Beyond BMD: Bone Quality and Bone Strength

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Disclosures

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Fractures = structural failure of the skeleton
Engineering approach to design a structure

- Consider what loads it must sustain
- Design options
  - Overall geometry
  - Building materials
  - Architectural details

Determinants of whole bone strength

- Quantity
  - size and mass (BMD)
- Distribution
  - shape or geometry
cortical : trabecular mass
  - microstructure
- Properties of Bone Matrix
  - mineralization
  - proteins
  - microdamage
  - …others?

Basic bone biomechanics

- Structural Properties (extrinsic)
- Material Properties (intrinsic)
Mechanical behavior of bone tissue and its constituents

Clinical assessment of bone (strength) today

Areal BMD by DXA
- Bone mass / area (g/cm\(^2\))
- Reflects (indirectly)
  - Bone size
  - Mineralization of matrix
- Misses many who fracture
- Neglects many structural aspects of bone strength

BMD explains > 70% of whole bone strength in ex vivo human cadaver studies

Proximal Femur (sideways fall)\n\[ r^2 = 0.71 \]

Vertebral body (L2) (compression + forward flexion)\n\[ r^2 = 0.79 \]
Age-related changes in bone structure

Changes from age 20 – 90 in women

<table>
<thead>
<tr>
<th>Trabecular density</th>
<th>-27%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical density</td>
<td>-22%</td>
</tr>
<tr>
<td>Cortical thickness</td>
<td>-52%</td>
</tr>
</tbody>
</table>

Khosla et al. JBMR 2006

Simulated bone atrophy at distal radius:
Bone strength more sensitive to cortical than trabecular bone loss

<table>
<thead>
<tr>
<th>Change in bone volume</th>
<th>Mechanism of bone loss</th>
<th>Decrease in strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20%</td>
<td>↓ Trab Number</td>
<td>-11%</td>
</tr>
<tr>
<td>-20%</td>
<td>↓ Trab Thickness</td>
<td>-9%</td>
</tr>
<tr>
<td>-20%</td>
<td>↓ Cortical Thickness</td>
<td>-38%</td>
</tr>
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</table>

Pistoia et al., Bone 2003

Age-related changes in bone structure

Changes from age 20 – 90

<table>
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<tr>
<th>Trabecular density</th>
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<tr>
<td>Cortical density</td>
<td>-24%</td>
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Mayhew et al. JBMR, Khosla et al. JBMR 2011
Effect of resorption cavities on trabecular bone strength

- 20% decrease in bone mass
  1) trabecular thinning
     ↓
  30% decrease in strength
  2) add resorption cavities
     ↓
  50% decrease in strength

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

Effect of Resorption on Buckling Strength

Buckling strength is Inversely proportional to (Length of column)^2

<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>
Porosity is profound in the aging femoral neck

19 elderly female cadavers (87 ± 8 yrs)
Intracortical porosity ranged from 5% to 39%
Bousson et al, JBMR, 2004

Cortical porosity with increasing age

50-64 yrs 65-79 yrs > 80 yrs

Bone loss (mg/HA)

Zebaze et al, Lancet 2010

Whole bone strength declines dramatically with age

Femoral Neck (sideways fall)
Lumbar Vertebrae (compression)

Bone Strength

Non-Invasive Imaging

SIZE & SHAPE
how much?
how is it arranged?

MATRIX PROPERTIES
mineralization
collagen traits

Bone Turnover
Markers

BONE REMODELING
formation / resorption

Osteoporosis Drugs, Diet, Exercise, Diseases, ....

Trabecular bone score (TBS)
(FDA-approved in 2012)

Silva et al JBMR 2014 (accepted)

TBS associated with fractures, weakly with BMD
- 29,407 postmenopausal women; 1668 (5.6%) had major OP frx
- Weak correlation to BMD: $r = 0.26-0.33$

Hans et al JBMR 2011
Meta-analysis of TBS and Fracture

- >17,000 subjects in 14 studies (59% women)
- 298 hip fx and 1109 major osteoporotic fx
- TBS associated with fracture independent of age, and FRAX (HR ~ 1.28 to 1.50)

QCT-based femoral neck measures and hip fracture risk

Hazard ratios per SD reduction
All models adjusted for age, BMI, race, clinic site
3347 men > 65 yrs, 42 incident hip fx

<table>
<thead>
<tr>
<th>QCT</th>
<th>HR per SD</th>
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<tr>
<td>↓ % cortical volume</td>
<td>3.4 (2.3–4.9)</td>
</tr>
<tr>
<td>↓ Fem Neck area (cm²)</td>
<td>1.6 (1.3–2.1)</td>
</tr>
<tr>
<td>↓ Trab vBMD (g/cm²)</td>
<td>1.6 (1.1–2.3)</td>
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Black, Bouxsein et al, JBoneMR 2008
QCT-based femoral neck measures and hip fracture risk

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<th>QCT + DXA</th>
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<td></td>
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Black, Bouxsein et al, JBMR 2008

QCT for Monitoring Treatment Response:
Changes in Spine Bone Density by DXA and QCT: the PaTH trial

Black et al, NEJM, 2003

HR-pQCT

82 µm voxel size
Peripheral skeleton only
< 3 μSv
HR-pQCT discriminates osteopenic women with and without history of fragility fracture
(age = 69 yrs, n=35 with prev frx, n=78 without fracture)

* p < 0.05 vs fracture free controls

Boutroy et al, JCEM (2005)

Race-related differences in microarchitecture

Putman, Yu et al, JBMR 2013

Pathophysiology of fragility in Type 2 Diabetes?

