# Osteoporosis Update

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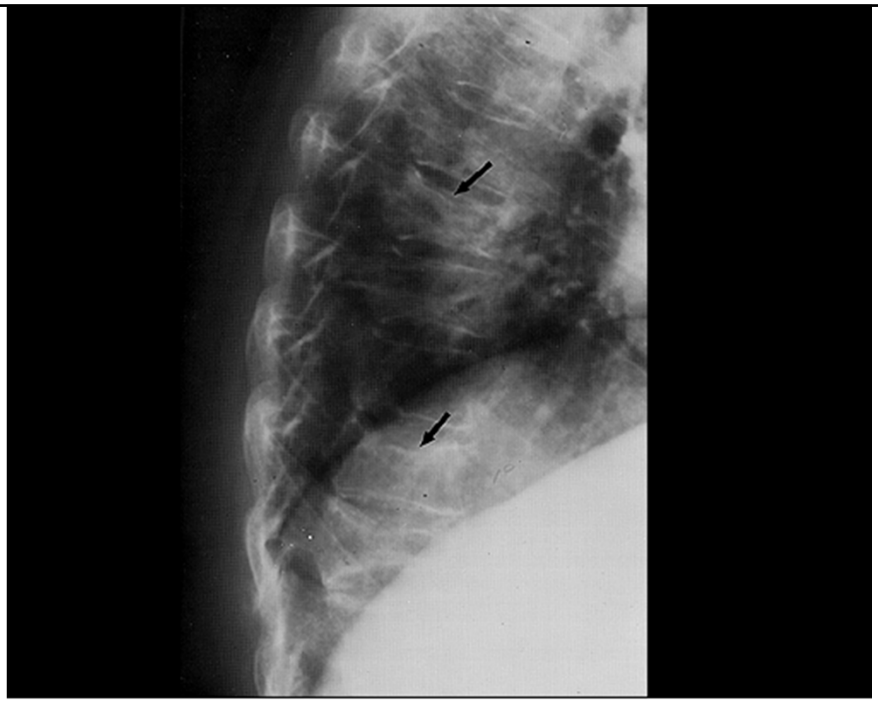
## Case 1: Monday morning, 8:15

- 68yoWF presents with mid-thoracic pain after lifting her ill husband out of his chair
- Height loss of 2.5" since youth
- PE with an apex of kyphosis, focal pain palpable at T10
- Labs all normal; plain X-ray with compression fracture at T10
- Does she have a diagnosis yet? What do you do?



# Case 2

- 53yo WF requests BMD for health maintenance
- PMHx:  GERD, treated HTN
- Menopause at age 49; no symptoms; never on HT
- PE:  normal, weight 142#, no kyphosis, no bony pain, height 5’4” unchanged from high school

# Case 2, cont

- **BMD:**
  - **$L_{1-4}$ T-score –1.8**
  - **Total hip T-score –2**
  - **Femoral neck T-score –2.1**

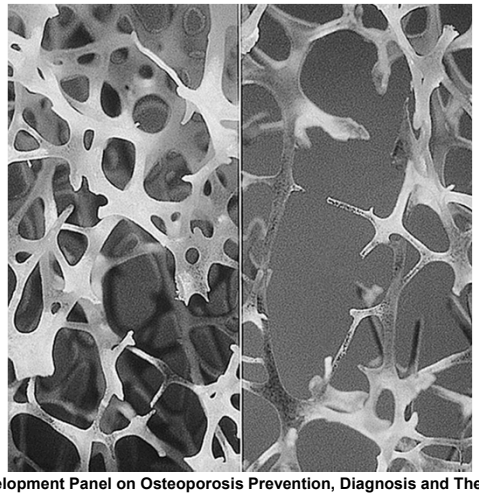
**Now What?**

# Case 3

- **65yo WF presents for her yearly exam**
- **She's not had any height loss, no personal history of fracture**
- **Smokes "6 cigarettes a day"**
- **Mom broke her hip at age 78**
- **Normal menstrual history; 3 pregnancies**
- **DXA: LS T-score -1.8, Fem Neck -2.1**

# Osteoporosis: Definition

- **Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk for fracture[1]**



**Author: Gtirouflet**

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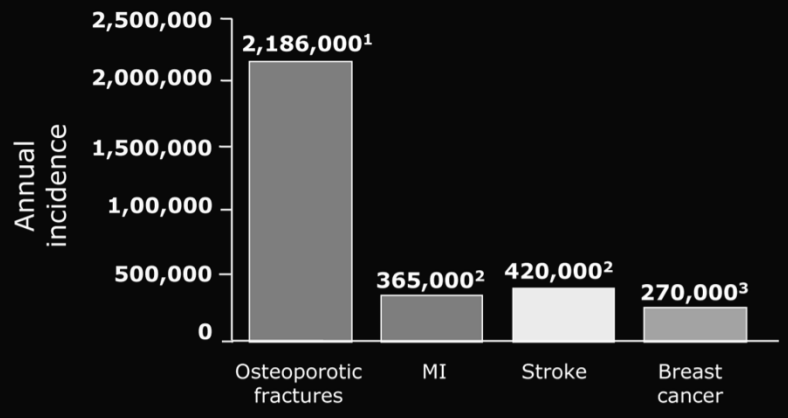
**NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis and Therapy.** ***JAMA*** **2001;285:785 - 795**

