

**SEMCME Postgraduate Course in OB/GYN  
William Beaumont Hospital  
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***Osteoporosis Management:  
A Practical Approach***

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**Disclosures**

- Grant Support: NIH & Lilly
- Advisory Board/Consultant: DiaSorin Inc.
- No direct conflict of interest for today's talk

**Objectives**

- Approach to the patient with low BMD/OP/Fx
- Scope & magnitude of osteoporosis problem
  - [I.e., Fracture Epidemiology](#)
- Therapy selection based on type of Fx risk assessment
  - [Hip versus Spine](#)
- Determinants of therapeutic efficacy
- Monitoring Rx: BMD Vs. Biomarkers & How Often?
- How long & how safe is BP anti-Fx-Rx?
- Vitamin D: How much is enough & how much is too much?
- Controversy about Ca supplements
- Concluding remarks

**LH-36932007**

78y Black woman  
Low BMD  
Spontaneous multiple vertebral fractures  
Pelvic fracture with trivial trauma  
Rheumatoid arthritis  
Long term prednisone therapy; currently on 10mg/day

**LH-78y Black woman**

LUMBAR SPINE [L1 - L4] -- Scan mode: F

Bone Mineral Density: 0.83g/cm2

T-score: -3.7

Z-score: -2.0

WHO Classification: **Osteoporosis**

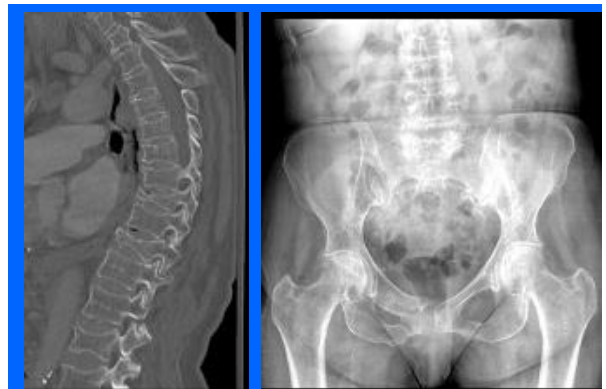
LEFT HIP [FEMORAL NECK] -- Scan mode: F

Bone Mineral Density: 0.595g/cm2

T-score: -3.7

Z-score: -2.1

WHO Classification: **Osteoporosis**



## How many risk factors does she have?

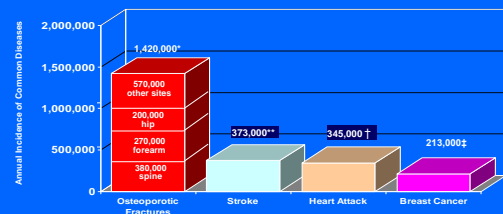
## Some Ground Rules

- **My remarks & presentation are**
  - Mostly evidence based
  - Partly eminence based (The Rao's principles!)
- **What we measure & follow are**
  - Largely surrogate measurements
    - BMD, BTMs, X-rays etc (Just like HgA1c, LDL, BP, etc)
  - ...not the events we intend to prevent-fragility Fxs (MI, Stroke, CRF)
- **Trial results are**
  - Selected population group based
  - May not necessarily applicable to the individual patient in the clinic
    - Value judgment/value imposition

## Scope & Magnitude of OP Problem

Fracture Epidemiology

## Osteoporotic Fractures Are More Common In Women Than Heart Attack, Stroke & Breast Cancer Combined



\* 2005 annual incidence all ages  
 † 2004 estimate  
 ‡ 2004 estimate, new and recurrent  
 § 2005 new cases, women all ages

1. Burge R et al. *J Bone Miner Res* 2007;22:465-475  
 2. Heart and Stroke Facts: 2007 Statistical Supplement, American Heart Ass'n  
 3. Cancer Facts & Figure: 2006, American Cancer Society

## Interesting Facts About Fractures

- Bone remodeling occurs every 15 seconds!
- Fxs occur every 3 seconds somewhere in world
- Each Fx increases the risk of another fracture
  - 1=3 fold; 2=5 fold; 3=9 fold!
- 2/3rds of vertebral Fx are asymptomatic
- Wrist Fx is a harbinger of future Fx esp. of hip
- Both vert & hip Fxs carry morbidity & mortality
- A previous Fx implies “poor” architecture

