Aging and Osteopenia

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Epidemiology of Osteoporotic Fractures

• 1.5 million fractures in US annually

• 44 million individuals in US at risk for fracture
  – Treatable hypertension: 30 -50 million
  – High cholesterol: 40 million

• At age 50, a woman’s lifetime risk of fracture exceeds combined risk of breast, ovarian & uterine cancer
  – 1/3 women will have a fracture

• At age 50, a man’s lifetime risk of fracture exceeds risk of prostate cancer
  – 1/5 men will have a fracture

Surgeon General’s Report on Bone Health, 14 October 2004
Osteoporosis in Men, International Osteoporosis Foundation, Oct 2004
Hip fractures are associated with increased morbidity and mortality

One year after a hip fracture:
- Death within one year: 20%
- Permanent disability: 30%
- Unable to walk independently: 40%
- No longer able to live independently: 50%

• Direct costs: > $10 billion / yr
  - Cost of hip fracture > $80,000 per person

Overall incidence of fractures

Annual incidence (rate/1000)

Johansen et al, 1997

5-year Risk of Fracture: Role of Age and Sex

<table>
<thead>
<tr>
<th>Age Group, yr</th>
<th>35-39</th>
<th>≥ 85</th>
</tr>
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<tbody>
<tr>
<td>Hip BMD T-score (SD)</td>
<td>-3</td>
<td>0</td>
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Men

Women

Kanis et al, 2004

Age and BMD Are Independent Risk Factors for Hip Fracture

> 5-fold increase in fracture probability from age 50 to 80

Cooper C et al. J Bone Miner Res 1992

Kanis et al, 2004
BMD explains > 70% of whole bone strength in ex vivo human cadaver studies

Roberts et al, IBMS 2009

Femoral Neck BMD (g/cm²) vs. Femoral Strength (N)

$r^2 = 0.71$

Vertebral body (L2) (compression + forward flexion)

Proximal Femur (sideways fall)

Bouxsein © 1999

Moro et al, CTI, 1995

Does not distinguish several attributes of whole bone strength

- 3D geometry
- Microarchitecture
- Intrinsic properties of bone matrix

Bone Strength

MORPHOLOGY
size & shape microarchitecture

MATRIX PROPERTIES
mineralization collagen traits etc...

BONE REMODELING
formation / resorption

OSTEOPOROSIS DRUGS

Bouxsein, Best Practice in Clin Rheum, 2005
**BONE MODELING** – process that shapes bones as we grow & develop – BUT also occurs at low rate throughout life; resorption and formation are uncoupled and they occur on different surfaces (KIDS >> adults)

**BONE REMODELING** – process of coupling between resorption and formation that maintains bone mass in adult life; takes place in BMU

**WHAT PURPOSE DOES BONE REMODELING SERVE?**

- Allows skeleton to respond to mechanical loading
- Prevents accumulation of micro-damage in bone (quality control on material properties of bone)
- Releases minerals (Ca, phosphate) & growth factors stored in matrix into circulation

*Imbalances in remodeling – underlie pathogenesis of age-related, menopausal, and most forms of pathologic bone loss – both local and systemic*

Most treatments target remodeling – but some may have ++ effects on modeling – and that would be more effective strategy
Advancing age is associated with a negative BMU.
Trabecular and Cortical Bone Loss with Age

Age-Related Changes in vBMD and Geometry by 3D-QCT
(368 women, 320 men, aged 20-97 yrs; Riggs et al JBMR 2004)

<table>
<thead>
<tr>
<th>% Change, ages 20-90 yrs</th>
<th>Women</th>
<th>Men</th>
<th>F vs M (P-value)</th>
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<tr>
<td>Lumbar spine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total area</td>
<td>+14**</td>
<td>+15**</td>
<td>0.253</td>
</tr>
<tr>
<td>Trabecular vBMD</td>
<td>- 54**</td>
<td>- 47**</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cortical vBMD</td>
<td></td>
<td></td>
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For age regressions: *P<0.05, **P<0.005
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<td><strong>Femoral neck</strong></td>
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<td></td>
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<tr>
<td>Total area</td>
<td>+13**</td>
<td>+7*</td>
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### Age-Related Changes in Trabecular Microarchitecture

Decline in bone mass and deterioration of trabecular bone structure both contribute to decreased bone strength.
Effects of Sex and Age on Trabecular Microstructure (Ultradistal Radius)

Khosla et al, JBMR (2006)
Microarchitectural changes that influence bone strength

Force required to cause a slender column to buckle:

- Directly proportional to
  - Column material
  - Cross-sectional geometry
- Inversely proportional to
  - (Length of column)$^2$

