening



**American Society for Bone and Mineral Research (ASBMR) Task Force on Atypical Femur Fractures**

# ASBMR Task Force

- Define atypical femoral fractures
- Assess what is/is not known about atypical femoral fractures & their relationship to BP use
- Recommend non-invasive diagnostic & imaging techniques to characterize & diagnose the disorder
- Recommend a research agenda to further investigate the incidence, pathophysiology & etiology of atypical femoral fractures & their relationship to BPs
- Recommend orthopaedic & medical management of atypical femoral fractures

# Atypical Femur Fractures: Major Features

- Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
- Associated with no or minimal trauma
- Simple transverse or oblique (<30 degrees) fracture
- Non-comminuted
- Complete fractures extend through both cortices & may be assoc w/ a medial spike; incomplete fractures involve only the lateral cortex



# Atypical Femur Fractures: Major Features

- Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare
- Associated with osteoporosis
- Simple (1 fracture line, <math>90^\circ</math> degrees), fracture
- Non-comminuted
- Complete fractures extend through both cortices & may be assoc w/ a medial spike; incomplete fractures involve only the lateral cortex

**ALL MAJOR FEATURES  
ARE REQUIRED**



# Atypical Femur Fractures: Excluded

- Femoral neck fractures
- Intertrochanteric fractures with subtrochanteric extension
- Pathologic fractures associated with primary or metastatic bone tumors
- Peri-prosthetic fractures

# Atypical Femur Fractures: Minor Features

- Localized periosteal reaction of the lateral cortex (beaking/flaring)



# Atypical Femur Fractures: Minor Features

- Localized periosteal reaction of the lateral cortex (beaking/flaring)
- Generalized tenderness
- Prodromal symptoms in groin
- Bilateral fractures & symptoms
- Delayed healing
- Comorbid conditions: vit D def, rheum arthritis
- Use of drugs: steroids, BPs, PPIs