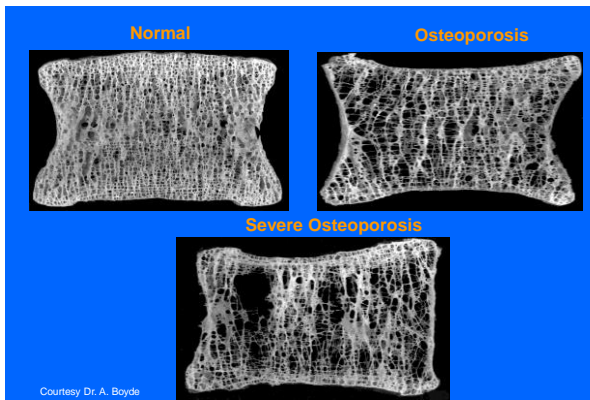
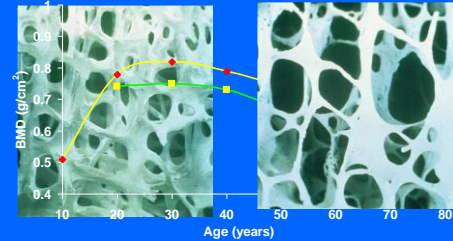
## Osteoporosis Definition

“A systemic disorder characterized by decreased bone mass micro-architectural deterioration and increased susceptibility to fractures in the absence of other recognizable causes.”

## World Health Organization criteria for the diagnosis of osteoporosis

	T-score
Normal	$\geq -1.0$
Osteopenia	-1 to -2.5
Osteoporosis	$\leq -2.5$
'Established' osteoporosis	$\leq -2.5$ + presence of one or more fractures

## Pathogenesis of Osteoporosis & Fracture



## Minimal Evaluation of a Patient

- Detailed H & P
  - Risk factor assessment
  - Personal history of fragility fractures after age 25y
  - Parenteral history of hip fractures
  - Accurate height measurement & assessment
  - Costo-pelvic interval (Rao Index!)
- Diagnostic Evaluation
  - BMD and VFA  $\pm$  X-ray spine
  - Lab tests as appropriate or dictated by H & P
    - Biochemical profile, 25-OHD, & 24h urine Ca, Na, Cr
    - PTH, TSH
- Application of FRAX for therapeutic decision
  - <https://www.sheffield.ac.uk/FRAX/>

## Risk Factors for Osteoporosis

- **Primary (Non-modifiable)**
  - Aging
  - Female gender
  - Low peak adult bone mass
  - Caucasian, Asian,
  - Estrogen deficiency
  - Family history of osteoporosis
  - Thin and/or small frame (?)
  - Use of certain medications (corticosteroids, anticonvulsants)
- **Secondary (Modifiable)**
  - Cigarette smoking
  - Excessive use of alcohol
  - Lack of physical activity
  - **Vitamin D deficiency**
  - **Inadequate lifetime calcium intake**
  - Dietary deficiencies or excesses (protein, sodium, caffeine)

## The Big Three!

1. Age of the patient
  2. Personal history of fracture after age 25y
    - Fractures of skull, clavicle(?), fingers & toes don't count!
  3. **Maternal/paternal** history of **hip** fracture
- BMD is a distant fourth!
    - Contributes about 35-40% to a fracture

## Classification of Osteoporosis

### 1. Primary

- Type I (Postmenopausal): Accelerated bone loss
- Type II (Age-related): Constant slow bone loss
- Type III (?Senile): Unclear?

