Beyond BMD: Bone Quality & Bone Strength

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Fractures = structural failure of the skeleton

Design of a Structure

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

Disclosures

- Advisory board: Merck, Eli Lilly, Radius
- Consultant: Agnovos, Acceleron Pharma
- Research funding: Merck, Amgen
Determinants of whole bone strength

Quantity
size and mass (BMD)

Distribution
shape or geometry
cortical : trabecular mass
microstructure

Properties of Bone Matrix
mineralization
collagen
microdamage
…others

Basic bone biomechanics

Structural Properties (extrinsic)

Material Properties (intrinsic)

Mechanical behavior of bone tissue and its constituents

It is not really practical to do three point bending on a patient.

Slide courtesy of Paul Hansma, PhD
Clinical assessment of bone (strength) today

Areal BMD by DXA
- Bone mass / area (g/cm²)
- 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

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

TBS enhances 10-yr prediction of fx risk

Hans et al JBMR 2011
Leslie et al Osteop Int 2014
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)

TBS changes following ALN or TPTD treatment in GIO

McCloskey et al, JBMR 2016

TBS changes following ALN or TPTD treatment in GIO

Saag et al, Arthritis and Rheum 2016

DXA-based methods

QCT
HR-pQCT
Finite Element Analysis
Reference point indentation

QCT
- ~300-500 µm voxel size
- Trabecular & cortical bone density, geometry
- Axial and appendicular skeleton
- Associated with fracture
- Less sensitive to soft tissue variability than DXA
- Novel applications
- Limited micro-structure
- Few prospective fx studies
- No standard analysis
- Lack of reference data
- Radiation exposure?

Engell et al, Curr OP Report 2013
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>QCT + DXA</th>
</tr>
</thead>
<tbody>
<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/cm³)</td>
<td>1.6 (1.1–2.3)</td>
</tr>
<tr>
<td>↓ Fem Neck aBMD (g/cm²)</td>
<td>2.1 (1.1–3.9)</td>
</tr>
</tbody>
</table>

Black, Bouxsein et al, JBMR 2008

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

Mean Change (%)

PTH | PTH/ALN | ALN

Black et al, NEJM, 2003

Cortical thickness mapping to identify ‘local’ osteoporosis

Poole et al, PLoS ONE, 2011
DXA-based methods
QCT, HR-QCT

HR-pQCT

Finite Element Analysis
Reference point indentation

82 µm voxel size
Peripheral skeleton only
< 3 µSv

Separation of cortical and trabecular compartments

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)
Osteopenic by DXA BMD
(70 yr old woman)

Distal Tibia

Distal Radius

Worse bone architecture in premenopausal women with distal radius fracture
(40 premenopausal wrist fx, 80 age-matched controls)

\[ \Delta Fx - Cont (\% ) \]

* P < 0.05
* * P < 0.05 UDR adj

Wrist Frx
Control

Rozental, Bouxsein et al, JBJS (2013)

Race-related differences in microarchitecture

Caucasian

African-American

Pathophysiology of fragility in Type 2 Diabetes?

T2DM have same or higher BMD, but markedly higher (+36 to 120%) cortical porosity vs non-diabetic controls

Control Diabetes Diabetes + Frx

Burghardt et al, J Clin Endo Metab (2010)

Putman, Yu et al, JBMR 2013
DXA-based methods
QCT
HR-pQCT
**Finite Element Analysis**
Reference point indentation

**Finite element analysis in clinical practice**

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

- $r^2 = 0.78$
- $p < 0.001$
- SEE = 900 N

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

<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>40 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

¹ Orwoll et al, JBMR 2009; ² Kopperdahl 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

DXA t-score vs FEA “fragile bone strength”
How do we assess bone material and tissue level mechanical properties?

- Estimated
  - elastic modulus
  - ult. strength
  - toughness

- assessed
  - elastic modulus
  - ult. strength
  - toughness
  - hardness

Assessing bone tissue level biomechanical properties with reference probe indentation

Bone Strength
- SIZE & SHAPE
  - how much?
  - how is it arranged?
- MATRIX PROPERTIES
  - mineralization
  - collagen traits
- BONE REMODELING
  - formation / resorption
- Osteoporosis Drugs, Diet, Exercise, Diseases, ....

"Impact microindentation" (Osteoprobe)
- Hand-held, portable
- 2.5 µm at tip of test probe
- Single impact indentation, anterior mid-tibia
- Reproducibility = 1.65% (Farr et al., JBMR 2014)

Bone Material Strength Index (BMSi)
Indentation distance into subject’s bone normalized by indentation distance into reference material

In vivo reference point indentation

Bridges et al, Rev Sci Instr 2012
Randall et al, J Med Devices 2012

Bone material strength index (BMSi)
in clinical studies

- Diabetes\(^1\)
  ~ 10% lower BMSi in postmenopausal women with longstanding T2D

- Fracture prediction\(^2\)
  ~ 5% lower BMSi in those with prior hx of fragility fracture, independent of BMD

- Glucocorticoid-induced osteoporosis\(^3\)
  BMSi declines after initiation of glucocorticoids

\(^1\) Farr et al, 2014; \(^2\) Malgo et al, 2015; \(^3\) Mellibovsky et al 2015
### 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

### Trochanteric soft tissue thickness and hip fracture

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

<table>
<thead>
<tr>
<th>Trochanteric soft tissue thickness and hip fracture</th>
<th>Odds Ratio for Hip Fracture (per 1 SD increase or decrease)</th>
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<tbody>
<tr>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>↓ Fem Neck BMD</td>
<td>2.36 (1.77, 3.15) **</td>
</tr>
<tr>
<td>↑ Fall force</td>
<td>1.67 (1.25, 2.25) **</td>
</tr>
<tr>
<td>↓ Trochanteric Soft Tissue Thickness</td>
<td>1.79 (1.35, 2.37) **</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?

<table>
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<tr>
<th>Trochanteric soft tissue thickness (mm)</th>
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<tbody>
<tr>
<td>Male Controls</td>
</tr>
<tr>
<td>Male Cases</td>
</tr>
<tr>
<td>Male Cases, Low BMD</td>
</tr>
<tr>
<td>Male Cases, Normal</td>
</tr>
<tr>
<td>Female Cases</td>
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<tr>
<td>Female Cases, Low BMD</td>
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<tr>
<td>Female Cases, Normal</td>
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644 women (129 hip fx); 1183 men (237 hip fx)
Biomechanics of vertebral fractures

- Vertebral fx are 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 fx

Occurrence of vertebral fractures varies along the spine

Relative fracture prevalence from 13562 European women and men over age 50 (Ismail et al, 1999)
Standing 51
Rise from chair 173
Stand, hold 8 kg, arms extended 230
Stand, flex trunk 30°, arms extended 146
Lift 15 kg from floor 319
for a 162 cm, 57 kg woman

Non-invasive assessment of bone strength: where are we today?

- A few techniques have recent FDA approval
  - TBS may add to BMD predictions of fracture
  - QCT-based FEA may expand number of individuals diagnosed
- Techniques are well suited for clinical research and clinical trials
  - Pathophysiology & differentiate mechanism of action
- Not yet clear how to use in routine clinical practice
  - QCT & FEA: No clear advantage over BMD for fx prediction
  - Indentation — early stage & many questions remain
- Examining non-BMD aspects of fracture risk (ie, loading) may provide important insights

Our vision: a clinically relevant tool

Bone strength estimates

Improved fracture risk prediction?

Patient-specific loading estimates
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