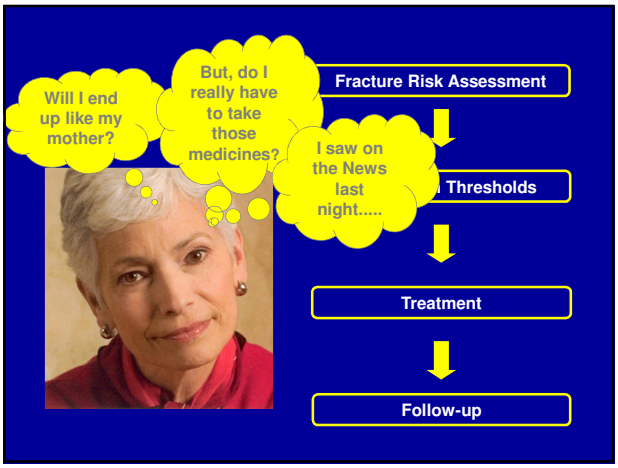
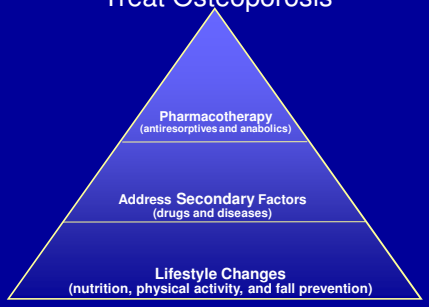
OSTEOPOROSIS
"The silent thief"

GL Muntingh
Dept of Pharmacology



Leading the Effort to Help Prevent and Treat Osteoporosis



Pyramid for Osteoporosis Prevention and Treatment

What does this mean for your patients?

But First....

A Few Facts about Osteoporosis

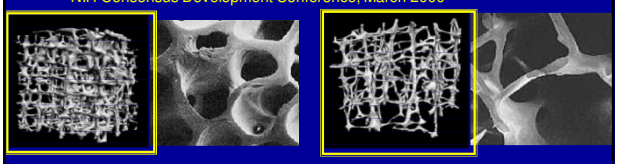
and

Bone Density Measurement

Osteoporosis

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture.

NIH Consensus Development Conference, March 2000



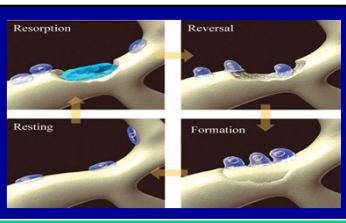
Normal Bone Osteoporotic Bone

Practical Definition of Osteoporosis

- A fall from a sitting or standing height that causes a fracture

Bone Mineral Density Testing

"Quantitating the Bone Mass"



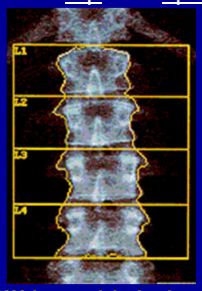
- Bones are made up of collagen, a protein that provides the basic framework, and calcium phosphate, a mineral that hardens the bone.
- Osteoporosis occurs when there is an imbalance between new bone formation(Osteoblasts) and old bone resorption (Osteoclasts).
- The body may fail to form enough new bone, or too much old bone may be reabsorbed, or both.
- Calcium is essential for proper functioning of the heart, brain, and other organs. To keep those critical organs functioning, the body reabsorbs calcium that is stored in the bones to maintain blood calcium levels.

- If calcium intake is not sufficient or if the body does not absorb enough calcium from the diet, bone production and bone tissue may suffer.
- Thus, the bones may become weaker, resulting in brittle and fragile bones that can break easily. The greatest change in a woman's bone density comes in the five to seven years after menopause.
- The leading cause of osteoporosis is a lack of certain hormones, particularly estrogen in women and androgen in men.
- Menopause is accompanied by lower estrogen levels and increases a woman's risk for osteoporosis.
- Other factors that may contribute to bone loss in this age group include inadequate intake of calcium and vitamin D, lack of weight-bearing exercise, and other age-related changes in endocrine functions (in addition to lack of estrogen).

Central Dual-energy X-ray absorptiometry (DXA)

Measures bone density at the hip and spine

DXA image of the hip



DXA image of the lumbar spine

Who Should be Tested?

