

Current Issues in Osteoporosis

Orthopedic Version



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Handout (slides) available at http://www.orost.com/mm_pres.htm

Conflicts of Interest

I receive research grants and/or consulting fees from the following companies:

Amgen

Lilly

Merck

Novartis

Procter & Gamble

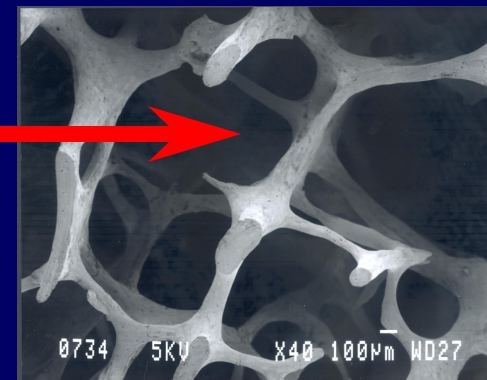
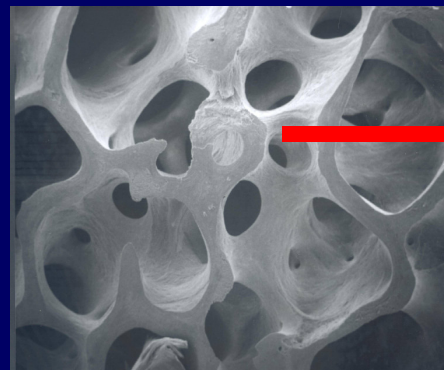
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Michael McClung, MD

June 2008

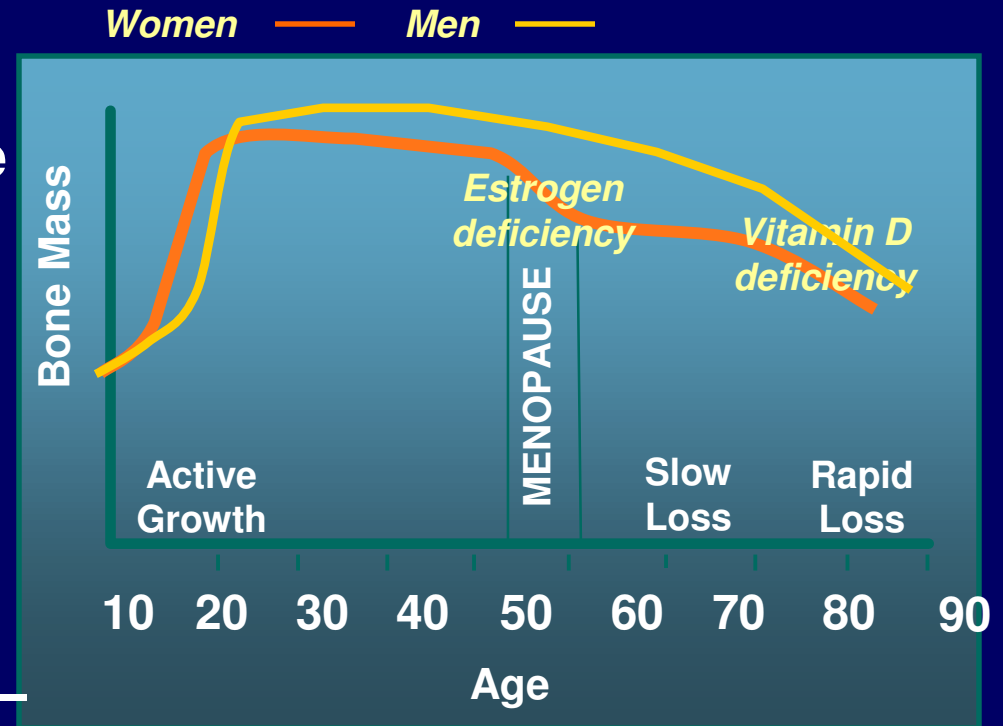
Osteoporosis: The Definition

- impaired bone strength
 - low BMD
 - poor bone quality
- *increased fracture risk*
- due to bone loss



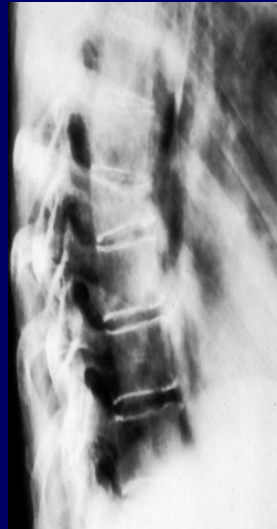
Bone Loss

- Minimal in healthy women until just before menopause
- Accelerates at menopause due to estrogen deficiency
- Continues throughout life
- Increases in old age
- Influenced by other factors – nutrition, diseases, medications, activity, etc



Fracture - Consequences

- acute and chronic pain
- kyphosis & height loss
- impaired function
- increased mortality
- increased fracture risk *