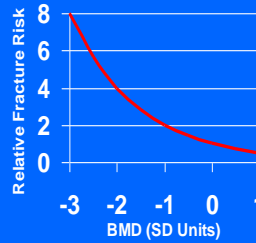
### 2. Secondary Osteoporosis

- A large number of conditions & disorders
- Corticosteroid Rx is the most common

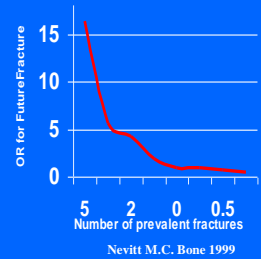
### 3. Others

- Drugs: aromatase inhibitors; anticonvulsants etc
- Transplant bone disease
- Idiopathic osteoporosis (?male osteoporosis)

Relationship of BMD To Future Fx Risk

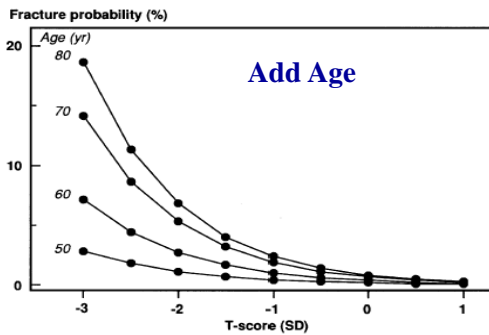


Relationship of Prevalent VF to Future Fx Risk

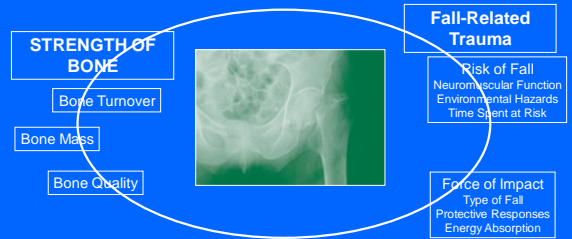


Nevitt M.C. Bone 1999

## Fracture Probability According to Age & BMD



## Assessing the Risk for Hip Fracture



## FDA Approved Therapies for Osteoporosis Prevention & Treatment

### Prevention (Antiresorptive)

- Estrogens\*
- Calcitonin\*
- Bisphosphonates
  - Alendronate
  - Risedronate
  - Ibandronate (oral & IV)
- SERMS (Raloxifene)

### Treatment (Antiresorptive & Anabolic)

- Calcitonin\*
- Bisphosphonates
  - Alendronate (daily/weekly)
  - Risedronate (daily/weekly/monthly)
  - Ibandronate (oral monthly & IV 3m)
  - Zoledronate (IV-yearly or less often)
  - Denosumab (Prolia) SC-6 monthly
- SERMS (Raloxifene)\*
- Teriparatide (Anabolic)\*
- Abaloparatide (Anabolic)\*

## Each was evaluated in well designed RCT

- Very few head to head trials
- In general: ERT/HRT, CT, SERM are "weaker" with respect to BMD change
  - However, vertebral Fx reduction is "comparable"
  - CT trial is probably the weakest of all trials
  - BP trials are the strongest as is the denosumab trial
- BPs have long "skeletal residence half time"
  - Concern about SSBT (Severe Suppression of Bone Turnover) & Femoral shaft Fxs
  - ONJ?
  - How long & how safe?
- Tereparatide & Abaloparatide are the only anabolics currently available
  - Slightly faster & more robust increase in BMD
  - No "direct" evidence for hip Fx reduction
- Denosumab is a bit unique and different from BPs
  - "non-accumulating"

### Baseline Characteristics, Changes in BMD & Reductions in Incident Vertebral Fractures

	Change in Spine BMD	Reduction in Vert Fx	Spine T-score	Baseline Vert Fx
ALN-FITII	7.9%	47%	-2.5	90%
RIS-US	5.4%	41%	-2.4	?100%
ZOL	7.5	65%	-2.8	50%
Ralox	2.6%	40%	-2.6	37%
CT	1.2%	36%	<-2.0	75%
TPTD	15%	65%	-2.6	90%
Deno	8.8%	68%	-2.8	23%

### Currently Available Tools to Monitor Therapy

- Height measurement
  - Methods, accuracy, pitfalls & advantages
- Bone Mineral Density (BMD)
  - Definition, methods, precision & accuracy, interpretation etc
- Bone Turnover Markers (BTMs)
  - Formation versus resorption or both & which ones?
  - What do they mean/represent?
- X-ray procedures
  - Which ones & when?
- Bone Biopsy for histomorphometry
  - What, when, & why?