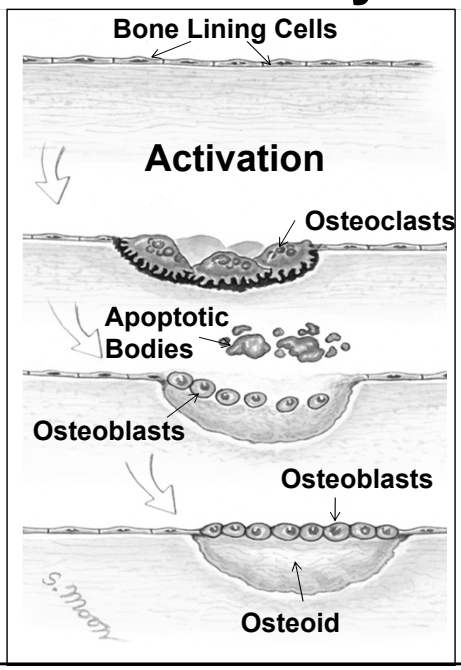
## Osteoporosis is Common Among US Women

- 10 million Americans have established osteoporosis, 80% of whom are women[1]




1. National Osteoporosis Foundation (NOF). Available at: http://www.nof.org/osteoporosis/diseasefacts.htm. Accessed February 2008. 2. American Heart Association. Heart Disease and Stroke Statistics. 2008 Update. Available online at http://www.americanheart.org. Accessed June 2008. 3. American Cancer Society. *Breast Cancer Facts & Figures.* 2005-2006. Available online at http://www.cancer.org. Accessed June 2008.

# The Life Cycle of Bone




Resting

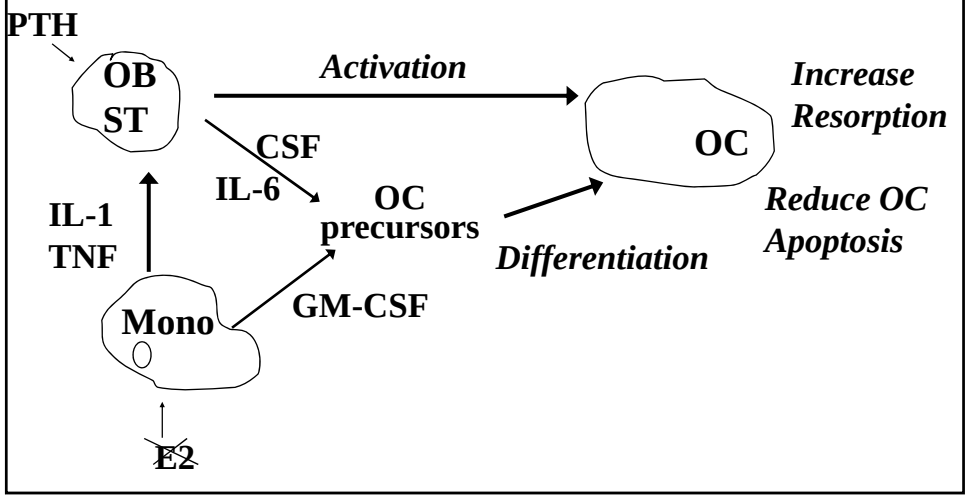
Resorption

Reversal

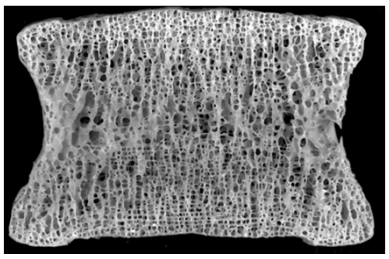
Formation --- Mineralization

Steve Moon, MS,, Professor, School of Allied Medical Professions, OSU COM, Atwell Hall

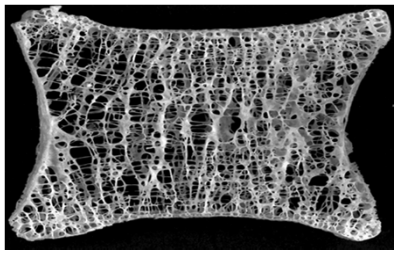
# Local Mechanism of Estrogen Effects on Bone Loss



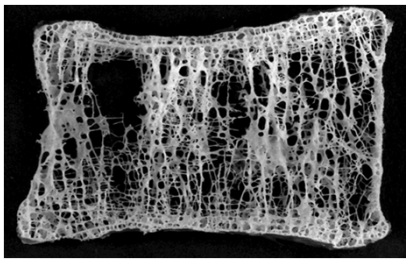
## Normal



## Moderate Osteoporosis



## Severe Osteoporosis



Courtesy Dr. A. Boyde

# Hip Fractures

- Result in excess mortality of 10-20% within the first year
- Prognostic of further fracture – RR 2.5
- 20% of patients with hip fracture require long-term nursing home care
  - Decreased independence, depression, loss of quality of life
- Only 40% regain full independence follow hip fracture
- Account for 14% of all fractures but 72% of cost
  - In 2005 accounted for over 400,000 hospital stays
  - $12.5 billion annually