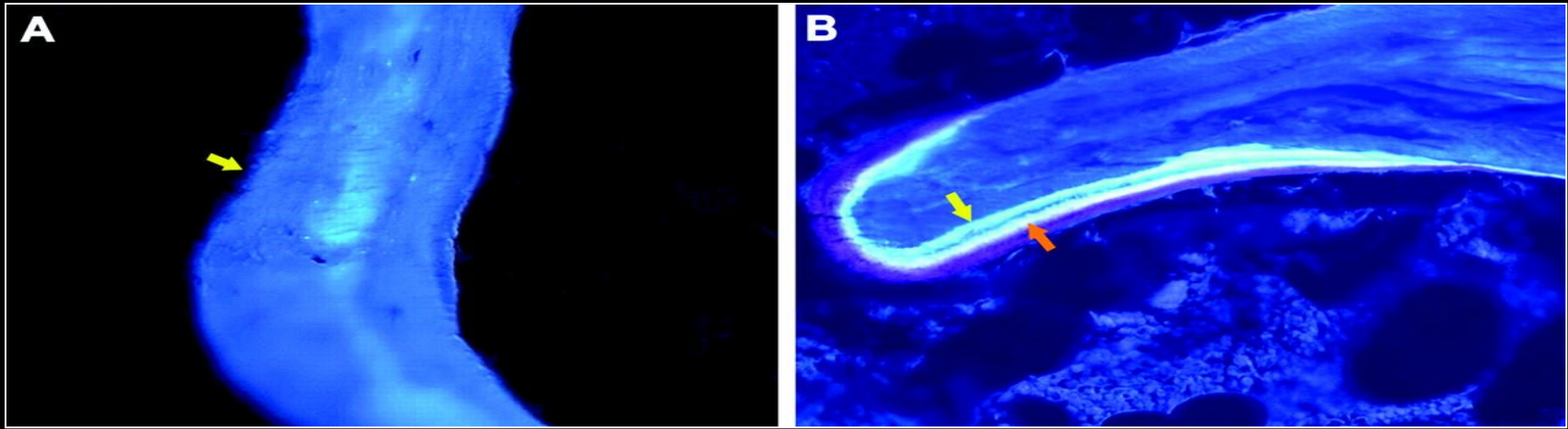
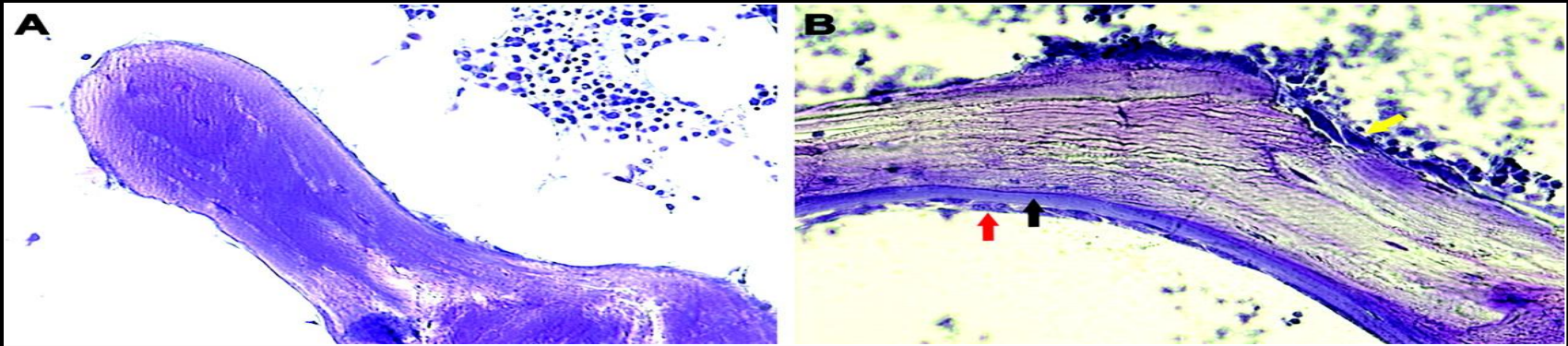
**NONE of the MINOR  
FEATURES  
ARE REQUIRED**

# Epidemiology

# First Case Report

- 8 F, 1 M on ALN 3-8 yrs, all with nonspinal atraumatic fractures
- 5 pts (4 F, 1 M) had femur fractures
- 2 pts on steroids, 3 pts on HRT
- Poor fracture healing seen in some pts after fracture (lack of adequate callus/filling in of fracture gap)
- Transiliac crest biopsy indicated severely reduced bone remodeling; markers of bone turnover varied widely

# Bone Biopsy



# Femur Fracture Incidence

- **In a Finnish study:**

- 25% of femoral shaft fractures occurred in context of low energy trauma
- 74% of those cases in patients >60 years of age

**Moran *et al.* J Bone Joint Surg Br 1990.**

- **Minnesota residents 1965-1984:**

- Incidence of subtrochanteric, diaphyseal & distal femoral fractures in women all increased exponentially with age
- 80% of pts w/ fractures assoc w/ modest trauma had prior evidence of osteoporosis or a predisposing condition

**Arneson *et al.* Clin Orthop Relat Res 1988.**

# Database Studies

# Hospital Discharge Rates\* of Closed Femur Fractures in Women: National Hospital Discharge Survey

	1996	1998	2000	2002	2004	2006	P value
Hip	598	489	497	449	445	428	<0.001
Sub-trochanteric	17	21	16	12	15	16	0.19
Femoral shaft	16	18	13	22	21	19	0.77
Lower femur	23	29	34	31	29	18	0.13

\*Per 100,000 persons

Overall hospital discharge rates for hip fractures decreased from 600 to 400/100,000 person-years from 1996 to 2006.

Subtrochanteric, femoral shaft & lower femur rates remained stable from 1996-2006, each ~ 20/100,000 person-years.