### Monitoring Frequency for BMD

	AACE	NAMS	ISCD
Preferred Site	Spine & Hip	Hip ± Spine	Spine & Hip
Instrument	DEXA	DEXA	DEXA
Frequency	Normal Baseline BMD: every 3-5y	Untreated: every 5y	On Rx: Yearly till therapeutic effect
	Prevention: 1-2y till stable; then 2-3y	Treated: every 2y	Longer intervals
	On Rx: yearly till stable; then q 2 y		

### BTMs are also “validated” in RCTs

Treatment	Formation	Resorption	Outcome
Alendronate	BSAP, P1NP, PICP & OC	uNTX, sCTX, DPD	Fracture & BMD
Risedronate		uNTX, uCTX, uDPD	Fracture & BMD
Raloxifene	BSAP, P1NP, OC	uCTX	Fracture
Teriparatide	BSAP, P1NP, PICP	uNTX, sCTX, DPD	Fracture & BMD

### BTMs: What do they mean/reflect?

- Whole body bone turnover
  - By contrast BMD is site specific
- Diurnal variation
- Biologic variation
- Measurement variations
- Short term response

### How to Identify Non-responders ? Real vs. Apparent

- **Apparent**
  - Positioning, Instrument, & other technical issues
  - Artifacts and surgeries
    - Laminectomy, hip replacement etc
  - Age related changes at the sites of measurement
  - Regression to mean
- **Real**
  - Adherence to therapy
  - **Problems in taking Rx**
  - Intercurrent illnesses and/or therapy
    - Steroid therapy
    - Inadequate vitamin D & Ca intake/supplements
  - Occult malabsorption

### What are our concerns, constrains & questions?

- How do we define efficacy?
- What constitutes a “non-response”?
  - *Densitometric?*
  - *Biochemical?*
  - *Clinical?*
- Fracture assessment during therapy
  - Reduction versus elimination
  - “Usual” versus “Unusual” fractures
- Treatment Failure
  - Decline in BMD on “optimal” therapy during follow-up
  - An incident fracture on therapy ≠ treatment failure?

### The Last Word!

- Monitoring chronic diseases, such as OP, that require long-term Rx is critical, because adherence to Rx is often inadequate.
- Serial BMD, BTM, VFA (& accurate height measurements to be sure) allow physicians to monitor efficacy of therapy, improve adherence, & as a result, the intended outcomes.
- Discussions between physicians & patients about patient progress enhances adherence.
- Proper use of monitoring tools provides feedback to patients; if not, the management of OP therapy will simply be a guesswork.
- To be useful, however, these tools require strict quality control and proper interpretation, which is sorely lacking at present.

### What is required to make monitoring worthwhile?

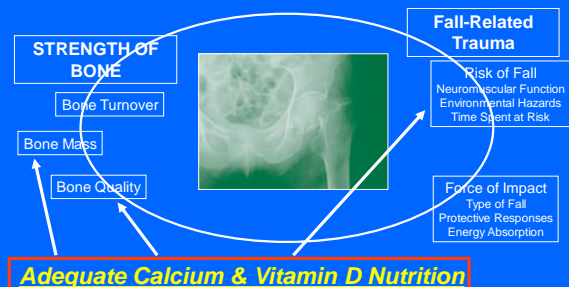
- Test should reliably categorise change within an appropriate timescale
- Test should predict clinical outcome
- Result of test should influence physician management and/or modify patient behaviour
- Use of test for monitoring should be cost-effective

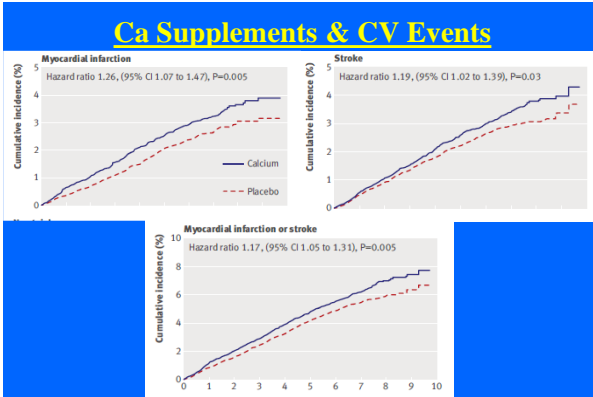
## Role of Calcium & Vitamin D Nutrition in Osteoporosis