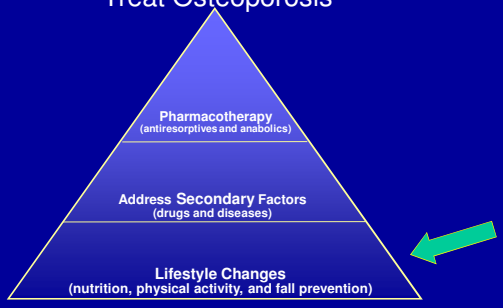
- **Women age 65 and older**
- **Men age 70 and older**
- **Women and men over 50 with risk factors**
- **Patients with a fracture after age 50**

WHO Diagnostic Criteria Based on BMD

- Normal: BMD T-score (number of standard deviations from "young normal" adult) at –1.0 and above)
- Osteopenia (low bone mass): BMD T-score between –1 and –2.5
- Osteoporosis: BMD T-score at or below –2.5
- Severe osteoporosis (established osteoporosis): BMD T-score at or below –2.5 and a history of ≥1 fracture

WHO. *World Health Organ Tech Rep Ser.* 2003;921:1-164.

Leading the Effort to Help Prevent and Treat Osteoporosis



Pyramid for Osteoporosis Prevention and Treatment

What does this mean for your patients?

Lifestyle Issues

- Tobacco- eliminate it
- Alcohol – moderate it
- Food – eat it
- Exercise – do it
- Fall Prevention – work on it

Lifestyle Issues

- Tobacco - eliminate it
- Alcohol – moderate it
- Nutrition - adequate weight, protein--magnesium, trace elements....*multivite*
- Exercise – strength, aerobic, flexibility, balance
- Fall prevention- home safety, shoes, walking aids, glasses

Nutrition

- Appropriate Body Weight
  - BMI 22 - 25
- Adequate nutrition
  - Protein
- Multi-vitamin daily
  - C, D, K, Copper, Manganese, Zinc, Phosphorus
- Nutritional supplements
  - Ensure, Boost

Nutrition

Milk, Yogurt

- Calcium, magnesium, potassium, phosphorus, zinc, protein, vitamin A, vitamin D, vitamin B12, riboflavin

Risk reduction for

- Osteoporosis, hypertension, obesity, colon cancer, diabetes, metabolic syndrome

Exercise

- Walking reduces hip fracture risk
  - 4 hours per week reduced hip fracture by 41% in a study of 61,200 women
    JAMA 2002
- Activity of any type reduces fracture risk- Balance, Strength, Flexibility, Aerobic

Falling

- Medications, Alcohol
- Balance programs
- Strength training
- Safety at home
- Hip protectors
- Walking aids

Hip Protectors

Calcium 1200 mg

"Calcium has been singled out as a major health concern today because it is critically important to bone health and the average American consumes levels of calcium that are far below the amount recommended for optimal bone health."

Calcium 1200 mg

- Dietary
- Fortified foods
- Calcium citrate
  - Taken with or without food
- Calcium carbonate
  - Taken with food
- Divided doses

Vitamin D 800-2000 IU ?

"Vitamin D is important for good bone health because it aids in the absorption and utilization of calcium. There is a high prevalence of Vitamin D deficiency in nursing home residents, hospitalized patients, and adults with hip fractures."

…..and many others

Vitamin D

- Sufficiency > 32 ng/ml → **Comfort zone- 40s, 50s**
  - Many wellness relationships
- Insufficiency < 32 ng/ml
  - Disease states

New England Journal of Medicine July 19 2007
Medical Progress: Vitamin D Deficiency
M F Holick

800-1000 IU daily for patients 50 +

...although some elderly patients may require 2000 IU/day.....

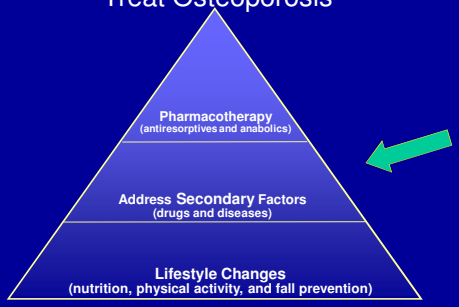
NOF Clinician's Guide 2008

Vitamin D

- Improves calcium absorption
- Direct action on building bone matrix
- Decreases FALLS
- Increases muscle mass and strength
- Etc etc.....

If you're fair skinned, 10 minutes in the midday sun—in shorts and a tank top with no sunscreen → 10000 IU Vit D

Leading the Effort to Help Prevent and Treat Osteoporosis



Pyramid for Osteoporosis Prevention and Treatment

What does this mean for your patients?