# Hospital Discharge Rates\* of Closed Femur Fractures in Men: National Hospital Discharge Survey

	1996	1998	2000	2002	2004	2006	P value
Hip	274	327	265	252	261	248	0.03
Sub-trochanteric	16	10	4	10	11	11	0.37
Femoral shaft	13	6	14	8	12	10	0.74
Lower femur	7	11	9	9	5	11	0.68

\*Per 100,000 persons

Overall hospital discharge rates decreased from 1996 to 2006.

Subtrochanteric, femoral shaft & lower femur rates remained stable from 1996-2006.

# Incidence Rates\* of Fragility Fractures in Women, MarketScan

	2002	2003	2004	2005	2006	P value
Hip	260	261	296	281	266	0.58
Sub-trochanteric	10	10	12	12	9	0.96
Femoral shaft	13	13	14	13	13	0.50
Lower femur	16	17	18	17	18	0.33

\*Per 100,000 persons

No evidence of increasing incidence of any femoral fracture.  
Incidence of each of the more rare femur fractures is stable over time.

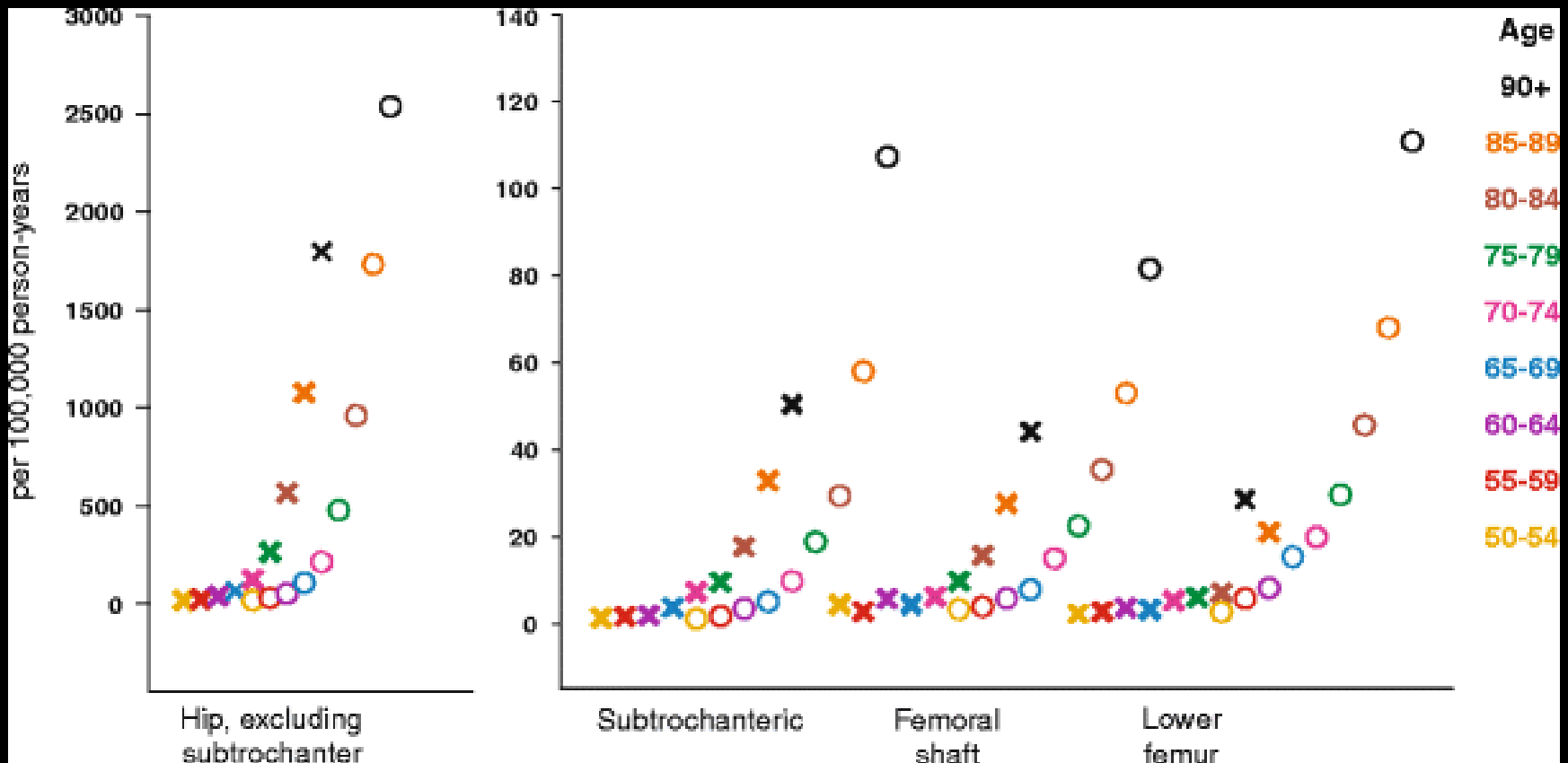
# Incidence Rates\* of Fragility Fractures in Men, MarketScan