### Non-pharmacologic aspects of fracture prevention strategies

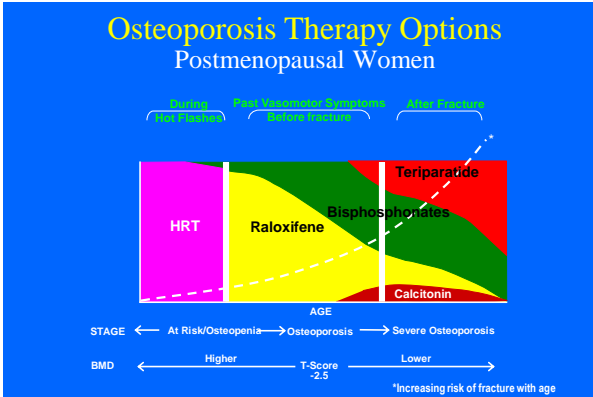
- All RTCs of Osteoporosis
  - Calcium Supplementation 500-1000 mg/day
  - Vitamin D 200-400 IU/day
- Ca: 1500-2000 mg/d & Vitamin D: 800-1000 IU/d
  - Rao DS., J Clin Densitometry, December 1999
  - Guardia et., al Osteoporosis Int 2008
- **Fall prevention and its monitoring**
- **Hip protectors in selected cases**

### Assessing the Risk for Hip Fracture





- ### The Bottom Line
- A wide variety of drugs are now available for prevention & treatment of both low bone density and fractures; many are in pipe line
    - *Ale Carte or smorgasbord*
  - For good bone balance...target the peak bone mass
    - *Osteoporosis is really a pediatric disease*
  - Bone balance is better than bank balance!**



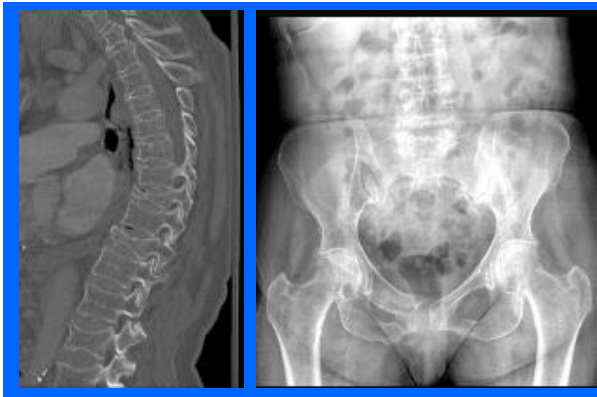
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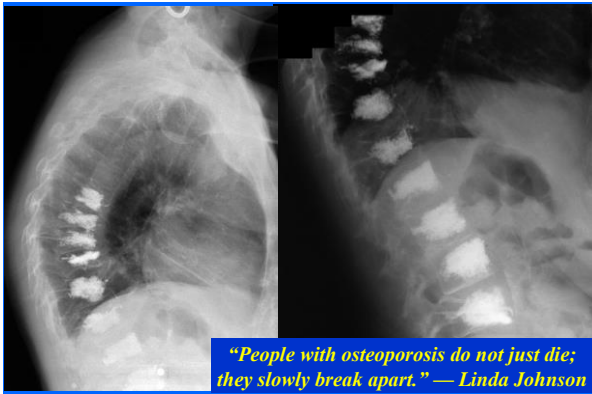
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## How many risk factors does she have?

- Older age
- Menopause without HRT
- Rheumatoid arthritis
- Long term prednisone therapy
- Low BMD
- Multiple fractures

## Natural History of Osteoporosis



*"People with osteoporosis do not just die; they slowly break apart." — Linda Johnson*

## The paradox of Evidence Based Medicine

- It's not what the data say, it's what you say about the data
- Statistics mean you never have to say you're certain

## Continuing Medical Education

**"Education is not the filling of a pail,  
but the lighting of a fire"**

...William Butler Yeats (1865-1939)

[www.quotesandsayings.com](http://www.quotesandsayings.com)

Source: *BMJ* 332:518, 4 March 2006

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