# NOF Screening Guidelines

- DXA:
  - Women ≥65
  - Men ≥70
  - Postmenopausal women and men aged 50-69 based on risk factor profile
  - Postmenopausal women and men over age 50 who have had a fragility fracture
  - Screening of premenopausal women decided individually by clinician
  - Only to be done at facilities using accepted quality assurance
- Vertebral Imaging:
  - All women >70 and all men >80 with DXA T-score < -1.0
  - Women >65 and men ≥70 if T-score ≤ -1.5
  - In those with low trauma fracture in adulthood
  - Those with height loss 1.5" or more
    - Or a documented height loss of > 0.8" based on reliable office measurement
  - Recent or ongoing long term glucocorticoid treatment

* Can be VFA or lateral thoracic and lumbar spine plain x-ray

www.nof.org; Clinician's Guide to Prevention and Treatment of Osteoporosis, updated 4/2014

# Uses of BMD by DEXA

- Diagnosis of Osteopenia or Osteoporosis
  - Postmenopausal women
  - Glucocorticoid use
  - Metabolic bone disease
  - Osteopenia on plain radiograph
  - Previous fragility fracture or loss of height
- Prognosis – fracture risk assessment
- Monitor therapeutic response

Permission by GE Healthcare

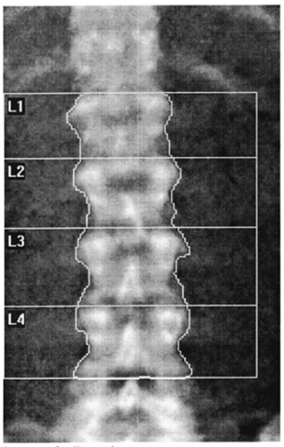
DXA of the hip

Scanning the Spine

# Diagnosis – T-score
# WHO criteria

- **Normal - > -1**
- **Osteopenia - <-1 and >-2.5**
- **Osteopororsis - <-2.5**
- **“Severe” Osteoporosis - <-2.5 + Hx Fx**

- ****Osteoporosis is also diagnosed in patients with a history of fragility fracture, regardless of BMD**




**Basically normal LS DXA:**
**L1-L3 – U or Y shaped**
**L4 – H shaped**
**L5 – “I on its side”**

**DXA Results Summary:**

| Region | Area (cm²) | BMC (g) | BMD (g/cm²) | T - score | PR (%) | Z - score | AM (%) |
|---|---|---|---|---|---|---|---|
| L1 | 12.83 | 13.95 | 1.087 | 1.5 | 117 | 1.7 | 121 |
| L2 | 13.71 | 16.36 | 1.193 | 1.5 | 116 | 1.8 | 120 |
| L3 | 16.37 | 19.97 | 1.220 | 1.2 | 113 | 1.5 | 116 |
| L4 | 16.36 | 21.10 | 1.289 | 1.6 | 116 | 1.9 | 119 |
| **Total** | **59.28** | **71.38** | **1.204** | **1.4** | **115** | **1.7** | **119** |

Total BMD CV 1.0%
WHO Classification: Normal
Fracture Risk: Not Increased

**Increase from L1 to L2; Increase from L2 to L3; also increase in L3 to L4, though this increase is often <50% seen in other increments and occasionally you may see a slight decline**

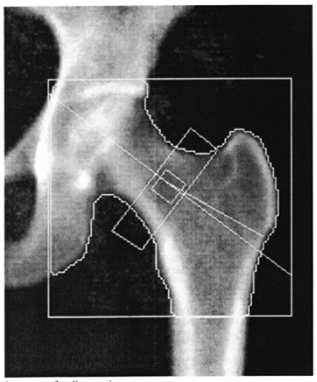


Image not for diagnostic use
100 x 99
NECK: -53 x 15

**Total femur does not include hip joint**

**Should see just a small portion of lesser trochanter - this gives the lowest femoral neck T-score.**
**To achieve this positioning, internally rotate the femur 15-20 degrees**

**DXA Results Summary:**

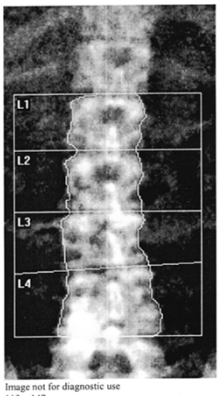
| Region | Area ($cm^2$) | BMC (g) | BMD ($g/cm^2$) | T-score | PR (%) | Z-score | AM (%) |
|---|---|---|---|---|---|---|---|
| Neck | 5.40 | 4.74 | 0.879 | 0.3 | 104 | 0.6 | 108 |
| Total | 32.50 | 34.76 | 1.070 | 1.0 | 114 | 1.2 | 117 |

Total BMD CV 1.0%
WHO Classification: Normal
Fracture Risk: Not Increased

**Total femur includes femoral neck, Ward's area, trochanteric region and the shaft**

**DXA Pitfalls:**
**Report: "The LS bone density T-score is -3.3, falling into the range of osteoporosis.**
**The previous T-score was -2.1. Over the past 3 years there has been a 13% decline in bone density at the spine."**

**2011**
**T-score -2.1**

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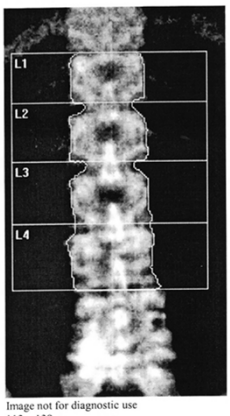
112 x 147