	2002	2003	2004	2005	2006	P value
Hip	163	174	182	181	159	0.97
Sub-trochanteric	7	5	7	7	7	0.59
Femoral shaft	7	11	7	7	6	0.30
Lower femur	5	6	5	5	5	0.98

\*Per 100,000 persons

No evidence of increasing incidence of any femoral fracture.  
Incidence of each of the more rare femur fractures is stable over time.

# Age-specific Incidence Rates in Men (X) & Women (O) for the 4 Fracture Groups (MarketScan)



# Study of Osteoporotic Fractures

- Prospective population-based study of 9704 white women > 65 yrs old
- Fracture incidence:
  - Subtrochanteric 3/10,000 patient yrs
  - Hip fracture 103/10,000 patient yrs
- 48 subtrochanteric fractures in 45 women (3.4% of hip fractures)
  - 9 women were on BPs
- Predictors of subtrochanteric fracture: older age, lower total hip BMD, history of falls

# Denmark's National Hospital Discharge Register

- Cross sectional study in 2005
- Compare age-specific fracture rates, exposures & trauma mechanisms between the different types of femur fractures

	<b>Subtrochanteric</b>	<b>Diaphyseal</b>	<b>Hip</b>
Number	898	720	10,326
Age SD	80.7 9.4	79.6 10.0	81.5 8.9
<b>F:M</b>	<b>2.4:1</b>	<b>2.5:1</b>	<b>2.7:1</b>
Incidence rate per 1000 person-yrs			
60-64	0.21/0.24	0.27/0.24	1.86/1.58
65-74	0.47/0.33	0.40/0.27	5.09/2.82
75-84	1.41/0.71	1.11/0.61	18.07/9.94
85+	3.63/2.70	2.75/1.43	43.70/27.81
Low:high trauma	1.9:1	2.0:1	2.0:1
ALN use	6.7%	7.1%	6.7%
GC use	10.9%	8.4%	6.5%

# Denmark's National Hospital Discharge Register

- Subtrochanteric & diaphyseal fractures show an age, sex & trauma mechanism pattern similar to that of the classical osteoporotic hip fracture
- Patients with these atypical femur fractures were no more likely to be on ALN than patients with classic hip fractures, but oral steroid use more prevalent

# FIT, FLEX & HORIZON-PFT

- **3 large, controlled, blinded, randomized trials of BPs with >14,000 patients & >51,000 patient-years of follow-up for up to 10 years**
  - **FIT:** 6459 PWM >65 yo randomized to daily ALN or to placebo for 3-4.5 yrs
  - **FLEX:** 1099 FIT women assigned to ALN then randomized to ALN or placebo for 5 yrs
  - **HORIZON Pivotal Fracture Trial:** 7736 women randomized to annual infusion Zoledronate or placebo for 3 yrs

# FIT, FLEX & HORIZON-PFT: Fracture Reporting

- Subjects were asked about fractures at study visits; investigator would then obtain a preoperative radiology report or a surgical medical record
- Original radiographs not obtained
- *If radiographs available*, evaluated for atypical features
- Atypical features in radiology report noted