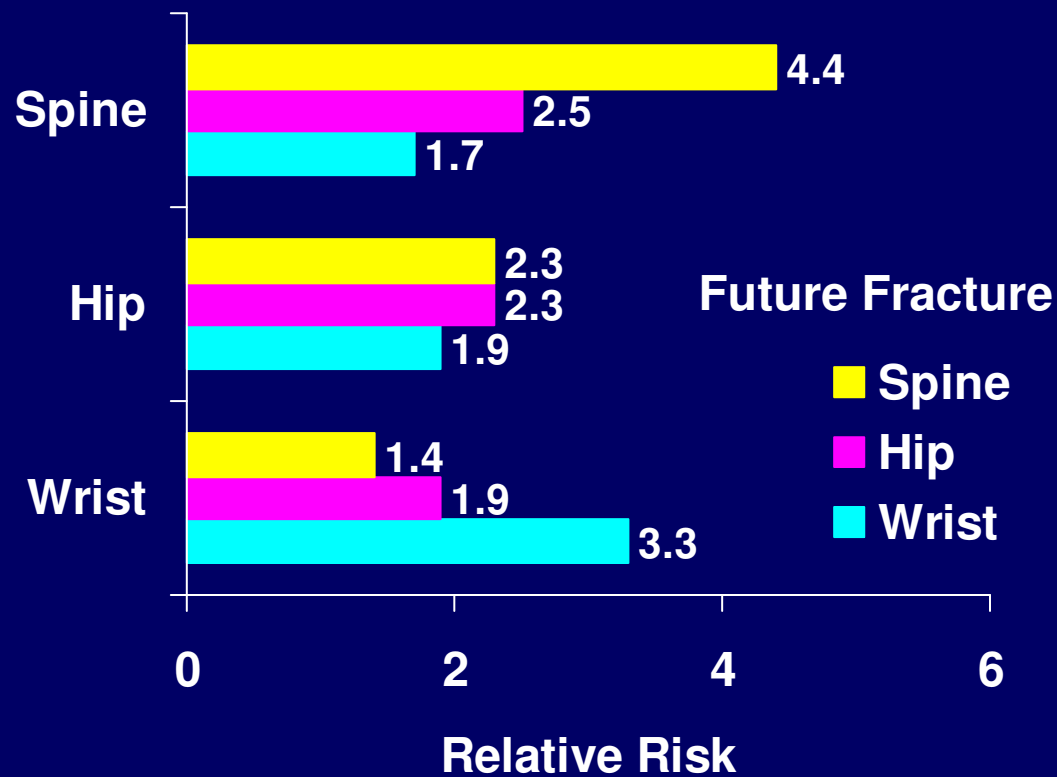


- 200,000 women and 100,000 men with hip fractures each year
- Average age = 84
- Increased mortality and morbidity
- Major reason for NH admission
- 30% of patients do not regain their pre-ambulatory status