WHO Risk Factors

Age (50-90), gender and clinical risk factors:

- **BMI**
- **Prior fragility fracture**
- **Parental history of hip fracture**
- **Current tobacco smoking**
- **Ever long-term use of glucocorticoids**
- **Rheumatoid arthritis or other secondary causes**
- **Alcohol intake 3 or more units daily**

Kanis *Osteoporos Int* 2008;19:385-397

Recognizing Osteoporosis: Risk Factors

- Personal history of fracture after age 50
- Current low bone mass
- History of fracture in a primary relative
- Being female
- Being thin and/or having a small frame
- Advanced age
- A family history of osteoporosis
- Estrogen deficiency as a result of menopause, especially early or surgically induced
- Amenorrhea
- Anorexia nervosa
- Low lifetime calcium intake
- Vitamin D deficiency
- Use of certain medications, such as oral corticosteroids and anticonvulsants
- Presence of certain chronic medical conditions
- Low testosterone levels in men
- An inactive lifestyle
- Current cigarette smoking
- Excessive use of alcohol
- Being Caucasian or Asian

National Osteoporosis Foundation. *Fast Facts*. 2004. Available at: http://www.nof.org/osteoporosis/diseasefacts.htm.

Frailty Factor

Acute Medical Illnesses

Chronic Medical Illnesses

Sarcopenia

Falling

Medication Check

- Corticosteroids
- Anticonvulsants
- Aromatase inhibitors
- PPIs
- SSRIs
- DepoProvera
- Narcotics
- Cancer Chemo-Rx
- Lithium
- Thiazolidinediones

Check Lab Tests

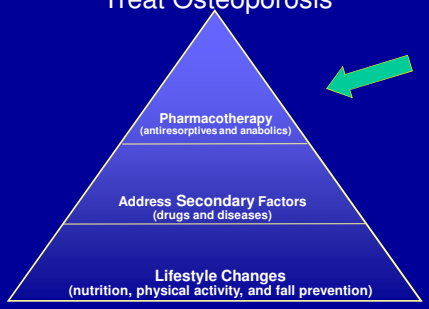
"Secondary Cause Work Up"

Blood count (CBC)
Chemistries (CMP)
- Calcium, Phosphorus
- Kidney tests
- Liver tests
- Alk Phos

Vitamin D (25hydroxyD)
Thyroid (TSH)
Parathyroid (intact PTH)

Malabsorption/Hypercalciuria (24 hr Urine Calcium)
Myeloma
Arthritis (ESR etc.)
Hormones (Testosterone)
Bone Turnover markers (NTX,CTX)

Leading the Effort to Help Prevent and Treat Osteoporosis



Pyramid for Osteoporosis Prevention and Treatment

What does this mean for your patients?

"Pharmacotherapy"

(Medications)

Two Primary Types of Pharmacotherapy for Osteoporosis

Antiresorptive Agents (reduce bone loss)

- Bisphosphonates
- Estrogen (HRT)
- Selective estrogen receptor modulators (SERMs)
- Calcitonin

Anabolic Agents (build bone)

- Synthetic parathyroid hormone

US Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General.* Rockville, MD: US Department of Health and Human Services, Office of the Surgeon General; 2004.

Anti-Resorptives (Anti-Catabolics)

- Bisphosphonates
- Estrogens
- SERMs
  - Raloxifene (Evista)
- Calcitonin
  - (Miacalcin, Fortical, Calcimar)

Biphosphonates
Alendronate
(Fosamax)

- Cuts fracture risk by ~50%

Formulations:

5mg, 10mg, 35mg, 70mg

Risedronate
(Actonel)

- Cuts fracture risk ~50%

Formulations:

5mg, 35mg, 35mg + 6 day calcium packet

Ibandronate
(Boniva)

- Cuts fracture risk ~50%

Formulations:

2.5mg, 150mg PO monthly

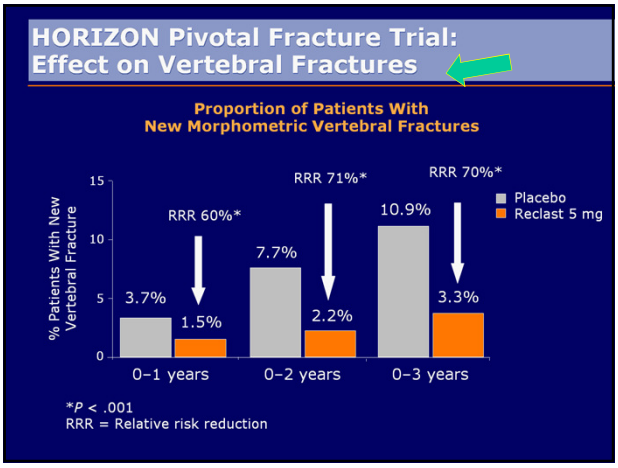
IV 3mg q 3 months

New Antiresorptive Therapies

Zoledronate (Reclast)-
5 mg IV annually

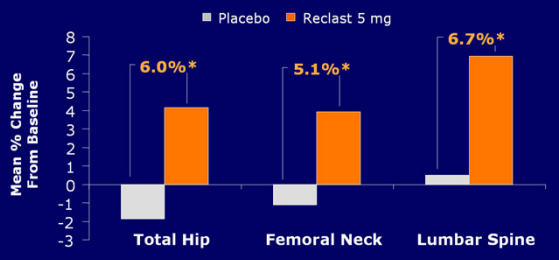
Zoledronate (Reclast)
5 mg IV annually

Will this change the way we view pharmacological treatment of osteoporosis? It has.



HORIZON Pivotal Fracture Trial: Effect on Bone Mineral Density (BMD)

- Reclast significantly increased BMD at the lumbar spine, total hip, and femoral neck, relative to placebo over 3 years



Values are least square mean difference, Reclast vs placebo
*P < .0001, P-value computed from 3-way ANOVA with treatment, stratum and region as explanatory variables.

Zoledronate (Reclast)
5 mg IV annually

- **Reduction**
  - **Spine & non spine fractures 35%**
  - **Mortality 28%**

Zoledronate (Reclast)
5 mg IV annually

Approved for Use in Men

Bisphosphonates

- Adverse events
  - GI - ulcers in the esophagus, acid reflux, and nausea
  - Flu-like "Acute Phase Reaction"
  - Bone pain
  - Hypocalcemia
  - Iritis/Uveitis
  - ONJ with IV

Current Thought

- 5 year plan
- 10 year plan

Anabolic Therapy

Action on the Osteoblast

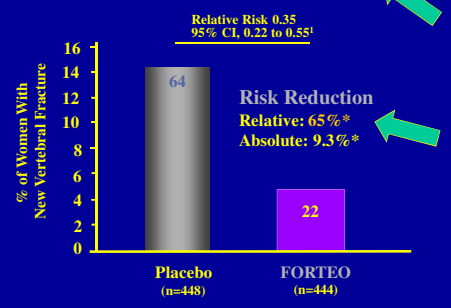
rather than the

Osteoclast

Forteo
Teriparitide (PTH 1-34)

- The only anabolic agent for osteoporosis
  - Acts on the osteoblast
  - Indications- severe osteoporosis,
  - Given for 12 - 24 months
  - Followed with an antiresorptive agent

FORTEO® (teriparatide [rDNA origin] injection) Reduces the Risk of ≥1 New Vertebral Fractures



1. *N Engl J Med.* 2001;344:1434-1441.

*p <.001

• See Black Box Warning (slide 32) and Important Safety Information for FORTEO (slides 1, 16, 34-36).
• Full Prescribing Information for FORTEO is available at this presentation.

Teriparatide

- Adverse events
  - Hypercalcemia 11% vs 1%
  - Dizziness 2.6% vs 1.4%
  - Leg cramps 2.6% vs 1.3%

SERM's

Hormone replacement therapy, once used widely for menopause symptoms, is an option for osteoporosis, but it's used less than other medications because of concerns about the risk of cancer, blood clots, heart disease, and stroke.

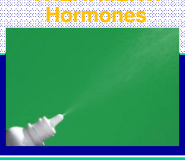
SERMs

- Oral selective estrogen receptor modulator(SERM) that has estrogenic actions on bone and anti-estrogenic actions on the uterus and breast.
- The SERMs are developed to reap the benefits of estrogen while avoiding the potential side effects of estrogen.
- Examples include Raloxifene (Evista).

SERMs C/I and AE

- C/I in women with active or past history of venous thromboembolic events, including DVT , pulmonary embolism, and retinal vein thrombosis
- AE: hot flashes and leg cramps.

TREATMENT: Hormones



- Calcitonin is a naturally occurring hormone in the body that slows bone loss.
- Two synthetic versions, Miacalcin and Fortical, are used against osteoporosis.
- Given as a nasal spray or injection, they can slow bone thinning in postmenopausal women and reduce risk of spine fractures.
- Side effects include a runny nose, headache, back pain, or nosebleed.
- The injection may cause flushing, nausea, allergic reactions, or skin rashes.
- **Forteo**, a synthetic parathyroid hormone, requires daily injections and actually builds new bone. Leg cramps and dizziness have been reported with Forteo use

