Beyond BMD: Bone Quality and Bone Strength

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Amgen, Merck
Structural failure of the skeleton

Outline

- Determinants of Bone Strength
- Limitations of BMD
- Beyond BMD
- Biomechanics of Fractures: Comparing applied loads to strength

Design of a Structure

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

Evolving View of Osteoporosis

Skeletal disorder characterized by decreased bone mass and architectural deterioration leading to an increased risk of fracture.

NIH Consensus Conference, 1993

Skeletal disorder characterized by compromised bone strength leading to an increased risk of fracture.

NIH Consensus Conference, 2000
Determinants of Whole Bone Strength

Morphology
- size (mass)
- shape (distribution of mass)
- porosity
- microarchitecture

Properties of Bone Matrix
- mineralization
- collagen
- microdamage
- others...

Hierarchical Structure of Bone
- Cell: nanometer
- Matrix: 100's nanometer
- Lamellar Osteonal: micron
- μ-architecture: micron to 100's micron
- Whole Bone: millimeter and beyond

Assessing Bone Biomechanical Properties
- Structural Properties
- Material Properties

Biomechanical Testing Key Properties
- Strength
- Stiffness
- Energy absorbed (toughness)
Mechanical Behavior of Common Materials

- Glass (brittle)
- Plastic (ductile)

Mechanical Behavior of Bone and Its Constituents

- Mineral
- Bone
- Collagen

Outline

- Osteoporosis & Bone Strength
- Limitations of BMD

Clinical Assessment of Bone Strength

- Areal BMD by DXA
  - Bone mineral / projected area (g/cm²)
  - Reflects (indirectly)
    - Bone size
    - Mineralization

- Moderate to strong correlation with whole bone strength ($r^2 = 50 - 90\%$)


Bouxsein et al, 1999
Age and BMD Are Independent Risk Factors for Hip Fracture

Kanis et al, 2004

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

History of Previous Fracture is a Risk Factor for Future Fracture, Independent of BMD


Fracture risk prediction:
Less than half of patients who fracture have osteoporosis by BMD testing
(le t-scores > -2.5*)

- Only 34% of women and 21% of men suffering a non-vertebral frx had BMD in osteoporotic range
  (Schuit et al, 2004; 2006)

- Only half of elderly women with incident hip frx had BMD in osteoporotic range at baseline
  (Wainwright et al, JCEM 2005)

Treatment monitoring

- Changes in BMD underestimate reduction in fracture risk

- Changes in BMD explain a small proportion of reduction in fracture risk

* Based on WHO guidelines for Osteoporosis Diagnosis

More later …. Dr. Bauer, Friday afternoon
Outline

• Osteoporosis & Bone Strength
• Limitations of BMD
• Beyond BMD

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

Distribution of Mass Affects Mechanical Behavior

Moment of Inertia proportional to $d^4$
Effect of cross-sectional geometry on long bone strength

- aBMD (by DXA) = = =
- Compressive Strength = ↑ ↑
- Bending Strength = ↑↑ ↑↑

Role of Geometry in the Prediction of Hip Fracture by QCT: MrOS

- MrOS - a prospective, observational study
  - 5995 men > 65 yrs from six US sites
    - QCT subset, n=3358
- Used QCT to measure femoral neck vBMD & geometry
- Followed prospectively for fracture, mean 5 ± 1 yrs
- 40 hip fractures in QCT cohort
- Analyses adjusted for age, BMI, race, and clinic

Femoral neck measures and hip fracture risk: Multivariate analyses

Hazard ratios per SD reduction
All models adjusted for age, BMI, race, clinic site