Prior Fracture as a Predictor of Fracture Risk

Previous Fracture

Prior fracture increases risk by 1.77



Osteoporosis and Fractures

Association

Strong

Questionable

Weak

vertebral

pelvis

face

hip

ribs

hands and feet

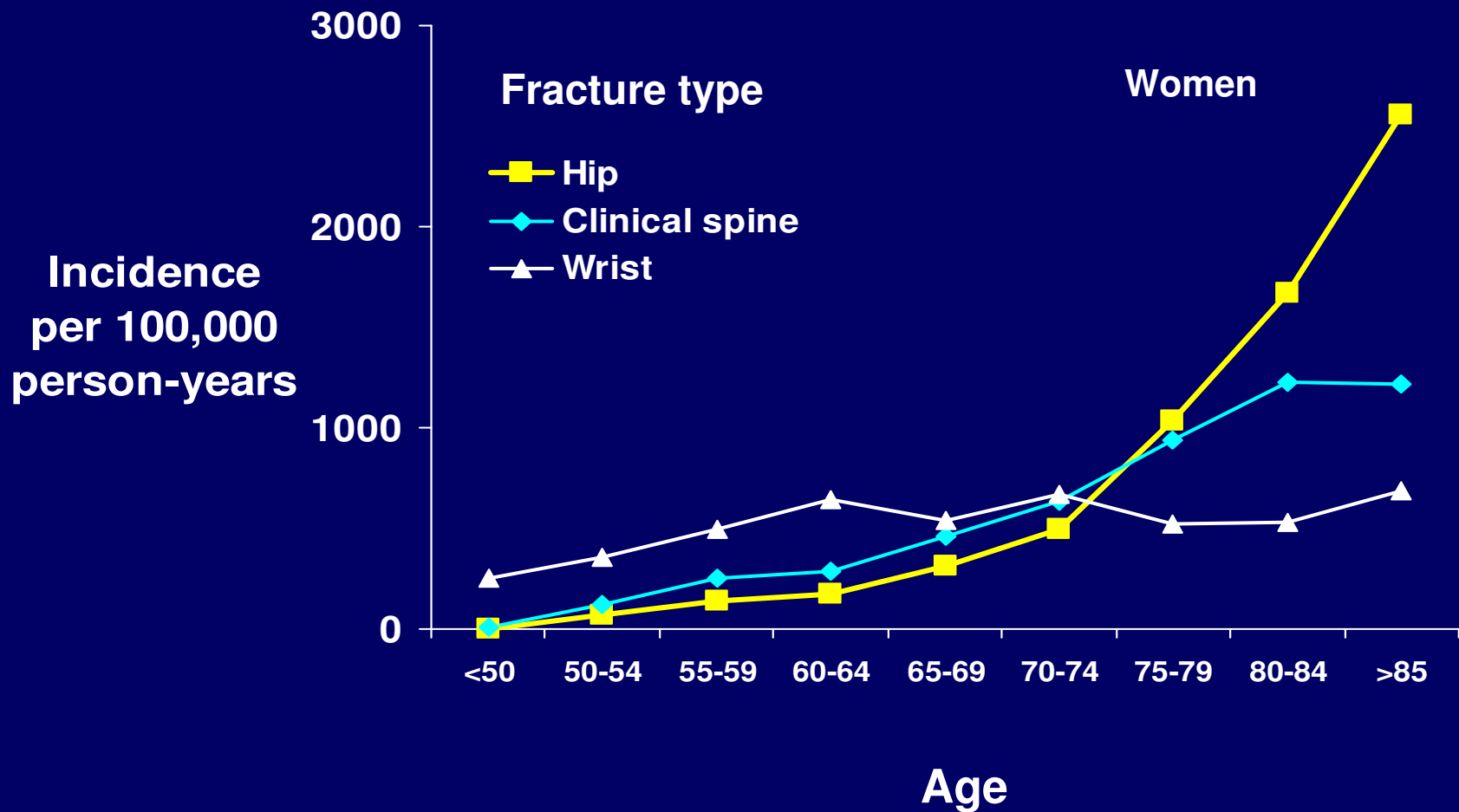
proximal humerus

ankle

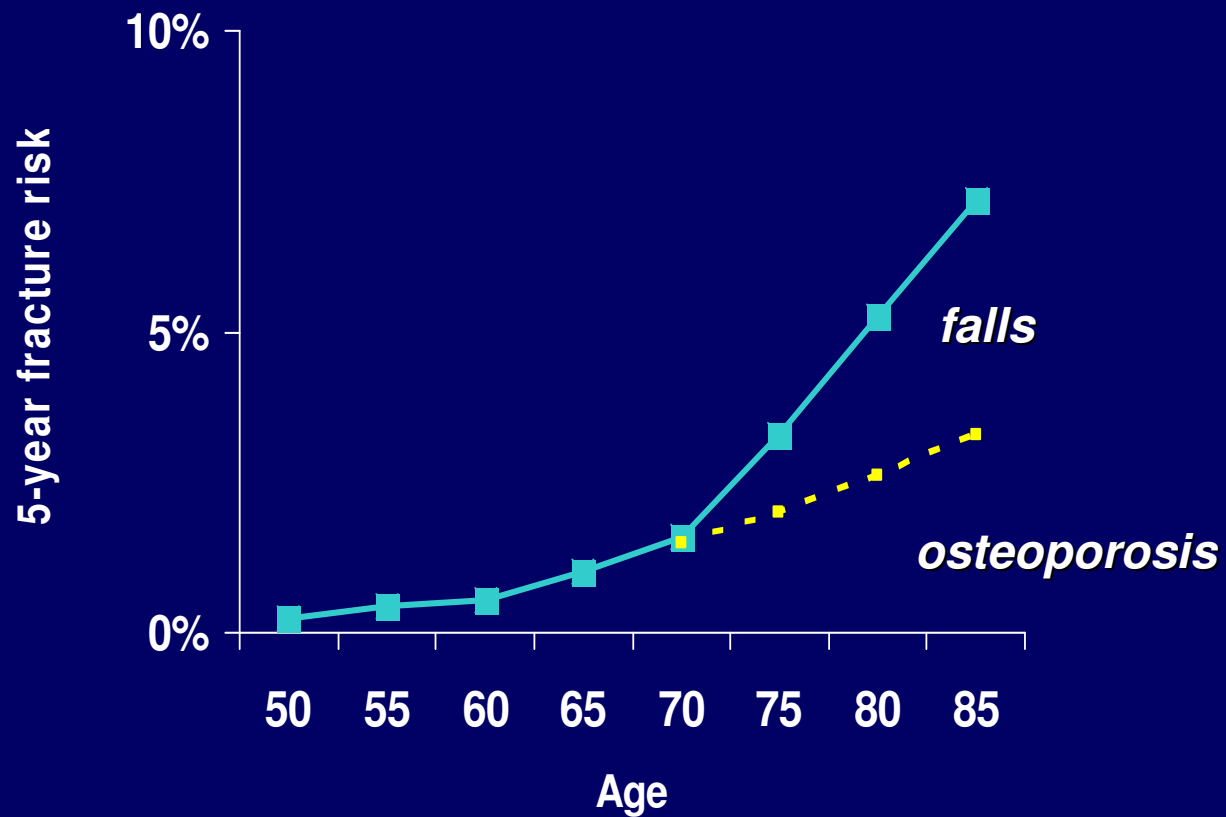
wrist

distal lower extremity

Incidence of Fractures in Women