Burghardt et al, J Clin Endo Metab (2010)

TZDM have same or higher BMD, but markedly higher (+36 to 120%) cortical porosity vs non-diabetic controls
Finite element analysis in clinical practice

Experimentally measured femoral strength vs FEA-predicted strength
(sideways fall, 73 human femora, aged 55 to 98 yrs)

QCT-based FEA vs femoral BMD for prediction of hip fracture

Hazard Ratio (95% CI)*

<table>
<thead>
<tr>
<th></th>
<th>Fem Neck BMD</th>
<th>QCT-FEA strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older men (Mr OS)1</td>
<td>4.4 (2.4-9.1)</td>
<td>6.5 (2.3-18.3)</td>
</tr>
<tr>
<td>49 hip fx vs 210 controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older men (AGES)2</td>
<td>3.7 (2.5-5.6)</td>
<td>3.5 (2.3-5.3)</td>
</tr>
<tr>
<td>Older women (AGES)</td>
<td>2.7 (1.9-3.9)</td>
<td>4.2 (2.6-6.9)</td>
</tr>
<tr>
<td>171 hip fx vs 877 control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age, race

1Orwoll et al, JBMR 2009; 2Kopperdahl et al, JBMR 2014
CT procedures amenable to bone strength evaluation - CT colonography, CT Enterography

Osteoporosis screening in IBD patients undergoing contrast-enhanced CT Enterography

Loading conditions

Fracture?

Bone "strength"

Weber et al, Am J Gastroenterology, 2014

R² = 0.84

Women

Men
Independent risk factors for hip fracture in elderly fallers

<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

Sideways Falls

- In young volunteers, only 2/6 were able to break the fall
- 85% of impact force delivered directly to femur
- Force ↑ by ↑ body wt
- Force ↓ by ↑ thickness of trochanteric soft tissue

Peak impact forces applied to greater trochanter:
270 - 730 kg (600 - 1600 lbs) (for 5th to 95th percentile woman)


Trochanteric soft tissue thickness and hip fracture

644 women (129 hip fx); 1183 men (237 hip fx)

<table>
<thead>
<tr>
<th>Odds Ratio for Hip Fracture</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>644</td>
<td>1183</td>
</tr>
<tr>
<td>Fem Neck BMD ↓</td>
<td>2.4 (1.8, 3.2)**</td>
<td>3.3 (2.7, 4.2)**</td>
</tr>
<tr>
<td>Fall force ↑</td>
<td>1.7 (1.3, 2.3)**</td>
<td>1.2 (1.0, 1.5)*</td>
</tr>
<tr>
<td>Trochanteric Soft Tissue Thickness ↓</td>
<td>1.8 (1.4, 2.4)**</td>
<td>1.01 (0.8, 1.2)</td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.001

Framingham Osteoporosis Study, MrOS, and Rancho Bernardo Cohorts
Trochanteric soft tissue thickness: too little in men to make a difference?

---  Male control
---  Male hip fx
---  Female control
---  Female hip Fx

Circumstances surrounding vertebral fracture are unclear

<table>
<thead>
<tr>
<th>Reported Activity</th>
<th>% of fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls</td>
<td>44.0</td>
</tr>
<tr>
<td>Other severe trauma</td>
<td>7.1</td>
</tr>
<tr>
<td>No or minimal trauma</td>
<td>11.3</td>
</tr>
<tr>
<td>&quot;Spontaneous&quot; or Unknown</td>
<td>37.5</td>
</tr>
</tbody>
</table>

~50% occurred under unknown circumstances, or without specific trauma

Factor-of-risk = Applied Load / Strength
Predicted Loads on Lumbar Spine for Activities of Daily Living

<table>
<thead>
<tr>
<th>Activity</th>
<th>Load (% BW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rise from chair</td>
<td>173</td>
</tr>
<tr>
<td>Stand, hold 8 kg, arms extended</td>
<td>230</td>
</tr>
<tr>
<td>Stand, flex trunk 30°, arms extended</td>
<td>146</td>
</tr>
<tr>
<td>Lift 15 kg from floor</td>
<td>319</td>
</tr>
</tbody>
</table>

for a 162 cm, 57 kg woman

Load to strength ratio for L3

Factors Affecting Bone Strength and Fracture Risk

Material | Micro architecture | Size & Shape | Loading