Bone:

- Bone is a metabolically active organ
- Continuous change
- Physiologic function
- Structural function
Why Do Bones Break?
When load exceeds strength

Loads applied to the bone

Bone Strength

Applied Load

Bone Strength

FRACTURE?

Bouxsein, 2001
Main Determinants of Bone Strength

**Bone Mass**
- Bone remodeling
  - Bone matrix properties

**Bone Quality**
- Macroarchitecture
  - Degree of bone mineralization
- Microarchitecture
  - Type and organisation of collagen

**Bone Strength**
- Connectivity and thickness of trabeculae
  - Thickness and porosity of cortical bone
C cancellous and cortical bone

Cancellous
- Trabecular Number
- Trabecular Thickness
- Trabecular Separation
- Trabecular Connectivity

Cortical
- Thickness
- Porosity

Iliac crest biopsy

Lower photo courtesy D. Dempster
Osteoporosis Results in Changes in Cancellous Bone Mass and Architecture

Normal

Osteoporotic

Horizontal Disconnections

Courtesy of D. Dempster
Cortical Porosity and Age

Age (Yrs)

29

67

90

Zebaze et al. Lancet 2010;375 (9727):1729-1736
Strength:

- 7 %

if Cancellous Bone was Removed from Femoral Neck
Bone Structure: Intimate Relationship Between Mineral and Collagen

Landis et al, 1996
Mineral and Collagen Deficiencies

Courtesy of Dr. Papapoulos
BONE REMODELING IN ADULTHOOD

Systemic hormones → Mechanical stimuli

Bone cells and cells in marrow → Local cytokines and growth factors

Osteoblasts → Bone formation

Osteocytes → Bone resorption
Trabecular Perforation: May Decrease Cancellous Bone Strength

Dempster and Lindsay, 1993
How Increased Remodeling Can Predispose to Bone Fragility

Parfitt AM, 1991
Definition: Osteoporosis

A systemic skeletal disease characterised by:

– Low bone mass
– Micro architectural deterioration of bone tissue
– Increased bone fragility
– Susceptibility to fracture
Osteoporotic bone
Clinical picture of osteoporosis

- Asymptomatic
- Low trauma fractures
- Stress fracture
- Wrist fracture
- Vertebral fracture
- Hip fracture
Osteoporosis:
Common Fracture Sites

- Spine
- Hip
- Wrist

Courtesy of J A Kanis
Osteoporosis – Clinical view

[Image of an elderly person and a spine X-ray]
# Estimated lifetime fracture risk (at 50 years-old)

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>17.5 (16.8-18.2)</td>
<td>6.0 (5.6-6.5)</td>
</tr>
<tr>
<td>Vertebra</td>
<td>15.6 (14.8-16.3)</td>
<td>5.0 (4.6-5.4)</td>
</tr>
<tr>
<td>Forearm</td>
<td>16.0 (15.7-16.7)</td>
<td>2.5 (2.2-3.1)</td>
</tr>
<tr>
<td>Any of the above</td>
<td>39.7 (38.7-40.6)</td>
<td>13.1 (12.4-13.7)</td>
</tr>
</tbody>
</table>

*breast cancer: 9%  cardiovascular disease: 40%*

Melton 1991
Lifetime Fracture Risk: a 50 Year Old White Woman

- Hip Fracture
- Wrist Fracture
- Spine Fracture
- Any Fracture

Cummings et al. Arch Intern Med 1989; 149: 2445-

Meunier et al. Clin Ther 1999; 21: 1025-
Consequences of Osteoporosis

◆ Increased morbidity
  • acute pain and temporary disability
  • deformity, permanent disability, lower quality of life

◆ Increased mortality
  ◆ Following hip and vertebral fracture

Mortality Following Hip and Vertebral Fractures

Hip Fracture Outcomes

- 24% mortality rate within first year*
- 30% mortality rate in men after first year
- 50% of patients are unable to walk without assistance†
- ~33% are totally dependent‡
- Up to 95% of women with recent hip or wrist fracture were not being treated with anti-osteoporotic regimens§

†Riggs BL, Melton LJ III. Bone. 1995;17(5 suppl):505S-511S.
Vertebral Fractures:
Can Result in Physiological Changes
Prevalent Fractures and Future Fracture Risk

