Pathogenesis of Fragility Fractures: A Biomechanical View

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Outline

• Pathogenesis of fractures and determinants of bone strength

• Age-related changes that contribute to skeletal fragility

• Interaction between skeletal loading and bone strength

• Non-invasive assessment of bone strength
Design of a structure

- Consider what loads it must sustain
- Design options to achieve desired function
  - Overall geometry
  - Building materials
  - Architectural details
Determinants of whole bone strength

- **Geometry**
  - Gross morphology (size & shape)
  - Microarchitecture

- **Properties of Bone Material / Bone Matrix**
  - Mineralization
  - Collagen characteristics
  - Microdamage
Hierarchical nature of bone structure

Macrostructure

Microstructure

Matrix Properties

Cellular Composition and Activity

Seeman & Delmas
Biomechanical approach to fractures

- Fall traits
  - Protective responses
  - Bending, lifting
- Loads applied to the bone
- Bone strength
- Bone Mass
  - Geometry
  - Material properties

Factor of risk: \[ \frac{\text{Applied load}}{\text{Bone strength}} > 1 \Rightarrow \text{fracture} \]

Pathogenesis of fragility fractures

Age-related changes that contribute to fragility fractures:

1) Decreased bone strength

2) Increased propensity to fall
Assessing bone biomechanical properties

- Structural Properties
- Material Properties

Force vs. Deformation graph
Biomechanical testing

Key properties

- Displacement
- Force
- Failure load
- Stiffness
- Energy absorbed
Review of the relevant material & geometric properties vs loading mode

Material:
- Elastic modulus
- Ultimate strength

Elastic modulus:
- $E \propto (\text{density})^a$

Ultimate strength:
- $S \propto (\text{density})^b$

Cross-section area, $A \propto r^2$
- Axial rigidity, $E \cdot A$

Moment of inertia, $I \propto r^4$
- Section modulus, $Z \propto r^3$
- Bending rigidity, $E \cdot I$
Effect of cross-sectional geometry on long bone strength

aBMD (by DXA) = = ↓
Compressive strength = ↑ ↑
Bending strength = ↑↑ ↑↑↑

Bouxsein, Osteoporos Int, 2001
Bone strength

SIZE & SHAPE
- macroarchitecture
- microarchitecture

MATERIAL
- tissue composition
- matrix properties

BONE REMODELING
- formation / resorption

OSTEOPOROSIS DRUGS

Bouxsein. Best Practice Res Clin Rheumatol, 2005; 19:897-911
Outline

• Determinants of bone strength

• Age-related changes that contribute to skeletal fragility
### Age-related changes in mechanical properties of bone tissue

<table>
<thead>
<tr>
<th>Bone Type</th>
<th>Elastic modulus, E</th>
<th>Ultimate strength, S</th>
<th>Toughness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortical bone</strong></td>
<td>-8%</td>
<td>-11%</td>
<td>-34%</td>
</tr>
<tr>
<td><strong>Cancellous bone</strong></td>
<td>-64%</td>
<td>-68%</td>
<td>-70%</td>
</tr>
</tbody>
</table>

% loss 30-80 yrs

Whole bone strength declines dramatically with age

Femoral neck (sideways fall)

Lumbar vertebrae (compression)

Age-related changes in geometry
Adaptation to maintain whole bone strength

Age-related changes in femoral neck vBMD, geometry, and strength indices

<table>
<thead>
<tr>
<th>% Change, ages 20-90 yrs</th>
<th>Women</th>
<th>Men (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trabecular vBMD</strong></td>
<td>- 56**</td>
<td>- 45** &lt;0.001</td>
</tr>
<tr>
<td><strong>Cortical vBMD</strong></td>
<td>- 24**</td>
<td>- 13** &lt;0.001</td>
</tr>
<tr>
<td><strong>Total area</strong></td>
<td>13**</td>
<td>7* ns</td>
</tr>
<tr>
<td><strong>MOI\text{ap}</strong></td>
<td>- 1</td>
<td>- 21** ns</td>
</tr>
<tr>
<td><strong>Axial rigidity</strong></td>
<td>- 39**</td>
<td>- 31** ns</td>
</tr>
<tr>
<td><strong>Bending rigidity</strong></td>
<td>- 25**</td>
<td>- 24** ns</td>
</tr>
</tbody>
</table>