BMD

**2014**
**T-score -3.3**

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# Osteoporotic Fracture Risk

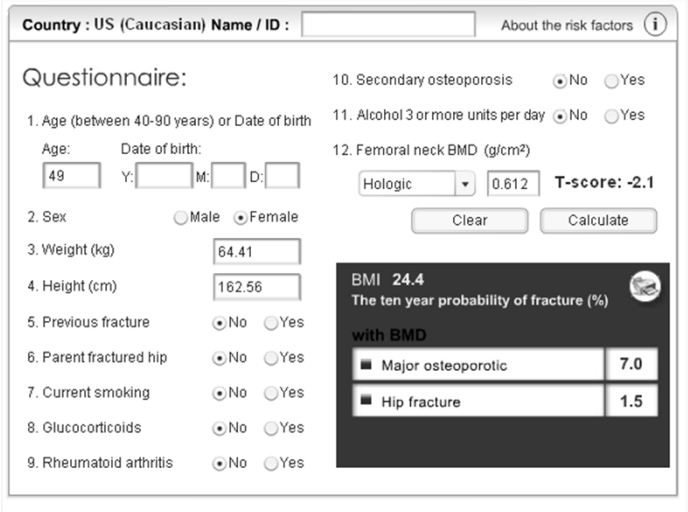
- Personal History of Fx
- Family history of Fx after age 50
- Weight <127#
- Current Smoker
- Age
- White Race
- Alcoholism
- Low physical activity
- Recurrent falls
- Dementia

## National Osteoporosis Foundation guidelines for therapeutic management

- A hip or vertebral (clinical or morphometric) fracture
- T-score < -2.5 at the total hip, femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the FN, TH or LS) AND a 10-year probably of a hip fracture >3% or of a major osteoporotic fracture of >20% based upon FRAX
- Clinician's judgement and/or patient preference may indicate treatment for people with 10-year fracture probabilities above or below these levels

www.nof.org; Clinician's Guide to Prevention and Treatment of Osteoporosis, updated 4/2014

# FRAX Fracture Calculation Tool



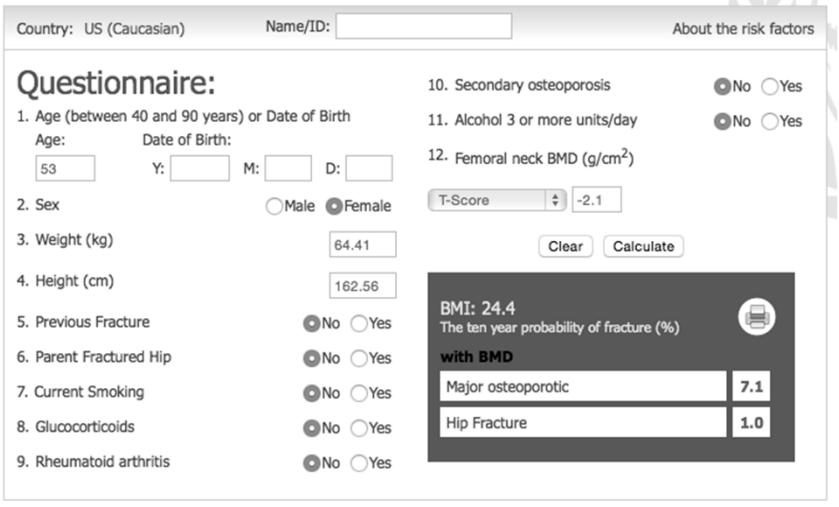

**NOF Treatment Guidelines:**

**10 year probability For major Osteoporotic Fx: 20%**

**10 year prob for Hip fracture: 3%**

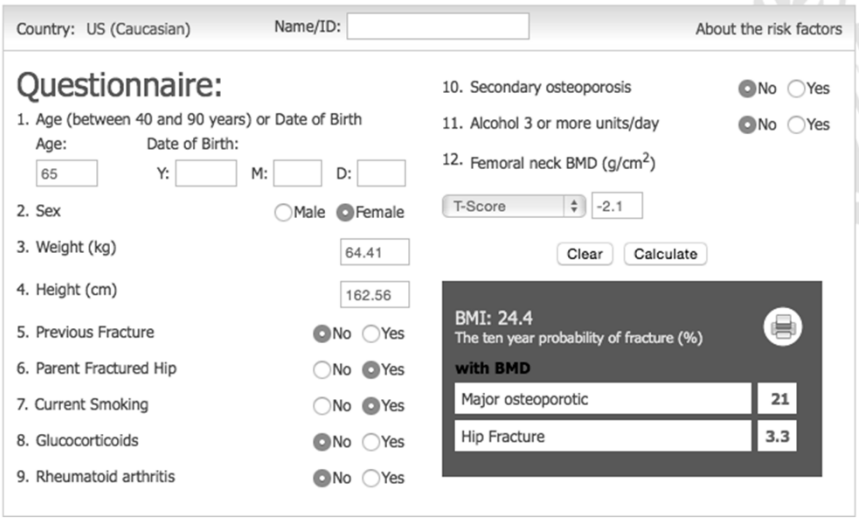
**http://www.shef.ac.uk/FRAX/tool.jsp**

# So, what about our 53yo with osteopenia on DXA, who seems to have no other risk factors for fracture?
# Femoral neck T-score -2.1




