Clinical Assessment of Bone Strength and Fracture Risk: Beyond BMD

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Disclosures

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- Consultant: Agnovos
- Research funding: Merck, Amgen
Structural failure of the skeleton

Design of a Structure

- Consider what loads it must sustain
- Design options
  - Overall geometry
  - Building materials
  - Architectural details
Determinants of Whole Bone Strength

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

**Properties of Bone Matrix**
- mineralization
- collagen
- microdamage
- non-collagenous proteins
  - and more...

Mechanisms underlying bone strength at multiple length scales

Zimmerman et al, PNAS 2011
Standard 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 ($r^2 = 50 - 90\%$)

- Strong predictor of fracture risk in untreated women

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

Does not distinguish several attributes of whole bone strength

- 3D geometry
- Microarchitecture
- Intrinsic properties of bone matrix
Many fractures occur in those who have BMD t-scores better than -2.5

E. Siris, et al, NORA study, > 200,000 women in US

BMD has limitations in clinical use

- Less than half of patients who fracture have osteoporosis by BMD testing (i.e., t-scores > -2.5*)
  - Only half of elderly women with incident hip fracture had BMD in osteoporotic range at baseline

- Change in BMD underestimates anti-fracture efficacy of drugs

- Measurements are subject to artifacts
  - Obesity, vascular calcification, OA

Men have larger but less dense vertebrae than women matched for aBMD

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Diff (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional area (cm²)</td>
<td>12.39</td>
<td>10.33</td>
<td>+20%*</td>
</tr>
<tr>
<td>Integral vBMD (g/cm³)</td>
<td>0.156</td>
<td>0.215</td>
<td>-8%*</td>
</tr>
<tr>
<td>Trabecular vBMD</td>
<td>0.137</td>
<td>0.150</td>
<td>-9%*</td>
</tr>
<tr>
<td>Compressive strength (N)</td>
<td>4425</td>
<td>3003</td>
<td>+10%*</td>
</tr>
</tbody>
</table>

981 pairs
Spine aBMD (± 1%) Age (± 1 yr)

Bone Strength

SIZE & SHAPE
how much? how is it arranged?

Matrix Properties
mineralization collagen traits

Bone Remodeling
formation / resorption

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

Non-Invasive Imaging

Bone Turnover Markers

Bruno et al, JBMR 2014
DXA-based methods
QCT, HR-QCT
HR-pQCT
QCT-based Finite Element Analysis
Reference point indentation
Hip Structure Analysis (HSA)

- Uses standard 2D DXA scans to estimate femoral geometry

**Key assumptions:**
- Constant mineral density
- Neck, Shaft = circular
- Troch = elliptical
- % of cortical bone constant
  - Shaft = 100%
  - Fem neck = 60%
  - Troch = 70%

- Highly correlated to femoral BMD

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

TBS and Fracture

Cross-sectional studies

Prospective studies

Silva et al JBMR 2014
TBS enhances 10-yr prediction of fx risk

- 33,352 women (40 - 100 yrs), 4.7 yrs of follow-up
  - 1,754 deaths and 1,872 major osteoporotic fx

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>Major OP Fx</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBS</td>
<td>1.36 (1.30-1.42)</td>
<td>1.33 (1.27-1.39)</td>
</tr>
<tr>
<td>Spine BMD</td>
<td>1.47 (1.40-1.55)</td>
<td>1.03 (0.98-1.08)</td>
</tr>
</tbody>
</table>

Lowest TBS (~ 10th percentile)
1.5 - 1.6 fold greater risk of major OP fracture

Leslie et al Osteop Int 2014
TBS updates: towards clinical utility

- **Age-specific reference values**
  - US non-hispanic white women (Simonelli et al, JCD 2014)
  - Japanese women (Iki et al, Osteop Int 2015)

- **Association with fracture**
  - Men and women
  - Women with osteopenia
  - Diabetics

- **Utility in special patient populations**
  - Diabetes
  - GIOP
  - 1° HPTH
  - Androgen deprivation
  - CKD
  - RA


DXA-based methods

- **QCT, HR-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?

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### 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></th>
<th>% Change, ages 20-90 yrs</th>
<th>F vs M (P-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lumbar spine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total area</td>
<td>+14**</td>
<td>+15** 0.253</td>
</tr>
<tr>
<td>Trabecular vBMD</td>
<td>- 54**</td>
<td>- 47** &lt;0.001</td>
</tr>
<tr>
<td><strong>Femoral neck</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total area</td>
<td>+13**</td>
<td>+7* 0.557</td>
</tr>
<tr>
<td>Trabecular vBMD</td>
<td>- 56**</td>
<td>- 45** &lt;0.001</td>
</tr>
<tr>
<td>Cortical vBMD</td>
<td>- 24**</td>
<td>- 13** &lt;0.001</td>
</tr>
</tbody>
</table>

For age regressions: *P<0.05, **P<0.005
**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>Measure</th>
<th>QCT</th>
<th>QCT + DXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ % cortical volume</td>
<td>3.4 (2.3–4.9)</td>
<td>2.5 (1.6–3.9)</td>
</tr>
<tr>
<td>↓ Fem Neck area (cm²)</td>
<td>1.6 (1.3–2.1)</td>
<td>1.5 (1.1–2.0)</td>
</tr>
<tr>
<td>↓ Trab vBMD (g/cm³)</td>
<td>1.6 (1.1–2.3)</td>
<td>1.2 (0.8–1.9)</td>
</tr>
<tr>
<td>↓ Fem Neck aBMD (g/cm²)</td>
<td></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*