For age regressions: *P<0.05, **P<0.005

368 women, 320 men, aged 20-97

Riggs et al. J Bone Miner Res. 2004; 19:1945-54
Riggs et al. J Bone Miner Res. 2006; 21(2):315-23
Age-related changes in trabecular microarchitecture

- Decreased bone volume, trabecular thickness and number
- Decreased connectivity
- Decreased mechanical strength

Image courtesy of David Dempster
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
  - $(\text{Length of column})^2$

www.du.edu/~jcalvert/tech/machines/buckling.htm
Theoretical effect of cross-struts on buckling strength

<table>
<thead>
<tr>
<th># Horizontal Trabeculae</th>
<th>Effective Length</th>
<th>Buckling Strength</th>
</tr>
</thead>
<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>

Bouxsein. Best Practice Res Clin Rheumatol, 2005; 19:897-911
Cortical porosity increases with age
(41 iliac biopsies, age 19-90)

4-fold increase in cortical porosity from age 20 to 80

Increased heterogeneity with age

Brockstedt et al. Bone 1993; 14:681-91
Age-related changes in femoral neck cortex and association with hip fracture

Those with hip fractures have:

- Preferential thinning of the inferior anterior cortex
- Increased cortical porosity

Mayhew et al, Lancet 2005

20-year-old  80-year-old

Jordan et al. Bone, 2000; 6:305-13
Age-related changes in bone properties associated with fracture risk

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

Images from L. Mosekilde, Technology and Health Care. 1998
Outline

• Determinants of bone strength

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Etiology of age-related fractures

- Loads applied to the bone
- Bone strength

FRACTURE?
The factor of risk concept

$$\Phi = \frac{\text{Applied load}}{\text{Bone strength}}$$

- $\Phi > 1$, Frx
- $\Phi < 1$, no Frx

- Identify activities associated with fracture
- Use biomechanical models to determine loads applied to bone for those activities
- Estimate bone failure load for those activities

Falls and hip fracture

• Over 90% of hip fx’s associated with a fall

• Less than 2% of falls result in hip fracture

• Fall is necessary but not sufficient condition

• Sideways falls are most dangerous

• What factors dominate fracture risk?
### Independent risk factors for hip fracture

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall to side</td>
<td>5.7 (2.3 - 14)</td>
</tr>
<tr>
<td>Femoral BMD</td>
<td>2.7 (1.6 - 4.6)*</td>
</tr>
<tr>
<td>Fall energy</td>
<td>2.8 (1.5 - 5.2)**</td>
</tr>
<tr>
<td>Body mass index</td>
<td>2.2 (1.2 - 3.8)*</td>
</tr>
</tbody>
</table>

* calculated for a *decrease* of 1 SD  
** calculated for an *increase* of 1 SD

Greenspan et al, JAMA, 1994; 271(2):128-33
Estimating loads applied to the hip during a sideways fall

- Human cadavers
- Human volunteers
- Crash dummy
- Mathematical models and simulations

Peak impact forces applied to greater trochanter:
270 - 730 kg (2400 - 6400 N)
(for 5th to 95th percentile woman)

Robinovitch et al. 1991; Biomech Eng. 1991; 113:366-74
van den Kroonenberg et al J Biomech. 1996; 29:807-11
Femur is strongest in habitual loading conditions

Femur is strongest in habitual loading conditions

\[ \Phi = \frac{\text{Applied load}}{\text{Failure load}} \]