**http://www.shef.ac.uk/FRAX/tool.jsp**

## How about the 65 year old with the exact same T-score by DXA, who smokes 5 cigarettes a day?




http://www.shef.ac.uk/FRAX/tool.jsp

## Calcium and vitamin D

- NOF and IOM Recs:
  - Calcium:
  - Men 50-70: 1000mg cal/d
  - Women ≥50, men ≥70 consume 1200mg calcium/d
  - Increasing dietary calcium is preferred over calcium supplements
  - Vitamin D recommendations:
    - NOF: adults ≥ 50: 800-1000u/d
    - IOM: <70, 600 units/day; ≥70 800 units/day
    - Safe upper limit: 4000 units/day
    - Goal: ≥ 30ng/mL serum level


Milk 8 oz: 300mg


Yogurt 6oz: 250mg

Cheese 1": 150mg

www.nof.org; Clinician's Guide to Prevention and Treatment of Osteoporosis, updated 4/2014

www.ncbi.nlm.nih.gov Reference intakes for calcium and vitamin D

# Osteoporosis: Treatment

**Steven W. Ing, MD, MSCE**
**Assistant Professor of Internal Medicine**
**Fellowship Program Director**
**Division of Endocrinology, Diabetes and Metabolism**
**The Ohio State University Wexner Medical Center**

# Objectives

- **Discuss FDA-approved drugs for treatment of osteoporosis**
- **Discuss safety**

# Case

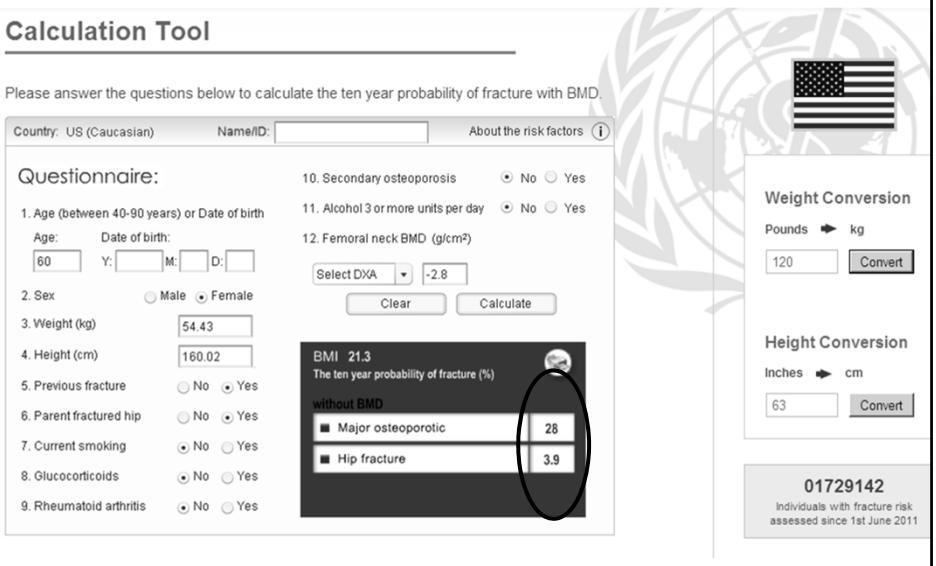
- 60 year old healthy white woman
- Wrist fracture after fall from standing height within past year
- Mother had hip fracture
- L1-L4 T-score -3.0
- FN T-score -2.8
- Height loss → x-rays show T7, T10 fracture

# Case: Patient's Perception

- "I've heard so much bad about osteoporosis medications"
- "I could die from those drugs, but nobody dies from a broken bone."

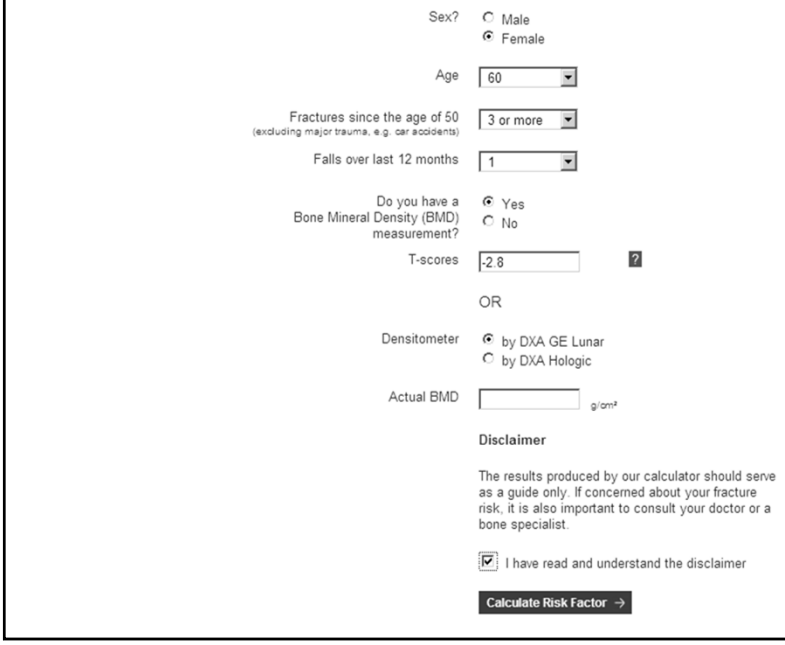
- Patient's Decision: "I would rather take my chances with having a broken bone than take the risks that come with one of those bad drugs."