Age and Hip Fracture Risk



BMD Interpretation

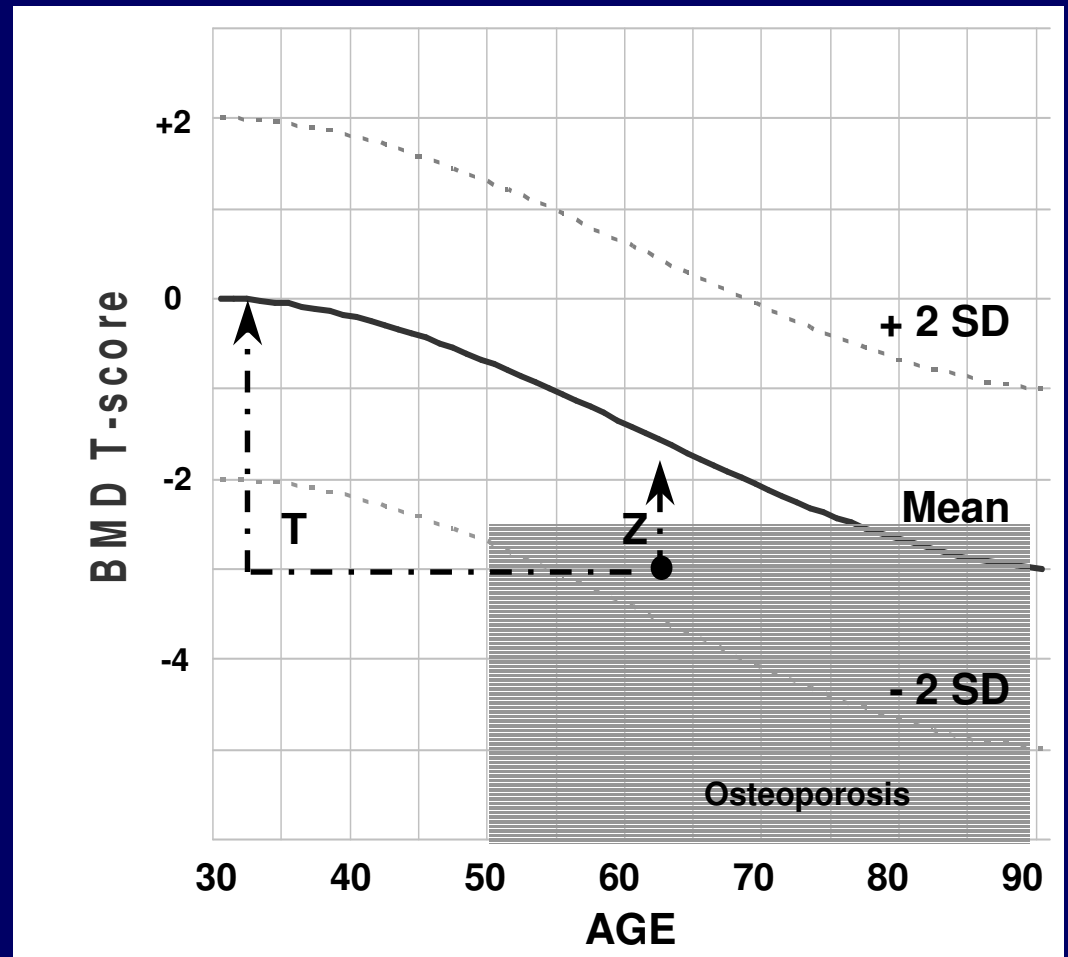
T score: SD from young normal values

Z score: SD from age-matched average values

This example:

T-score = -3.0

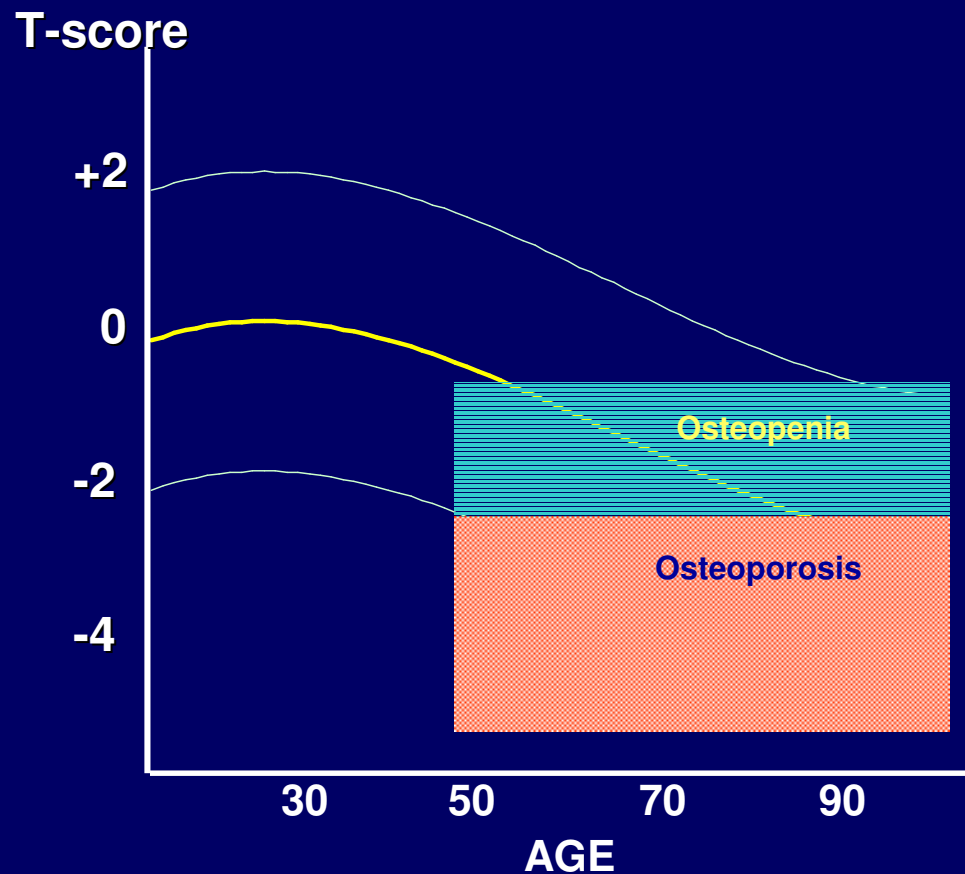
Z-score = -1.5



Osteoporosis – Making the Diagnosis

WHO Diagnostic category*	T-score
Normal bone mass	≥ -1
Low Bone Mass or OSTEOPENIA	-1 to -2.5
Osteoporosis	≤ -2.5