<table>
<thead>
<tr>
<th>QCT</th>
<th>HR per SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>% cortical volume</td>
<td>3.4 (2.3–4.9)</td>
</tr>
<tr>
<td>Min FNeck area (cm²)</td>
<td>1.6 (1.3–2.1)</td>
</tr>
<tr>
<td>Trab vBMD (g/cm³)</td>
<td>1.6 (1.1–2.3)</td>
</tr>
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<tr>
<td>% cortical volume</td>
<td>2.5 (1.6–3.9)</td>
</tr>
<tr>
<td>Min Fem Neck area</td>
<td>1.5 (1.1–2.0)</td>
</tr>
<tr>
<td>Trab vBMD</td>
<td>1.2 (0.8–1.9)</td>
</tr>
<tr>
<td>Fem Neck aBMD (g/cm²)</td>
<td>2.1 (1.1–3.9)</td>
</tr>
</tbody>
</table>

Black et al, JBMR 2008
Age-Related Changes in Trabecular Microarchitecture

Decline in bone mass and deterioration of trabecular bone structure both contribute to decreased bone strength.

Excessive Bone Resorption Weakens Trabecular Architecture

Stress concentration (focal weakness)

Perforation
Effect of Increased Bone Resorption on Trabecular Architecture

Perforation of Trabecular Strut
Trabecular Microfracture

L. Mosekilde, Tech and Health Care, 1998

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

van der Linden, et al, JBMR 2001

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

Silva and Gibson, Bone, 1997

Importance of Cross-struts
**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
  - \((\text{Length of column})^2\)

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**Theoretical effect of cross-struts on buckling strength**

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

<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 \times S)</td>
</tr>
</tbody>
</table>

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**High Resolution pQCT**

(X-treme CT, Scanco Medical AG)

- \(\sim 82 \, \mu\text{m}^3\) voxel size
- \(\sim 3\) min scan time, < 4 \(\mu\text{Sv}\)

Reproducibility:
- density: 0.7 to 1.5% *
- structure: 1.5 - 4.4 *

Peripheral skeleton only

Specialized equipment

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* Boutroy, et al, JCEM 2005*
**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)

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**Dramatic Changes in Trabecular Architecture in Early Postmenopausal Women**

*(52 yr old woman, 3 yrs post-menopause)*


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**Anti-Resorptive Tx Preserves Trabecular Architecture in Early Postmenopausal Women**

*(Placebo vs Risedronate, 5 mg/d, 1 yr)*

*P*<0.05 vs baseline.

†*P*< 0.05 vs PBO.

Monitoring of Teriparatide Treatment with HRCT
EUROFORS study, Forsteo 20 µg/d, n=62

Graeff et al, JBMR 2007

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


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 and trabecularization of the endocortical surface with age

Cortical bone loss increases with age. Prior studies have likely underestimated cortical bone loss

Zebaze et al, Lancet 2010
Bone Strength

**GEOMETRY**
- macroarchitecture
- microarchitecture

**MATERIAL**
- tissue composition
- matrix properties

**BONE REMODELING**
- formation / resorption

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**Mechanisms that may lead to increased BMD**

- Increase Trabecular Thickness
- Increase Trabecular Number
- Increase Mineralization

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**How is mineralization density influenced by rate of bone turnover?**

- Slow process of secondary mineralization
- Decreased bone turnover allows mineralization to proceed

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**Increased bone turnover with estrogen deficiency decreases mineralization density**

Meunier and Bolvin, *Bone*, 1997
Relationship between mineralization and biomechanical properties

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

Load vs. Displacement

Mineralization

↑ 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%

Bone remodeling & microdamage

What is “damage”?

- Repetitive loading
- No repair process
- ↓ Mechanical properties

Microdamage in Bone

- Associated with decreased mechanical properties in vitro
- Observed in human cortical and trabecular bone, increases with age
- Signal for remodeling & repair
- No direct relationship to fracture risk


Crack Density (#/mm²) vs. Age (yrs)

Women vs. Men
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

Fazzalari et al, Bone, 1998

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

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

Whole bone strength declines dramatically with age

Femoral Neck (sideways fall)

Lumbar Vertebrae (compression)


Outline

• Determinants of Bone Strength
• Limitations of BMD
• Beyond BMD
• Biomechanics of Fractures:
  Comparing applied loads to strength
Fracture Etiology

Bone Strength

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

Loads applied to the bone

- Direction & magnitude
- Bone strength

Geometry
- Microstructure
- Material Properties

Fall traits
- Protective responses
- Soft-tissue padding
- Impact surface

Propensity to fall
- Spine curvature
- Muscle strength
- Disc degeneration

Bending, lifting activity

FRACTURE?