# Case: Provider's Perspective

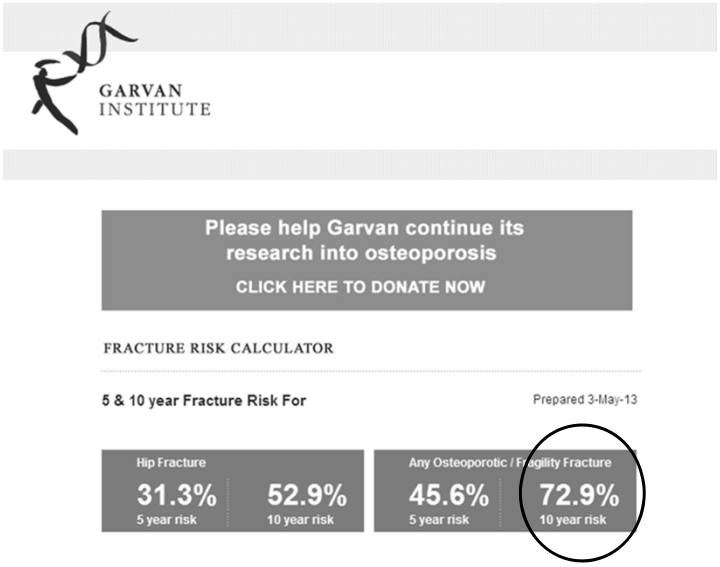



**http://www.shef.ac.uk/FRAX/tool.jsp?locationValue=9**

# Case: Provider's Perspective



# Case: Provider's Perspective




http://garvan.org.au/promotions/bone-fracture-risk/calculator/

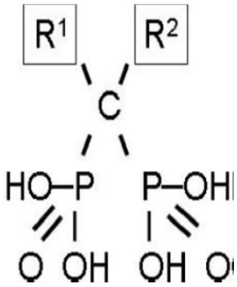
# Non-Drug Measures

- Calcium & vitamin D
- PT/OT:
  - home safety assessment and modification
  - walking aid/assistive devices
  - weight-bearing, strengthening, balance exercises
- Meds: gradually withdraw psychotropics
- Correct visual impairment
- Alcohol moderation & cigarette cessation

# FDA-Approved Drug Therapy

- bisphosphonate
- estrogen
- raloxifene
- calcitonin
- teriparatide
- denosumab

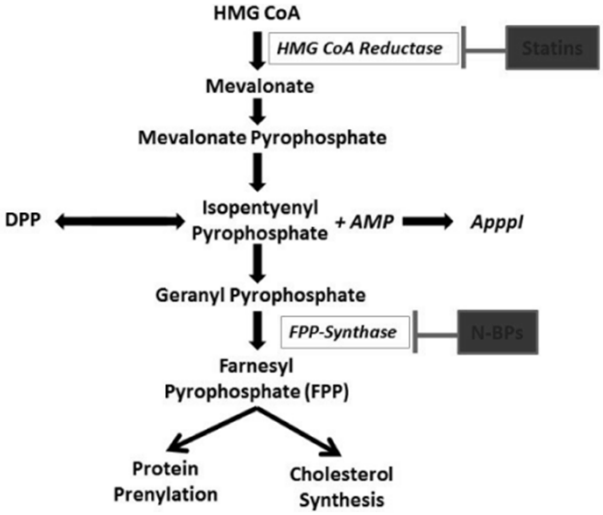
# Bisphosphonate: Chemical Structure




**$R^1$** OH group, binding to bone
**$R^2$** Binding to bone
Antiresorptive potency
**PO4** Binding to bone

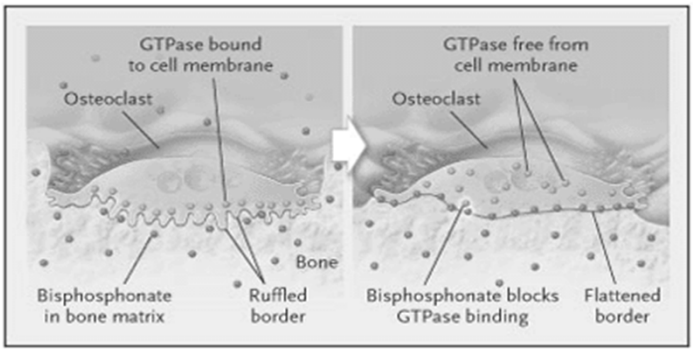
# Bisphosphonate Mechanism

## Mevalonate Pathway




Thea L Rogers, Ingunn Holen (CC BY 2.0)
J Transl Med. 2011; 9: 177. Published online 2011 October 17. doi: 10.1186/1479-5876-9-177

# Bisphosphonates




NEJM 2004;350(12):1172-1174

# Efficacy of Fracture Reduction

| Drug | Generic | Spine | Non-spine | Hip |
|---|---|---|---|---|
| alendronate | Yes | Yes | Yes | Yes |
| risedronate | Yes | Yes | Yes | Yes |
| ibandronate | Yes | Yes | | |
| zoledronate | Yes | Yes | Yes | Yes |
| teriparatide | No | Yes | Yes | * |
| denosumab | No | Yes | Yes | Yes |
| calcitonin | Yes | Yes | | |
| estrogen | Yes | Yes | Yes | Yes |
| raloxifene | Yes | Yes | | |