Black et. al, 1999
Public Health Issues - Osteoporosis in US

- In 1995, osteoporosis caused:
  - 3 million fractures
  - 100,000 deaths
  - 432,000 hospitalizations
  - 2.5 million outpatient visits
  - 180,000 nursing home admissions
  - $13.8 billion in direct healthcare expenditures
    - approximately 40% of cost due to non-hip fractures

Ray, NF et al., JBMR 1997
Why do we get osteoporosis:
Lifetime changes in bone mass

- Peak bone mass
- Age-related bone loss
- Menopausal bone loss
Factors affecting peak bone mass

Genetic

Nutritional → Bone mass → Hormonal

General health
Development of osteoporosis: Peak bone mass vs. rate of bone loss
Risk factors for osteoporosis

- Age
- Caucasian or Asian
- Previous fragility fracture
- Positive family history
- Early/surgical menopause/Estrogen deficiency/ hypogonadism in men
- Low body mass index (<19 kg/m²)
Lifestyle factors

- Diet:
  - Low calcium
  - High protein
  - Chronic high sodium
- Caffeine
- Phosphate beverages
- Smoking
- Alcohol
- Physical activity
Secondary causes of osteoporosis

- Drugs
  - Corticosteroids, Thyroxine
- Endocrine diseases
- Gastric surgery
- Multiple myeloma
- Hypopituitarism
- Inflammatory diseases
- Hypogonadism
Evaluation of osteoporosis:

• It’s all about risk
Osteoporosis: Diagnosis

- Bone density is the most important predictor of fracture risk
- Central dual-energy x-ray absorptiometry (DEXA) is the gold standard for diagnosis
## Bone Mineral Density

<table>
<thead>
<tr>
<th>Category</th>
<th>T - score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; -1.0</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>-1 to -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>&lt;=-2.5</td>
</tr>
<tr>
<td>Severe/established osteoporosis</td>
<td>&lt;=-2.5 and presence of one or more fractures</td>
</tr>
</tbody>
</table>

Note: An osteopenic patient may present with an osteoporotic fracture; the patient is then considered osteoporotic and treated as such.

Role of BMD in Fracture Prevention:

• 60%–80% of bone strength is related to BMD
  ▪ Decreases in bone density correspond to increases in fracture risk
  ▪ Increases in bone density correspond to fracture risk reduction
Who do we send for BMD testing?

- Risk factors for osteoporosis
- Use of any drugs that can affect bone
- Any illness that affects bone
- Low trauma fracture
- Radiographic osteopaenia
Evaluation of Osteoporosis

- Evaluate risk factors
- Evaluate for secondary causes
  - Full blood count, ESR
  - Liver functions, protein electrophoresis
  - Ca, Phosphate, parathyroid hormone, 25(OH) Vitamin D
  - Urine for Ca
  - Thyroid functions
  - Gonadal hormones
  - Markers of bone turnover
Bone markers:

• Bone formation:
  – Bone Specific ALP
  – Osteocalcin

• Bone resorption products
  – Pyridium crosslinks: Deoxypiridinoline
  – NTX
  – CTX
How do we decide on whether to treat:
FRAX™ WHO Fracture Risk Assessment Tool

Calculation Tool

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

Country: UK
Name: ID:

**Questionnaire:**

- Age (between 40-90 years) or Date of birth
  - Age: [ ]
  - Date of birth: [ ]
- Sex
  - Male [ ]
  - Female [ ]
- Weight (kg)
  - [ ]
- Height (cm)
  - [ ]
- Previous fracture
  - No [ ]
  - Yes [ ]
- Previous fracture at hip
  - No [ ]
  - Yes [ ]
- Current smoking
  - No [ ]
  - Yes [ ]
- Alcohol intake
  - No [ ]
  - Yes [ ]
- Personal history of BMD
  - Select [ ]

**Risk Factors:**

- Secondary osteoporosis [ ]
- Alcohol intake [ ]
- Previous fracture at hip [ ]
- Current smoking [ ]
- Personal history of BMD [ ]

**FRAX Result:**

- Ten year probability of fracture (%)
  - [ ]
  - [ ]

**Without BMD:**

- Major osteoporosis [ ]
- Hip fracture [ ]

**FRAX Result:**

- Ten year probability of fracture (%)
  - [ ]
  - [ ]

**Fig. 1** Input and output for the FRAX™ model

---

Significance for hip fracture probability, with a family history of fracture there was a fourfold increase in fracture probability.
Treatment modalities

• Adequate nutrition
• Regular physical activity
• Avoid unhealthy lifestyle
• Pharmacologic treatment
Pharmocologic treatment