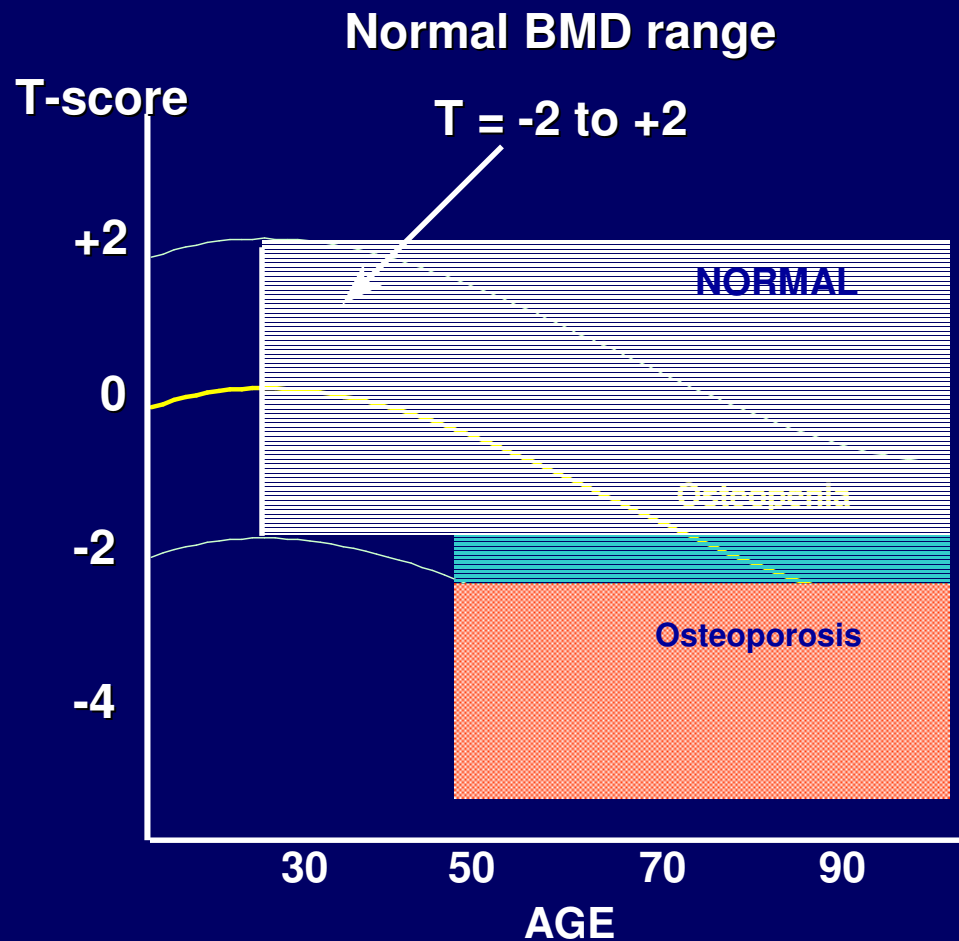
- * *Pertains only to postmenopausal women*
- *Pertains only to DXA*
- *Does not pertain to secondary causes of osteoporosis*



WHO Diagnostic Categories: Osteopenia

WHO Diagnostic category*	T-score
Normal bone mass	≥ -1
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Indications for BMD Testing

Should be driven by who we want to treat

- unexplained fracture after age 50 in men and women
“BONE ATTACKS”
- women 65 years and older
- younger postmenopausal women with risk factors for osteoporosis or fracture
 - thinness, family history of spine or hip fracture
- patients with secondary causes of osteoporosis
 - use of steroids or suppressive doses of T4, hypogonadism, hyperparathyroidism, immobilization, malabsorption

DDX of Low Bone Mass

Osteoporosis

Primary:

**postmenopausal
age-related
idiopathic**

Secondary

Osteomalacia

**Genetic disorders (e.g., osteogenesis imperfecta,
hypophosphatasia)**

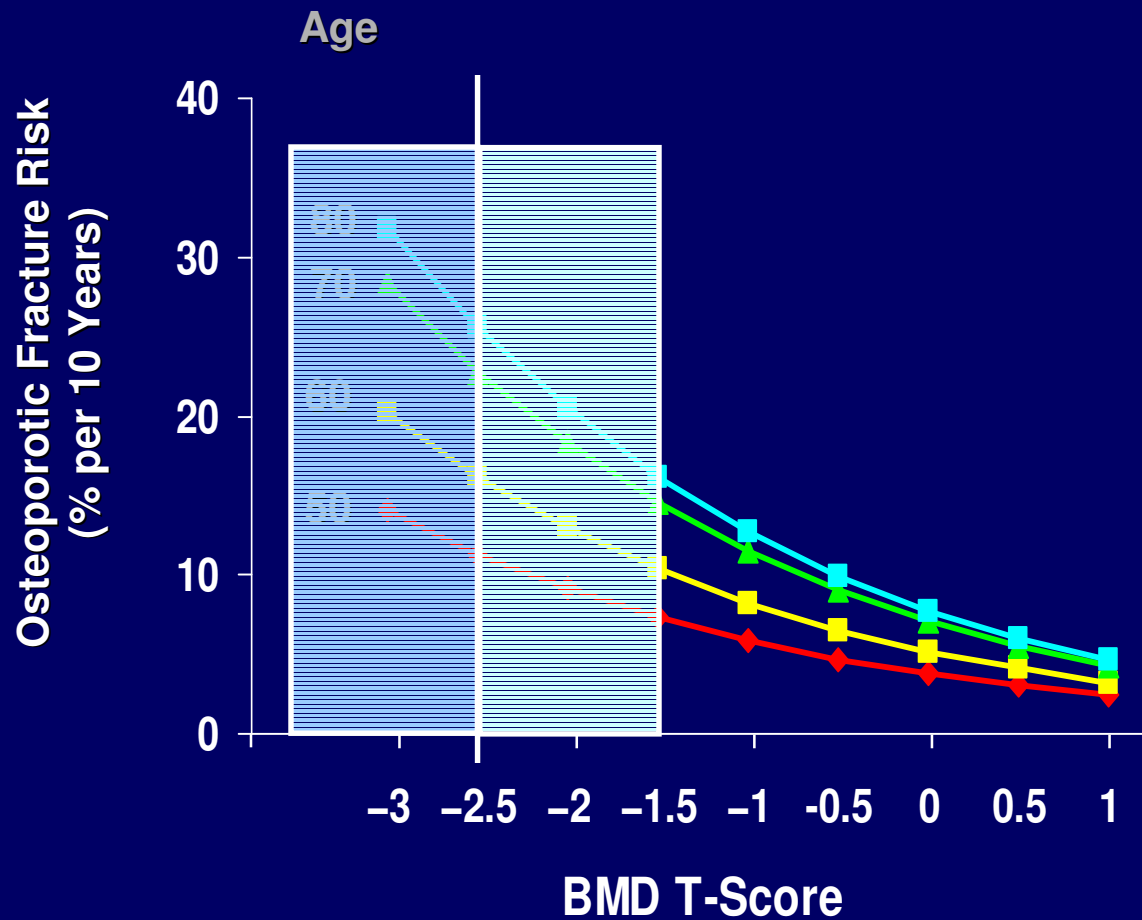
Marrow-based diseases (myeloma, mastocytosis)

Risk Factors for Hip Fractures

- **Skeletal**
 - *Low bone mass*
 - *Previous fractures*
 - High bone turnover
 - Bone geometry
- **Non-skeletal**
 - *Age*
 - *History of falls*
 - frailty
 - impaired neuromuscular function
 - poor vision
 - sedative medications



BMD, Fracture Risk and Treatment Threshold



Kanis JA, et al. *Osteoporos Int.* 2001;12:989-995.