# FDA-Approved Indications

| | Postmenopausal Osteoporosis | | Glucocorticoid-induced Osteoporosis | | Men |
|---|---|---|---|---|---|
| Drug | Prevention | Treatment | Prevention | Treatment | |
| alendronate | Yes | Yes | | Yes | Yes |
| risedronate | Yes | Yes | Yes | Yes | Yes |
| ibandronate | Yes | Yes | | | |
| zoledronate | Yes | Yes | Yes | Yes | Yes |
| teriparatide | | Yes | | Yes | Yes |
| denosumab | | Yes | | | Yes |
| calcitonin | | Yes | | | |
| estrogen | Yes | | | | |
| Raloxifene | Yes | Yes | | | |

# Drug administration

- Fasting, first thing in the morning
- Plain water (8 oz)
- Wait ≥30 minutes before PO intake, meds
- Contact provider for upper GI symptoms

# Balancing Benefits and Risks of Therapy

**Benefits**

- ↓ Fractures
- ↓ Mortality
- ↓ Cancers
- ↑ Quality of Life
- ↓ Health Care Cost

**Risks**

- Upper GI symptoms
- Acute phase reaction (IV)
- ONJ
- Atypical Femur Fracture

## Bisphosphonates May Decrease Mortality

| | Mortality Rate per 100 per-yrs | | |
|---|---|---|---|
| | Bisphosphonate | No Tx | HR |
| Women | 0.8 (0.4-1.4) | 3.5 (3.1-3.8) | **0.27** (0.15-0.50) |
| Men | 1.0 (0.3-3.9) | 4.30 (3.9-4.8) | **0.27** (0.07-1.00) |

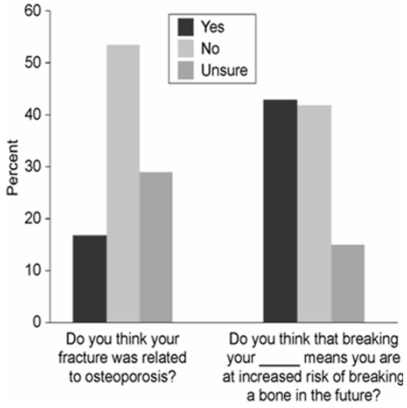
**Center, JCEM 2011;96(4):1006-1014**

## What do Seniors Fear Most?

- **2007 Interview age 65+**
- **"What do you fear most?"**
  - **26% Loss of independence**
  - **13% Moving out of home into nursing home**
  - **11% Giving up driving**
  - **11% Loss of family & friends**
  - **3% Death**

**http://www.slideshare.net/clarityproducts/clarity-2007-aginig-in-place-in-america-2836029**

## Patients Do Not Link Fragility Fracture with Osteoporosis




***"In summary, many individuals who suffer fragility fracture do not associate their fracture with osteoporosis."***

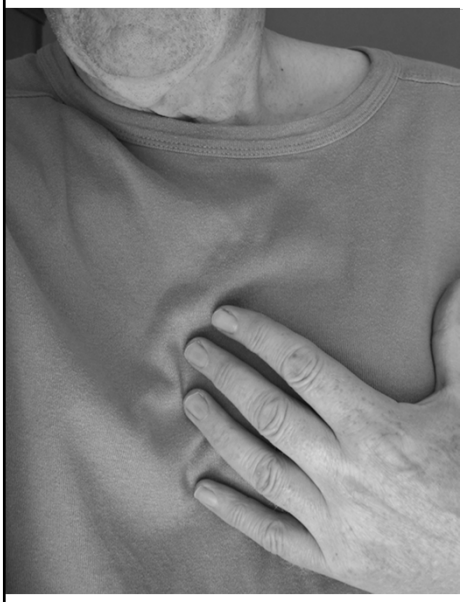
**Giangregorio BMC Musculoskeletal Disorders 2008;9:38**

## Diagnosis of Osteoporosis Changes the Perception of Fracture Risk

**"The odds of an individual responding, 'yes' to the question, 'Do you think that breaking your ___ means that you are at increased risk for breaking a bone in the future?' were higher for those that reported a diagnosis of osteoporosis (OR 22.9, p<0.001)."**

**Giangregorio BMC Musculoskeletal Disorders 2008;9:38**

## Osteoporotic Fracture Should be Viewed as a "Bone Attack"



**"I broke my ___ bone after I accidentally slipped and fell. Anyone could have fractured."**

**"No drug is absolutely safe; all drugs have side effects. Safe in this sense means that the benefits of the drug appear to outweigh the risk."**

FDA Consumer 2002;36(4):19-24

# Osteonecrosis of the Jaw

**Exposed bone in mandible or maxilla for ≥ 6-8 weeks, no prior XRT to area**

**Site of prior dental surgery**
**IV BP in cancer patient**
**Chemo, steroid use**
**Longer duration of BP**

**Risk in oral bisphosphonate:**
**1 in 10,000 - 100,000 pt-yrs**

Khosla J Bone Miner Res 2007:22:1479

# Atypical Femur Fracture

- **Treat 1000 women with BP x 5 years**
- **Prevent 35-50 non-vertebral fractures and**
- **50-115 vertebral fractures**
- **May see 5 atypical femur fractures**