![Graph showing changes in bone density](image)

- **aBMD by DXA**
- **vBMD by QCT (Trabecular)**

**Legend:**
- Red: PTH
- Green: PTH/ALN
- Blue: ALN

*Black et al, NEJM, 2003*

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**Femoral neck cortical thickness varies around neck circumference**

![Image of femoral neck with cortical thickness measurements](image)

Position (cm): 7.05
Cortical Thickness versus Angle

- 8 mm
- 6 mm
- 4 mm
- 2 mm
- 0 mm

Position (cm): 8.05
Cortical Thickness versus Angle

- 8 mm
- 6 mm
- 4 mm
- 2 mm
- 0 mm
QCT reveals asymmetry of cortical bone loss at femoral neck

Regional cortical thickness in femoral neck may predict hip fracture better than femoral BMD
AGES-REYKJAVIK study, 143 hip fx, 298 controls
Multivariable regression, Hazard Ratio adjusted for age, ht, wt

<table>
<thead>
<tr>
<th></th>
<th>Women (88 frx, 187 ctrl)</th>
<th>Men (55 frx, 111 ctrl)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fem Neck Frx</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sup-Ant CtTh</td>
<td>1.6 (1.0-2.8)</td>
<td>3.2 (1.8-5.7)</td>
</tr>
<tr>
<td>FN aBMD</td>
<td>1.2 (0.7-2.0)</td>
<td>1.4 (0.8-2.4)</td>
</tr>
<tr>
<td><strong>Troch Frx</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sup-Ant CtTh</td>
<td>1.6 (0.9-2.8)</td>
<td>2.3 (1.1-4.6)</td>
</tr>
<tr>
<td>Inf-Post CtTh</td>
<td>-</td>
<td>2.4 (1.3-4.5)</td>
</tr>
<tr>
<td>FN aBMD</td>
<td>1.5 (0.8-2.7)</td>
<td>1.5 (0.7-3.1)</td>
</tr>
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</table>

Johannesdottir et al, Bone 2011
Cortical thickness mapping to identify ‘local’ osteoporosis

Poole et al, PLoS ONE, 2011

Cortical deficits and fracture location in acute hip fx

- QCT-based cortical thickness mapping
  Poole et al 2011, 2013; Treece et al 2010, 2013

- 124 controls
- 144 acute hip fx
  – 53 trochanteric
  – 37 transcervical
  – 54 subcapital

Poole et al, ASBMR 2013
DXA-based methods
QCT, HR-QCT

HR-pQCT

Finite Element Analysis
Reference point indentation

HR-pQCT

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)

Boutroy et al, JCEM (2005)

* p < 0.05 vs fracture free controls
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)

Rozental, Bouxsein et al, JBJS (2013)
Race-related differences in microarchitecture

Caucasian

African-American

Pathophysiology of fragility in Type II Diabetes?

Control  Diabetes  Diabetes + Frx

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

Burghardt et al, J Clin Endo Metab (2010)
T2DM with history of fracture have increased cortical porosity

Patsch et al, JBMR 2013

DXA-based methods
QCT, HR-QCT
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Finite Element Analysis
Reference point indentation
Experimentally measured femoral strength vs FEA-predicted strength
(sideways fall, 73 human femora, aged 55 to 98 yrs)

$r^2 = 0.78$
$p < 0.001$

ON Diagnostics

Approved by FDA in 2012

3D geometry

material properties

Crawford, et al, Bone 2003

Hip and spine FEA

Image courtesy of T. Keaveny
Finite element analysis and hip fracture

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>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>
</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

Weber et al, Am J Gastroenterology, 2014
DXA-based methods
QCT, HR-QCT
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How do we assess bone material and tissue level mechanical properties?

- Estimated
  - elastic modulus
  - ult. strength
  - toughness

Assessing bone tissue level biomechanical properties with reference probe indentation

**Osteoprobe**
- Hand-held, portable
- Single impact indentation
- “Bone material strength index” (BMSi)

Bridges et al, Rev Sci Instr 2012

**In vivo reference point indentation**

Randall et al, J Med Devices 2012
Indentation properties worse in women with T2DM

- 30 postmenopausal women with T2DM (65.5±8.1 yrs) for > 10 yrs
- 30 age-matched, non-diabetic
- No difference in bone microarchitecture b/w groups (HR-pQCT)
- T2DM had 10.5% lower ‘bone material strength’ (p<0.001)

Farr et al, JBMR 2014

Atypical femoral fractures: issue with cortical bone “quality”?

- NIH-funded study to examine utility of RPI
- Postmenopausal women:
  - Treatment naïve
  - Long-term bisphosphonate users
  - Atypical femoral fracture
Neuromuscular function, Medications, Environmental hazards, Time spent at risk → Risk of fall

Fall direction, height, Protective responses, Energy absorption, Lifting activity → Force applied to bone magnitude, direction

Bone mass, Bone geom + µ-arch, Bone matrix prop's → Bone strength

Peak bone mass, Rate of bone loss → Fracture?
Biomechanics of 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

Occurrence of vertebral fractures varies along the spine

Relative fracture prevalence from 13562 European women and men over age 50 (Ismail et al, 1999)
Muscle Strength & Quality

Spinal Curvature

Activity

Loads applied to the vertebra

Vertebral strength

FRACTURE?

Estimating Loads on the Lumbar Spine
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*

Vertebral loading predicts fracture location
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) provides important insights into mechanisms

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