Biomechanics of 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

What is a high risk fall?

Independent Risk Factors for Hip Fx

<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
Estimating Loads Applied to the Hip

- 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)


Very high forces 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 (600 - 1600 lbs) (for 5th to 95th percentile woman)


Femoral ‘strength’ depends on loading direction

Femur is weak in atypical loading conditions

Stance

Sideways Fall

Failure Load (kN)

Stance

Sideways Fall

3.4-fold lower

P < 0.001

7378 ± 700 N

2318 ± 300 N

Keyak et al, J Biomechanics, 1998
Femoral strength in sideways fall declines markedly with age

Older femurs are half as strong and absorb 1/3 as much energy as young femurs

Effect of Aging on the Load / Strength Ratio
Sideways Fall Configuration

Thus, $\Phi$ is often $>1$ for sideways fall in elderly persons

Biomechanics of Vertebral Fractures

- Difficult to study
  - 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 Spine

Biomechanical model
- Simulate bending and lifting activities
- Height, weight, body position
- Determine compressive forces on vertebra for different activities
### 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>Standing</td>
<td>51</td>
</tr>
<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*

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### Ratio of load to strength for L3 during activities of daily living

<table>
<thead>
<tr>
<th>Activity</th>
<th>Load (% BW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Get up from sitting</td>
<td>1.5 0.6 0.4 0.3 0.2 0.2</td>
</tr>
<tr>
<td>Lift 15 kg knees straight</td>
<td>2.6 1.1 0.7 0.5 0.4 0.3</td>
</tr>
<tr>
<td>Lift 15 kg w/ deep knee bend</td>
<td>2.1 0.9 0.6 0.4 0.3 0.3</td>
</tr>
<tr>
<td>Lift 30 kg knees straight</td>
<td>3.7 1.5 1.0 0.7 0.6 0.5</td>
</tr>
<tr>
<td>Lift 30 kg w/ deep knee bend</td>
<td>3.0 1.3 0.8 0.6 0.5 0.4</td>
</tr>
<tr>
<td>Open window w/ 6 kg of force</td>
<td>1.1 0.5 0.3 0.2 0.2 0.1</td>
</tr>
<tr>
<td>Open window w/ 10 kg of force</td>
<td>1.4 0.6 0.4 0.3 0.2 0.2</td>
</tr>
<tr>
<td>Tie shoes sitting down</td>
<td>1.4 0.6 0.4 0.3 0.2 0.2</td>
</tr>
</tbody>
</table>

*Adapted from Myers and Wilson, Spine, 1997*

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### Factor of Risk for Vertebral Fracture (L2)

- **Men**: 11.9%
  - +28% over life**
- **Women**: 30.1%
  - +92% over life**

*Men: Bending forwards 90° with 10 kg weight in hands*

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

- **Incidence / 100,000 person-yrs**
  - Men: [Graph]
  - Women: [Graph]

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

*Bouxsein et al, JBMR 2006*
Fracture Prevention Strategies

Reduce the Loads Applied to Bone
- Decrease fall frequency / severity
- Safe-landing strategies
- Trochanteric padding
- Avoid high risk lifting / bending activities

Maintain or Increase Bone Strength
- Exercise, diet (Ca, Vit D), pharmacologic treatment

Summary: Factors Affecting Bone Strength and Fracture Risk

<table>
<thead>
<tr>
<th>Material</th>
<th>Micro architecture</th>
<th>Size &amp; Shape</th>
<th>Loading</th>
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