• Improving bone strength
Osteoporosis: Treatment targets

Bone Resorption

Keep bone remodeling active to remodel bone

Bone Formation
Treatment of osteoporosis

- Calcium and vitamin D
- Anti-resorptive
  - HRT
  - Raloxifene
  - Bisphosphonates
  - Strontium
- Anabolic agents
  - PTH
  - Strontium
Calcium in osteoporosis

• Help achieve better peak bone mass
• To maintain bone mass
• Prevent age related bone mass loss
Vitamin D
Vitamin D supplementation

- Normal diet 200IU/day
- Minimal non-toxic dose 2000IU/day
- Day in the sun 10000 IU/day
HRT: Benefits

- Improvement or maintenance in bone mass
- Relief of vasomotor symptoms
- Risk reduction of cardiovascular disease?
- Potential benefits for:
  - Alzheimer’s disease
  - Age-related macular degeneration
  - Colon cancer
HRT: Effect on BMD Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial

CEE, conjugated equine estrogen; continuous administration (daily throughout the month); cyclic administration (days 1–12 of each month); MPA, medroxyprogesterone acetate; and MP, micronized progesterone.

HRT: Effect on Fracture Reduction

Vertebral Fractures

- 12/34

42% Risk Reduction

- No prospective data studying hip fracture risk reduction with HRT

- Thought to be reduced by 50%, based on epidemiological data

Hip Fractures

- 7/34

When analyzed using the numbers of fractures method, a 61% risk reduction was observed ($P = 0.04$)

Placebo

HRT
4 Years of HRT Had No Effect on the Risk of Non-spine Fractures

<table>
<thead>
<tr>
<th>Type</th>
<th>E + P</th>
<th>Placebo</th>
<th>RH</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>12</td>
<td>11</td>
<td>1.1</td>
<td>.82</td>
</tr>
<tr>
<td>Any</td>
<td>130</td>
<td>138</td>
<td>1.0</td>
<td>.70</td>
</tr>
</tbody>
</table>

Hulley et al. HERS Study. JAMA. 1998; 280(7); August 19, 1998.
Hormone replacement therapy

Clinical Synthesis Panel on HRT
Lancet 1999:354;152-155

• Few prospective controlled trials
• Lowest dose that adequately prevents fracture unknown
• Long term use necessary to reduce fractures
Selective Estrogen Receptor Modulators (SERMs)

TAMOXIFEN (Nolvadex)
RALOXIFENE (Evista)
Raloxifene: Effect on BMD and Bone Turnover (MORE)

![Graphs showing the effect of Raloxifene on BMD and Bone Turnover](graphs)

**Lumbar Spine BMD**
- Median Percent Decrease
- 0% at 36 Months
- 60 mg N=2259
- Placebo N=2292

**Femoral Neck BMD**
- Mean Percent Change in BMD
- 1% at 36 Months

**CTx**
- Median Percent Decrease
- Placebo
- RLX 60 mg

Raloxifene: Benefits and Risks

Benefits
• Improved bone mass
• Reduced number of vertebral fractures
• No breast tenderness
• No uterine bleeding or spotting
• Potential for reduced risk of breast cancer

Risks
• Hot flashes
• Leg cramps
• Deep vein thrombosis and pulmonary embolism
Nasal Calcitonin: Effect on BMD and Bone Turnover (PROOF)

- Mean age 68
- N = 1255

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Change in Lumbar Spine BMD from Baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.5</td>
</tr>
<tr>
<td>100 IU</td>
<td>1.0</td>
</tr>
<tr>
<td>200 IU</td>
<td>1.2</td>
</tr>
<tr>
<td>400 IU</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Bisphosphonate treatment

• Most of these agents are very effective for treating patients with osteoporosis
  – Vertebral fracture by 60-70%
  – Multiple vertebral fractures by 75-96%
  – Hip fracture by 40-50%
  – Non-vertebral fracture by 20-35%

• In general are well tolerated

• In clinical trials, have been very safe
Bone Remodeling and Mechanism of Action

Remodeling completed

Resting stage

Initiation

Resorption

Osteoclast (~ 2-week process)

Reversal phase

Formation

Osteoblasts

Loss of ruffled border

Apoptosis

FOSAMAX™

Osteoclast

Ruffled border

Bisphosphonates: Benefits and Risks

Benefits
- Fracture reduction
- BMD increase
- Non-hormonal

Risks
- Nausea
- Upper gastrointestinal irritation
- Myalgias and arthralgias
Negative effects of bisphosphonates