# **FIT, FLEX & HORIZON-PFT**

- **12 subtrochanteric/diaphyseal fractures (4%) in 10 patients**
- **3 did not receive BPs**
- **Combined rate: 2.3 per 10,000 pt-years**

**Table 3.** Comparison of Number of Patients Who Would Need to Be Treated for 3 Years with Bisphosphonates to Prevent One Fracture and the Hypothetical Number Associated with an Increase of One Subtrochanteric or Diaphyseal Fracture.

Type of Fracture and Hypothetical Relative Risk	Patients Who Would Need to Be Treated*	Events per 1000 Patients Treated†
	<i>number</i>	
Type of fracture		
Any fracture		100
Any nonvertebral fracture	35	29
Hip only	90	11
Vertebral fracture (morphometric)	14	71
Hypothetical relative risk of subtrochanteric or diaphyseal femur fracture‡		
1.5	2899	0.3
2.0	1449	0.7
3.0	725	1.4

# **Case Series & Case Reports: BP Use**

- **310 cases**
  - **286 cases: BP use for osteoporosis**
  - **5 cases: BP use for malignancy**
  - **19 cases: did not identify BP use**
- **160/189 cases with ALN**
- **Duration of BP use: 1.3-17 yrs; median 7 yrs**

# Case Series & Case Reports: Atypical Features

<b>Feature</b>	<b>Cases</b>	<b>%</b>
<b>Prodromal pain</b>	<b>158/227</b>	<b>70</b>
<b>Glucocorticoid use</b>	<b>26/76</b>	<b>34</b>
<b>PPI use</b>	<b>14/36</b>	<b>39</b>
<b>Bilateral fractures</b>	<b>60/215</b>	<b>28</b>
<b>Bilateral radiologic changes</b>	<b>63/224</b>	<b>28</b>
<b>Delayed healing</b>	<b>29/112</b>	<b>26</b>
<b>Vitamin D deficiency</b>	<b>5/84</b>	<b>6</b>
<b>Osteopenia or normal</b>	<b>45/67</b>	<b>67</b>