McClung MR. *Current Osteoporos Reports* 2005;3:57-63.

WHO Absolute Risk Prediction Model

- Diagnosis of osteoporosis based on BMD
 - BMD is good predictor of fracture risk in untreated women
 - Independent risk factors
 - Age
 - Prior fracture
 - Glucocorticoid use
 - Treatment guidelines are based on BMD, modified by risk factors
- Parental H/O hip fracture
Smoking and alcohol
Falls

WHO Absolute Risk Prediction Model

- **Input of up to 7 clinical risk factors**
- **Output will be 10-year probability of experiencing a fracture of the hip, spine, humerus or wrist fracture**
- **Will be based, where possible, on country- or ethnic-specific fracture incidence rates**

FRAX™ WHO Fracture Risk Assessment Tool

HOME

CALCULATION TOOL

PAPER CHARTS

FAQ

REFERENCES

Calculation Tool

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



Weight Conversion:

pound:

[convert](#)

130 pound = 58.97 kg

Height Conversion:

inch:

[convert](#)

65 inch = 165.1 cm

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)

4. Height (cm)

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

[Clear](#)

[Calculate](#)

BMI 21.6

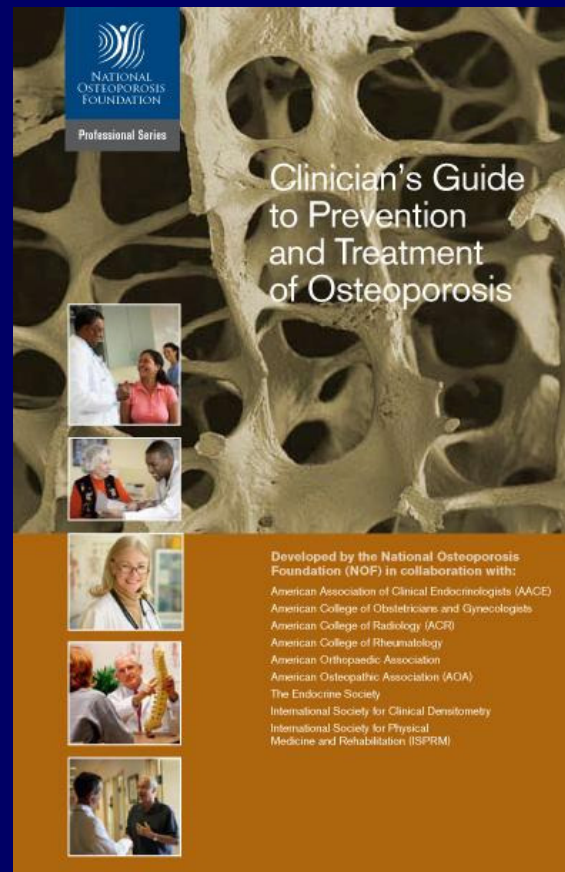
The ten year probability of fracture (%)

with BMD

<input checked="" type="checkbox"/> Major osteoporotic	24
<input checked="" type="checkbox"/> Hip fracture	3.10

Postmenopausal Osteoporosis: NOF-FRAX Indications for Treatment

http://nof.org/professionals/Clinicians_Guide.htm



NOF Guidelines 2008

Indications for therapy in postmenopausal women and men over age 50

1. after hip or spine fracture
2. BMD T-score in spine or proximal femur ≤ -2.5
3. BMD between -1 and -2.5 and one of following:
 - a. history of fragility fracture since age 50
 - b. 10 year risk of major fracture of 20% or more*
 - c. 10 year risk of hip fracture of 3% or more*

** Calculated by FRAX™ algorithm*

Evaluation of Patients with Low Bone Mass

- **All patients with osteoporosis deserve a limited evaluation to search for medical causes of bone loss**
 - careful medical history & examination
 - CBC, serum chemistry (calcium, creatinine, alkaline phosphatase, phosphate)
 - 24-hr urinary calcium
 - for special cases: serum PTH, 25-OH vitamin D, TSH, SPEP, urine cortisol, etc.
- **More tests or referral if**
 - hints from preliminary work-up of abnormalities
 - unexpectedly low BMD (Z-score < -1.5)

Diagnostic Considerations: Summary

- **BMD is used to diagnose osteoporosis**
- **Fracture risk assessment includes BMD and other risk factors**
 - **BMD alone does not predict fracture risk**
- **Differential diagnosis of low bone density must be considered**
- **A search for factors that contribute to bone loss is warranted**