**ASBMR Task Force, JBMR 2010**

# Atypical Femur Fracture Incidence

**Kaiser Study: 1,835,116 patients, age >45 yrs**
**188,814 used bisphosphonate (tracked with internal pharmacy records)**
**142 patients with AFF**
**128 with bisphosphonate exposure (14 w/o)**

| BP Duration (years) | # Cases | Incidence (per 100,000/yr) |
|---|---|---|
| 0 | 14 | 0.3 (0.3-0.4) |
| 0.1-1.9 | 10 | 1.8 (1.5-2.0) |
| 2.0-3.9 | 25 | 13.6 (10.3-17.0) |
| 4.0-5.9 | 27 | 16.1 (14.7-17.6) |
| 6.0-7.9 | 30 | 38.9 (26.5-51.3) |
| 8.0-9.9 | 25 | 113.1 (69.3-156.8) |
| >10 | 11 | 107.5 (48.1-166.9) |

**Dell, et. al JBMR 2012;27(12)**

# Typical Hip Fracture Incidence

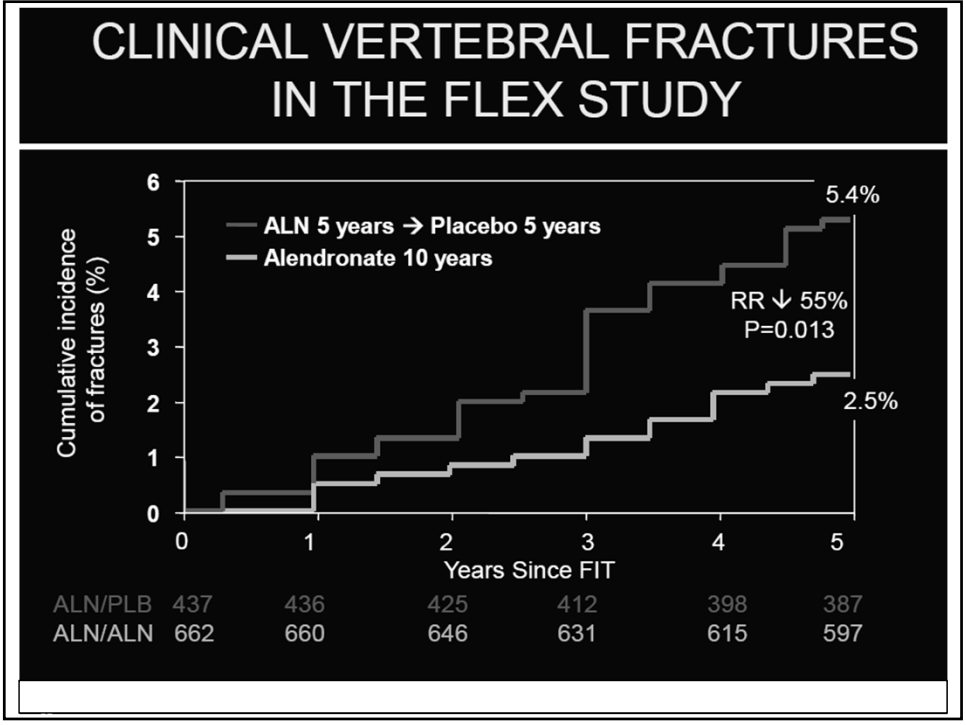
| | Hip Fracture Incidence in PLA (per 100,000 pt-yr) | RR Hip Fracture in Active Arm |
|---|---|---|
| Alendronate | 750 | 0.52 |
| Zolendronate | 833 | 0.59 |
| Risedronate | 1390 | 0.60 |

**Lancet 1996;348(9041):1535-41**
**NEJM 2007;356(18):1809-22**
**NEJM 2001;344(5):333-40**

# Alendronate FIT Long-term Extension (FLEX)

- Enrolled participants from Fracture Intervention Trial on ~5 years ALE
- Re-randomization to continue ALE (n=672) vs. switch to PLA (n=437)
- ALE x 10 yrs vs. stopping after 5 yrs
  - Clinical spine fractures ↓55%
  - Non-spine fractures ↓50% with T-score ≤ -2.5 at start of FLEX

Black et al, JAMA 2006;296:2927-2938
Schwartz et al, J Bone Miner Res 2010;25:976-982



# Bisphosphonate Holidays

- Osteoporosis (FN T-score ≤ -2.5) after 3-5 years of BP at highest risk for fracture and appear to benefit most from continuation of BP
- Prevalent vertebral fracture (FN T-score ≤ -2.0) may benefit from continuation of BP
- FN T-score > -2.0 have low risk for fracture and unlikely to benefit from continuation of BP

Black NEJM 2012;366;2051-2054

# Bisphosphonate Holidays

- For mild-moderate fracture risk, consider "drug holiday" after 4-5 years of stability
- For high fracture risk, consider drug holiday for 1-2 years after 10 years of treatment
- Follow DXA (and bone markers) during a drug holiday
- Restart therapy
  - Fixed period of time: e.g. 1-2 years
  - BMD falls significantly
  - Bone turnover markers increase
  - Fracture occurs

Watts, Endocrine Practice 2010