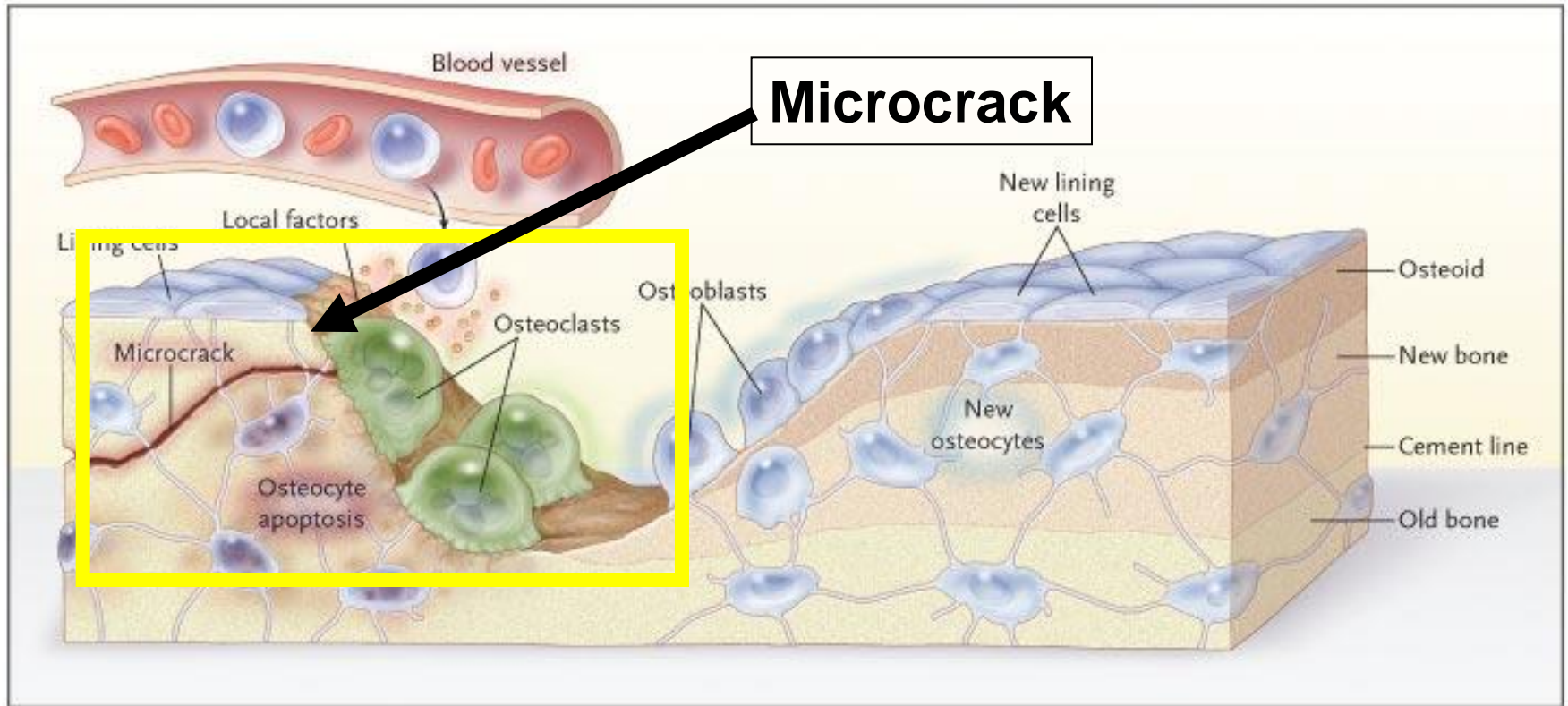
# FDA

- In June 2008, FDA requested information from BP manufacturers about this potential safety issue. Their review of the information did not show an increased risk for women using BPs.
- In March 2010, FDA stated that there was no “clear connection” between BP use & risk of these fractures.
- October 2010, FDA warns patients and health care providers of possible increased risk of atypical subtrochanteric and diaphyseal fractures with BPs.