FDA Indications for Osteoporosis

Drug	PMO		GIO (Women, Men)		Men
	Prevention	Treatment	Prevention	Treatment	
Estrogen	✓				
Alendronate PO (Fosamax®)	✓	✓		✓	✓
Risedronate PO (Actonel®)	✓	✓	✓	✓	✓
Ibandronate PO (Boniva®)	✓	✓			
Ibandronate IV (Boniva®)		✓			
Zoledronate IV (Reclast®)	✓	✓	✓	✓	✓
Calcitonin IN (Miacalcin®, Fortical®)		✓			
Raloxifene PO (Evista®)	✓	✓			
Teriparatide SC (Forteo®)		✓		✓	✓

BMD Response to Therapy

Medication	Spine	Hip
Estrogen	↑	↑
Alendronate (Fosamax®)	↑	↑
Risedronate (Actonel®)	↑	↑
Ibandronate (Boniva®)	↑	↑
Zoledronate (Reclast®)	↑	↑
Salmon Calcitonin (Miacalcin®, Fortical®)	-	-
Raloxifene (Evista®)	↑	↑
Teriparatide (Forteo®)	↑	↑

Fracture Risk Reduction in RCTs

Medication	Spine	Nonvertebral	Hip
Estrogen	↓	↓	↓
Alendronate (Fosamax®)	↓	↓	↓
Risedronate (Actonel®)	↓	↓	↓
Ibandronate (Boniva®)	↓		
Zoledronate (Reclast®)	↓	↓	↓
Calcitonin (Miacalcin®, Fortical®)	↓		
Raloxifene (Evista®)	↓		
Teriparatide (Forteo®)	↓	↓	

New and Emerging Treatments

Antiresorptive (anti-catabolic)
- Denosumab (Prolia)
- Odanacatib
- Lasofoxifene
- Bazedoxifene
- CE/bazedoxifene
- New delivery systems - oral salmon calcitonin

Osteo-anabolic (bone-forming)
- Sclerostin inhibitor
- Variations of PTH
- Endogenous PTH stimulation - calcium sensing receptor antagonist (calcilytic)
- New delivery systems – transdermal PTH

Strontium ranelate
Combinations of antiresorptive and anabolic

Denosumab (Prolia)

(Anti-resorptive agent)

- Approved June 1, 2010
- A fully human monoclonal antibody that binds with high affinity to, and inhibits the activity of, human RANK ligand, a key mediator of osteoclast activity

TREATMENT:
A Biologic Alternative

Given as an injection twice a year, it is for postmenopausal women at high risk for fractures who can't tolerate other osteoporosis drugs or who haven't been helped by other drugs.

Side effects include back pain, muscle pain, bone pain, a higher risk of infections, and lower calcium levels.

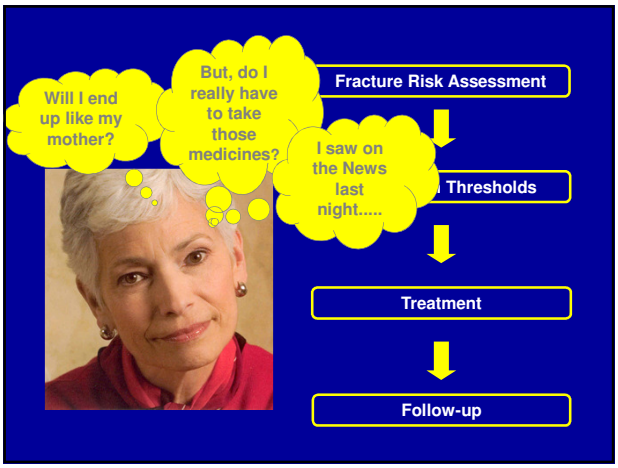
Clinical Challenges after Starting Treatment

- Motivating the patient to fill the prescription, take it correctly, regularly, for a length of time to benefit- Cost?
- Determining how, when, (or if) to follow and monitor the patient to assure that benefit is achieved
- Managing Nonresponders? Suboptimal Responders?
- Deciding when (if ever) to stop or change therapy
- Knowing when (if ever) to restart, if treatment is stopped- The Drug Holiday
- Managing side effects, perceived side effects, and fear of side effects

Conclusions

- **Exercise, ↓Fall Risk**
- **Nutrition**
- **No smoking, minimal drinking**
- **Calcium 1200 per day**
- **Vitamin D ~1200- 2000 per day**
- **Central bone density test - DXA & VFA**
- **Secondary Cause Review-Imaging & Lab workup**
- **Medications**

  Anti-resorptives, Anabolics


Will I end up like my mother?
But, do I really have to take those medicines?
I saw on the News last night.....
Fracture Risk Assessment
Thresholds
Treatment
Follow-up