Osteoporosis: Strategies of Therapy

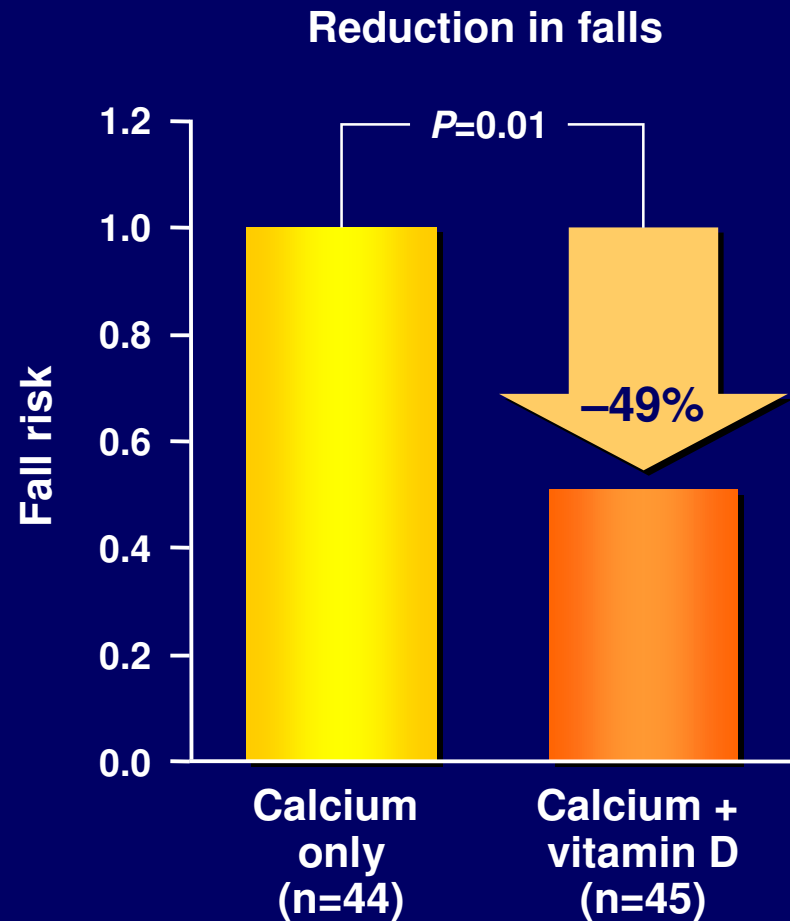
- **General measures:**
 - Adequate calcium and vitamin D intake
 - Regular physical activity
- **Injury prevention**
 - Exercise
 - Fall prevention
 - Hip protectors
- **Pharmacological therapy**

Calcium – Vitamin D

- **Calcium:**
 - **Recommended intake - 1200-1500 mg daily**
 - **Source of calcium unimportant**
- **Vitamin D**
 - **Under age 65:**
 - **1000 IU D3/d or 100,000 IU D2/mo**
 - **65 and over:**
 - **2000 IU D3/d or 50,000 IU D2/wk**

Vitamin D Decreases Risk for Falling

- N =122
- Ages: 63–99
- Randomized, double-blind, controlled trial
 - Calcium 1200 mg/d
 - Calcium 1200 mg/d + vitamin D 800 IU/d
- 12-week duration
- Mean serum 25(OH)D 12 ng/mL at baseline
- Women living in long-term care units

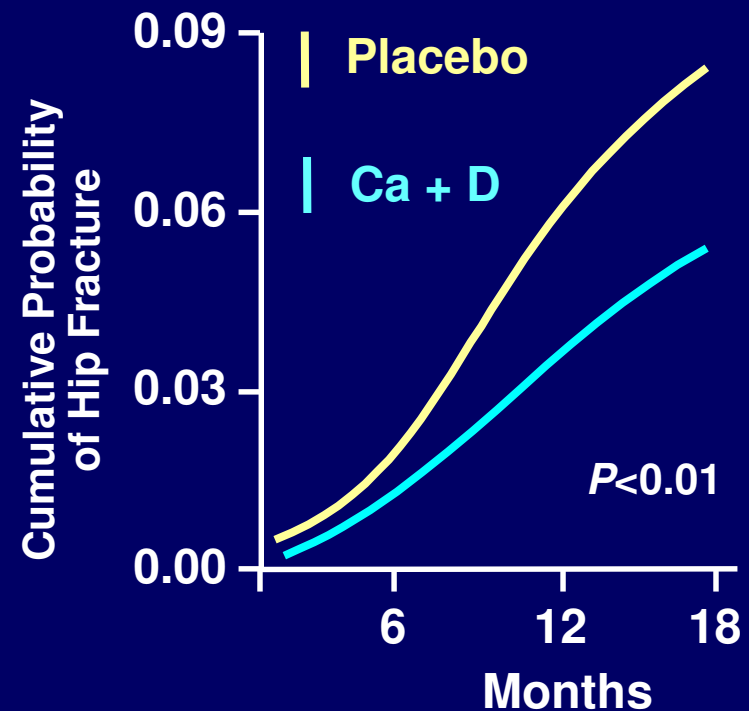


Calcium and Vitamin D Reduce Hip Fractures

Subjects: elderly women in French nursing home (n=3270)

Therapy: Calcium 1200 mg and vitamin D 800 IU daily

Outcome: 30% decrease in hip fracture risk over 18 months



Osteoporosis Therapy - 2008

Anti-remodeling drugs

- estrogen
- SERMs (Evista[®])
- calcitonin (Miacalcin[®], Fortical[®])
- bisphosphonates
(Fosamax[®], Actonel[®], Boniva[®], Reclast[®])

Anabolic agents

- parathyroid hormone analogues (Forteo[®])