# Pathogenesis

# The Bone Remodeling Cycle

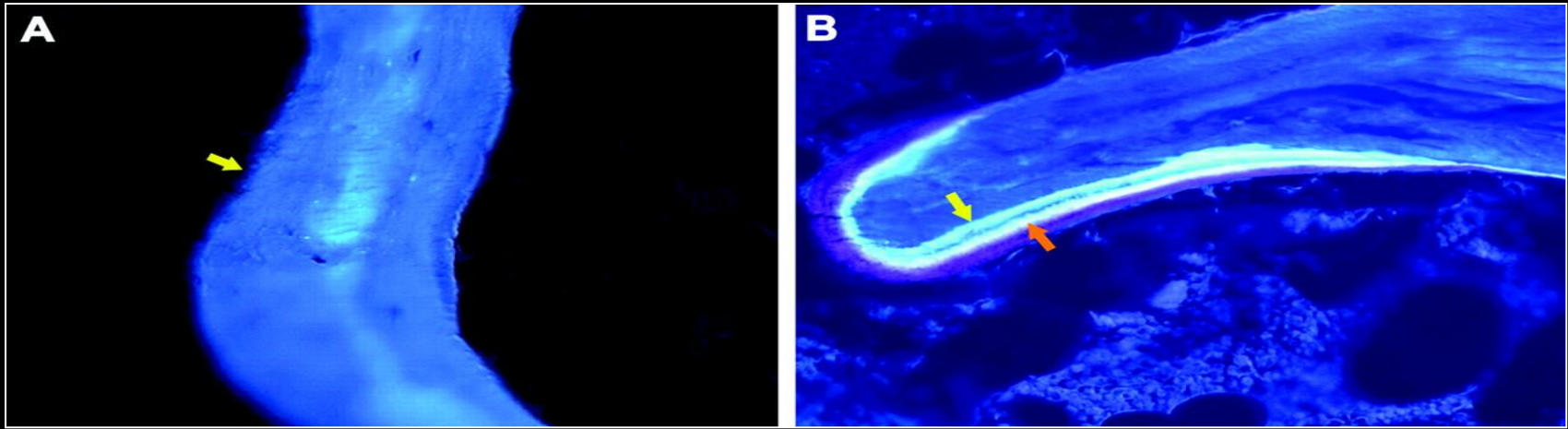
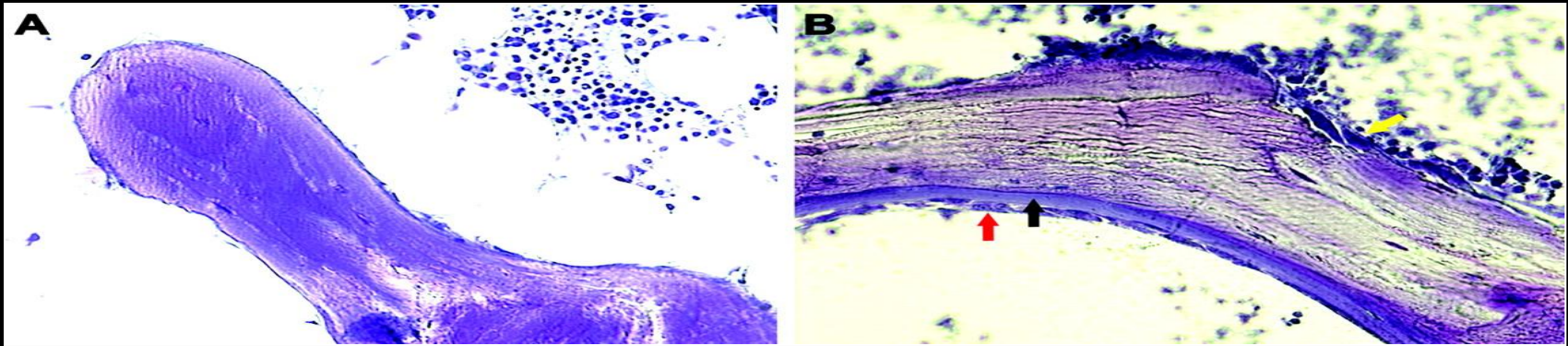
- Does long-term use of BPs inhibit the repair of microcracks & replacement of old bone, leading to poor bone quality?



# Possible Pathogenetic Mechanisms

- **Alterations in normal patterns of collagen cross-linking**
- **Microdamage accumulation**
- **Increased mineralization**
- **Reduced heterogeneity of mineralization**
- **Variations in rates of bone turnover**
- **Reduced vascularity and anti-angiogenic effects**

# Microdamage Accumulation



# Pathogenesis: Relation to Stress Fractures



- 70% of pts with femoral stress fractures have prodromal pain for weeks before diagnosis
- Periosteal callus seen in stress fractures is an attempt at bone repair
- Periosteal callus also seen in atypical fractures on the lateral cortex

# Relation to Comorbid Conditions

- **Glucocorticoids:** reduce bone formation & increase bone resorption
- **Diabetes mellitus:** high glucose levels result in accumulation of advanced glycation end-products (AGEs), which make bone more brittle

# Conclusions

- Subtrochanteric & femoral shaft fractures are much less common than hip fractures & most are likely related to underlying osteoporosis
- A subset of these subtrochanteric & femoral shaft fractures have unique clinical & radiological features, & in some cases there may be a relation to BP therapy
- More research needed to determine their epidemiology, including their incidence & etiology, & to identify susceptible individuals