Thus, \( \Phi > 1 \) for sideways fall in elderly persons

Vertebral fractures

• Difficult to study
  – Definition is controversial
  – Many do not come to clinical attention
  – Slow vs. acute onset
  – The event that causes the fracture is often unknown

• Poor understanding of the relationship between spinal loading and vertebral fragility
Estimating loads on the lumbar spine

Schultz et al. 1991; Spine. 1991; 16:1211-6
Wilson et al. 1994; Radiology. 1994; 193:419-22
Factor of risk for vertebral fracture (L2)
Bending forwards 90° with 10 kg weight in hands

Men

Women

11.9%
30.1%

+28% over life**
+92% over life** †

** P<0.005 for age-regressions
† p<0.01 for comparison of age-related change in M and W

Proportion of individuals with $\Phi \geq 1$, per decade

(Bending forwards 90° lifting 10 kg weight)

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Clinical assessment of bone strength by DXA

• Areal BMD by DXA
  – Bone mineral / projected area (g/cm²)

• Reflects (indirectly)
  – Geometry / Mass / Size
  – Mineralization

• Moderate to strong correlation with whole bone strength at spine, radius & femur
  \((r^2 = 50 - 90\%\))

• Strong predictor of fracture risk

• Does not distinguish
  – Specific attributes of 3D geometry
  – Cortical vs cancellous density
  – Trabecular architecture
  – Intrinsic properties of bone matrix

Bouxsein et al, 1999
Estimating hip geometry from 2D DXA

"Hip Strength Analysis"

Estimate femoral geometry and strength indices

- Use 2D image data to derive 3D geometry
- Requires assumptions that have not been tested for all populations and treatments

Beck et al. 1999, 2001
QCT assessment of bone density and geometry

Images courtesy of Dr. Thomas Lang, UCSF
Multi-detector computed tomography

Non-Fx
62 yr

Fx
62 yr

Potential to show trabecular architecture…
Higher resolution, but higher radiation dose

Ito et al. J Bone Miner Res. 2005; 20:1828-36
Trabecular architecture in vivo with high resolution pQCT

~ 80 µm³ voxel size

~ 3 min scan time, < 4 µSv

Distal radius and tibia only

Reproducibility:
  density: 0.7 - 1.5% *
  µ-architecture: 1.5 - 4.4% *

* Boutroy et al. J Clin Endocrinol Metab. 2005; 90:6508-15
Premenopausal Osteopaenia

Postmenopausal Osteoporosis

Postmenopausal Severe Osteoporosis

Boutroy et al. J Clin Endocrinol Metab. 2005; 90:6508-15
Discrimination of osteopaenic women with and without history of fracture by HR-pQCT
(age = 69 yrs, n=35 with prev frx, n=78 without fracture)

* p < 0.05 vs fracture free controls

Boutroy et al. J Clin Endocrinol Metab. 2005; 90:6508-15
MRI for architecture assessment in vivo

• Features of MRI
  – Non-invasive
  – No x-rays
  – True 3D
  – Oblique scanning plane
  – Clinical scanners
  – Image time: 12 - 15 minutes
  ~ 150 x 150 x 300 µm,
    60 x 60 x 100 µm
MRI assessment of trabecular structure

Images from two women with similar BMD

www.micromri.com
QCT-based finite element analysis

- FEA is a well-established engineering method for analysis of complex structures
- Integrates geometry and density information from QCT scan to provide measures of bone strength
- In some cases, more strongly associated with whole bone strength in cadavers than DXA
- Further clinical validation needed

Conclusions

• **Whole bone strength** is determined by bone mass, geometry, microarchitecture and characteristics of bone material

• **Hip fractures** result from an increase in traumatic loading — in particular, falls to the side — coupled with a deterioration in bone strength with increased age

• **Biomechanically based assessment of fracture risk** may improve diagnosis and understanding of treatment effects

• **New tools are being developed for non-invasive assessment of bone strength and fracture risk**