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Theoretical effect of cross-struts on buckling strength

$$\text{Buckling Strength proportional to } (\text{Strut Length})^2$$

<table>
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<tr>
<th># Horizontal Trabeculae</th>
<th>Effective Length</th>
<th>Buckling Strength</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>L</td>
<td>S</td>
</tr>
<tr>
<td>1</td>
<td>1/2 L</td>
<td>4 x S</td>
</tr>
</tbody>
</table>

Mosekilde, Bone, 1988
Excessive Bone Resorption Weakens Trabecular Architecture

Effect of Density Reduction on Strength: Change in Trabecular Thickness vs. Number

Residual Strength (%)

Silva and Gibson, Bone, 1997

L. Mosekilde, 1998
Trabecular and Cortical Bone Loss with Age

Differences between Men and Women in Periosteal Apposition and Bone Loss during Aging

Riggs et al. JBMR 2004

Distribution of Mass Affects Mechanical Behavior

Effect of cross-sectional geometry on long bone strength

Moment of Inertia proportional to $d^4$

aBMD (by DXA) =

Compressive Strength = $\uparrow$

Bending Strength = $\uparrow\uparrow$
hr-pQCT shows increased cortical porosity in postmenopausal women

- Cortical porosity 2 to 4-fold higher in postmenopausal vs premenopausal women

Nishiyama et al, JBMR 2010
Burghardt et al, JBMR 2010
Greater cortical porosity with older age independent of areal BMD

Nicks et al. JBMR 2012
Age and cortical bone loss


Ultradistal Radius

Bala et al. JBMR 2014
Cortical Porosity (3 levels) and Age

Porosity of compact cortex associated with prevalent fracture

Bala et al. JBMR 2014
Fracture costs: vertebral and non-vertebral sites

Cortical Bone

- Longitudinal studies in progress to determine if cortical microarchitecture will predict incident fracture

- Potential new target for therapies
Bone Strength

MORPHLOGY
size & shape
microarchitecture

MATERIAL
tissue composition
matrix properties

BONE REMODELING
formation / resorption

How is mineralization density influenced by rate of bone turnover?

- Slow process of $2^\circ$ mineralization
- Decreased bone turnover allows mineralization to proceed

<table>
<thead>
<tr>
<th>Time</th>
<th>Degree of Mineralization (%)</th>
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<tr>
<td>0</td>
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</tr>
<tr>
<td>3 months</td>
<td>Primary mineralization</td>
</tr>
<tr>
<td>1 year</td>
<td>Secondary mineralization</td>
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Graph showing the progression of mineralization over time.
Increased bone turnover with estrogen deficiency decreases mineralization density

Meunier and Boivin, Bone, 1997

Relationship between mineralization and biomechanical properties

- High (osteopetrosis)
- Normal
- Low (osteomalacia)

Load vs. Displacement

- Stiffness
- Strength
- Toughness
What do these changes in mineralization mean in terms of the bone strength?

- Independent of the quantity of bone -

**Strength of bone material** is related to mineralization in a non-linear fashion

Anti-resorptive therapies ↑ mineralization by 3 - 11%
((Roschger et al, 2001; Boivin et al 2003, Borah et al 2006))

↑ strength of trabecular bone by 13 - 20%

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**Bone remodeling & microdamage**

What is “damage”?

- Repetitive loading
- No repair process
- ↓ Mechanical properties
Microdamage in Bone

- Associated with decreased cortical bone strength
- Microcracks seen in human femur & vertebra, increase with age
- Signal for remodeling & repair
  - in animals, microdamage increases when remodeling is suppressed
- No demonstrated relationship with fracture risk


Age-related changes in bone properties that lead to decreased bone strength

- Decreased bone mass and BMD
- Altered geometry
- Altered architecture
  - Cortical thinning
  - Cortical porosity
  - Trabecular deterioration
- Altered matrix properties

Human femoral neck
Fazzalari et al, Bone, 1998

Images from L. Mosekilde, Technology and Health Care. 1998
Whole bone strength declines dramatically with age

Femoral Neck (sideways fall)

Lumbar Vertebrae (compression)

Whole Bone Strength (Newtons)

young

old

BONE REMODELING – process of coupling between resorption and formation that maintains bone mass in adult life; takes place in BMU

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0 2000 4000 6000 8000 10000

0 2000 4000 6000 8000 10000

young

old


Baron and Hesse, JCEM, 2012
Osteocytes

- Comprise 90-95% of cells in bone
  - Most abundant cell type in bone
  - Can live for decades
- Orchestrate bone remodeling
  - Regulate BOTH osteoclast & osteoblast activities
Serum sclerostin levels and age

Modder et al. 2011

Mechanisms of age-related changes in bone

Summary: Aging and Skeletal Fragility

- Bone loss due to net decrease in bone formation
- Reduced trabecular numbers
- Increased cortical porosity
- Aging of stem cells, osteoblasts and osteocytes
- New therapeutic targets