- Oesophageal irritation
- Muscle and bone pain
- Atrial fibrillation
- Long term skeletal safety
Atypical femoral fracture

- Link to bisphosphonates:
  - Bone suppression with bisphosphonates
- Minor and major features
- Starts as unicortical fracture
- Associated with prolonged use of bisphosphonates
Osteonecrosis of the jaw

- ? Predilection for the jaw
  - Mechanical stress
  - High bone turnover
  - Related to infection with actinomyces
    - Forms a biofilm in mouth
  - Jaw bone formed by intramembranous ossification
Do we stop the bisphosphonates after 5 years?
Bone forming agents:

• Selectively increase population and/or activity of the osteoblasts
• Induce a positive bone tissue balance.
Parathyroid hormone:

• Intermittent injections of 1-34 PTH
• Increases the amount of bone matrix
• Restores connectivity of cancellous bone
• Increases cortical thickness
• This is associated with a decrease in the degree of mineralization
Effect of PTH on the Risk of New Vertebral Fractures

\[ \text{RR } 0.31^* \]
\[ \text{RR } 0.35^\dagger \]

*95% CI, 0.19-0.50  †95% CI, 0.22-0.55

NOFSA GUIDELINES ON PTH USE

NOFSA has provided the following guidelines for the use of teriparatide:

• Severe established osteoporosis as defined by low BMD and at least 2 prevalent fractures

• Failed anti-resorptive treatment as defined by an incident fragility fracture while compliant to anti-resorptive treatment for at least 12 months or unacceptable loss of BMD on two occasions while on treatment

• Duration of therapy is presently limited to 18 months and should be followed by maintenance therapy with an anti-resorptive drug
Other anabolic agents

• Strontium ranelate
  – Antiresorptive effect with stimulation of osteoblastic activity

• An uncoupling of bone remodeling resulting in a bone anabolic effect
STRONTIUM RANELATE IMPROVES TRABECULAR & CORTICAL MICROARCHITECTURE

**Strontium Ranelate 36 Mo**

- Cortical Thickness: + 18%

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>BPHs</th>
<th>Strontium ranelate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural Model Index</td>
<td>NA (AL) NS (RIS)</td>
<td>- 22%</td>
</tr>
<tr>
<td>Trabecular separation</td>
<td>NS</td>
<td>- 16%</td>
</tr>
<tr>
<td>Cortical Thickness</td>
<td>NS</td>
<td>+ 18%</td>
</tr>
</tbody>
</table>

Strontium ranelate efficacy over 5 years

Vertebral fractures

Non-vertebral fractures

Patients (%)

0-5 years

Vertebral fractures

Non-vertebral fractures

Patients (%)

0-5 years

**Strontium ranelate efficacy over 5 years**

- **Vertebral fractures**
  - **RR:** -24%
  - **P**<0.001

- **Non-vertebral fractures**
  - **RR:** -15%
  - **P**<0.05


*P<0.05, ***P<0.001*
How we need to look at osteoporosis treatment outcomes

10-year fracture probability (FRAX)

Efficacy against fractures
Strontium ranelate is effective whatever the 10-year fracture probability (FRAX).

Efficacy (Hazard ratio)

Kanis JA, et al. Osteoporos Int. 2011 (epub)
Emerging therapies for osteoporosis: Anti-resorptives

• Present therapies:
  – RANKL inhibition
    • Denosumab: 6 monthly injection

• New targets for antiresorptives:
  – Cathepsin K inhibition
    • Odanacatib
New anabolic agents for bone:

• PTH
  – Shortening of molecule
  – Stimulation of PTH secretion (didn’t work)
• The Wnt signaling pathway
Looking for targets in rare diseases

- Sclerosteosis
- Hyperostosis corticalis
Sclerostin:

– Protein produced by osteocytes
– Produced in late stages of mineralisation
– Inhibits bone formation
– Bone loading decreases sclerostin
– Absent in sclerostosis and hyperostosis corticalis
– Target for medication:
  • Antibody to sclerostin
Sclerosteosis and Van Buchem Disease

- Associated with absence/reduced production of sclerostin
- Autosomal recessive disorders
- Characterized by endosteal hyperostosis
- Resistance to fracture
- Excessive height and syndactyly (sclerosteosis)

Courtesy of Wim van Hul