Postmenopausal Osteoporosis: Approved Treatment Options 2008

No head-to-head trials comparing fracture outcomes

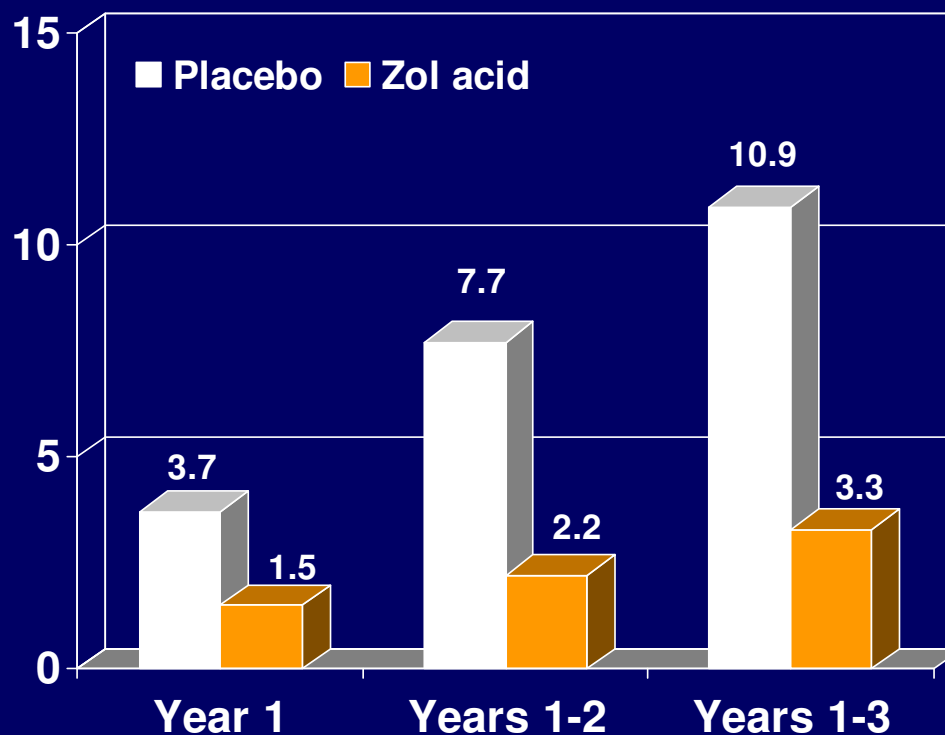
	Approved Indications *		Documented Fracture Reduction §			Comments
	Prevention	Treatment	Spine	Non-vertebral	Hip	
ANTIRESORPTIVE AGENTS						
Alendronate	X	X	X	X	X	Weekly dosing
Ibandronate	X	X	X			Monthly and IV dosing
Risedronate	X	X	X	X	X	Weekly and monthly dosing
Zoledronic acid	-	X	X	X	X	Annual IV dosing
Raloxifene	X	X	X			Extra-skeletal effects
Calcitonin	-	X	X			
Estrogen	X	-	X	X	X	Extra-skeletal effects
ANABOLIC AGENTS						
Teriparatide	-	X	X	X		

* X = FDA-approval § In clinical trials

Information from Package
Inserts of each agent

Zoledronic Acid: Effect on Vertebral Fractures

Incidence (%) of
new vertebral
fractures



Rel risk reduction :	60%	71%	70%
Conf interval:	43-72%	61-78%	62-76%

Zoledronic Acid: Fracture Reduction

<u>FRACTURE</u>	<u>Placebo</u>	<u>Zol acid</u>	<u>RRR</u>	<u>CI</u>	<u>p value</u>
Hip	2.5%	1.4%	41%	17,58	0.002
Non-vertebral	10.7%	8.0%	25%	13,36	<0.001
Clinical vertebral	2.6%	0.5%	77%	67,86	<0.001
Multiple vertebral	2.3%	0.2%	89%	77,95	<0.001

No difference by BMD, prior fracture or use of other drugs

Zoledronic Acid After Hip Fracture

- 2127 subjects (24% men) age 50 and older (mean 74.5) with a recent (90 days) hip fracture
- BMD not an entry criterion: 42% had FN T-score < -2.5
- Could take estrogen, SERMs or calcitonin (~10%)
- All received calcium (1000-1500 mg) + vitamin D (800-1200 IU after loading dose of 50-125K units)
- Randomly assigned to receive
 - Zoledronic acid 5 mg or placebo IV once yearly
- An event-driven trial:
 - Mean follow up 1.9 years (up to 5 years)

Zoledronic Acid After Hip Fracture

<u>FRACTURE</u>	<u>Placebo</u>	<u>Zol acid</u>	<u>RRR</u>	<u>CI</u>	<u>p value</u>
Clinical	13.9%	8.6%	35%	16,50	0.001
Non-vertebral	10.7%	7.6%	27%	2,45	0.03
Hip	3.5%	2.0%	30%	-19,59	0.18
DEATH	13.3%	9.6%	28%	7,44	0.01

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Bisphosphonates: Concern About Long-term Safety

- **Anecdotal reports of fractures and impaired healing**

- **Osteonecrosis of jaw**

- **Non-healing unusual fractures**

Odvin C et al. *J Clin Endo Metab.* 2005;90:1294-1301

- **Sub-trochanteric fractures**

(9/13 were on alendronate) Goh S-K, et al. *J Bone Joint Surgery,*
2007;89-B:349-353



Bisphosphonates and Non-healing Fractures - “Frozen Bone”?

- Several small series of cases experiencing unusual lower extremity fractures
 - Not always old
 - Time on therapy variable
 - Often on other drugs, esp. steroids
- Bone turnover: low normal resorption but very low or absent formation
- Slow or absent healing



Kazuhiro I, et al. *J Bone Mineral Metab* 2007. 25: 333-336.

Lenart BA, Lorich DG, Lane JM. *N Engl J Med*. 2008;358:1304-6.

Nevaser AS, et al. *J Orthop Trauma*. 2008;22:346-50.

Special Points for Orthopedists

- **Treat fragility fractures – especially of spine, hip, shoulder and wrist – as “BONE ATTACKS”**
 - **All patients need risk stratification and/or treatment**
 - **After a fracture –especially hip and humerus fractures – ensure adequacy of vitamin D intake**
- **Do not begin osteoporosis drug until after D deficiency is corrected**
- **Fracture healing**
 - **Not substantively altered by osteoporosis treatment**
 - **Markedly impaired by vitamin D deficiency**

Discussion