**How Long to Treat?**

# Expert Opinion Regarding Duration of BP Treatment

<b>Fracture Risk</b>	<b>Suggested Duration of Rx</b>	<b>Suggested Duration of Drug Holiday</b>
Low	Rx rarely needed	N/A
Mild	3-5yrs	Off BP until BMD decreases significantly or fracture occurs
Moderate	5-10yr	Off BP for 2-3+ yrs (or less if BMD decreases or fracture)
High	10yr	Off BP for 1-2+ yrs (or less if BMD decreases or fracture occurs); consider alternate medications during BP holiday

# WHO Fracture Risk Assessment Tool: FRAX™

<http://www.shef.ac.uk/FRAX/index.htm>

<b>Risk Factors Included in the FRAX™ Tool</b>	
<b>Current Age</b>	<b>Use of glucocorticoid therapy</b>
<b>Gender</b>	<b>Secondary osteoporosis/RA</b>
<b>Personal history of a fracture</b>	<b>Parental hip fracture</b>
<b>Femoral neck BMD</b>	<b>Current smoking</b>
<b>Low body mass index</b>	<b>Alcohol use <math>\geq</math> 3 drinks/day</b>

## Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.



Country : **US(Caucasian)** Name / ID :

[About the risk factors](#)

### Questionnaire:

10. Secondary osteoporosis  No  Yes

11. Alcohol consumption  No  Yes

### Weight Conversion

pound:

[convert](#)

### Height Conversion

inch:

[convert](#)

**For untreated patients, consider treatment if 10 yr fracture risk is:**  
 **$\geq 3\%$  for hip fracture**  
 **$\geq 20\%$  for major osteoporotic fracture**

6. Parent fractured hip  No  Yes

7. Current smoking  No  Yes

8. Glucocorticoids  No  Yes

9. Rheumatoid arthritis  No  Yes

# Recommendations

- No rationale to withhold BP therapy from patients with osteoporosis
- BPs should be considered to protect pts from rapid bone loss for specific clinical situations:
  - Organ transplantation
  - Endocrine or chemotherapy for breast/prostate cancer
  - Glucocorticoids
- Use FRAX to determine need to start a BP in a pt with osteopenia

# Recommendations

- Consider drug holidays; restart treatment if loss of BMD or fracture
- Ask about (and evaluate) thigh & groin pain in pts on BP therapy
  - Bilateral plain films
  - MRI or bone scan if suspicion is high

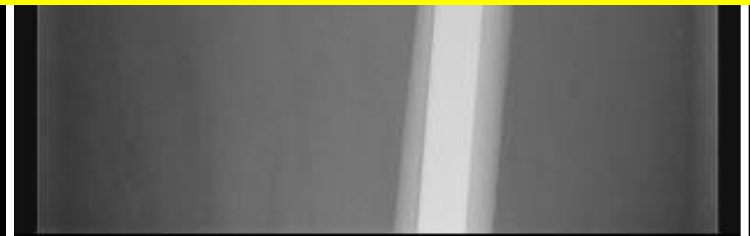
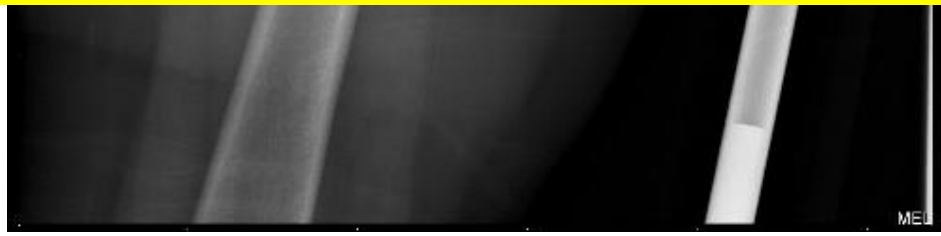
JAWN Lossy UVA  
Cano  
Nov



# Bisphosphonate failure???



# Bisphosphonate induced???



# Case Patient

- **Had multiple clinical & radiological findings reported in the literature**
- **Plan: weaned off prednisone, stopped ALN, started teriparatide**

**Thank You**