Imaging to Assess Bone Strength and its Determinants

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UCSF Osteoporosis Course
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Determinants of Whole Bone Strength

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

Properties of Bone Matrix
- mineralization
- collagen
- microdamage

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 ($r^2 = 50 - 90\%$)


Consultant / advisor:
- Amgen, Eli Lilly, Merck

Research funding:
- Amgen, Merck

Disclosures

Bouxsein, Osteop Int, 2003

Bouxsein et al, 1999
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

BMD has limitations in clinical use

- Less than half of patients who fracture have osteoporosis by BMD testing (i.e., t-scores < -2.5*)
  - Schuit et al. 2004; 2006; Wainwright et al. JCEM 2005
  - Only half of elderly women with incident hip fracture had BMD in osteoporotic range at baseline

- Association between BMD increase and anti-fracture efficacy varies by treatment and skeletal site
  - Low to moderate: alendronate, risedronate, raloxifene
    Cummings et al. 2002; Sarkar et al. 2002; Watts 2004, 2005
  - Moderate to high: denosumab and strontium ranelate
    Bruyere et al. 2007a,b; Austin et al. 2011

Non-invasive imaging

- Geometry
- Microarchitecture
- Bone strength

Bone Strength

- Non-Invasive Imaging
- 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 Approaches

Geometry

DXA-based Hip Structural Analysis (HSA)

Estimating Hip Geometry from 2D DXA

Hip Structure Analysis (HSA)

- Use 2D DXA-data to derive 3D geometry
- Many HSA variables highly correlated to femoral BMD
- Requires assumptions that have not been tested in all populations and treatments

Image courtesy of TJ Beck, Johns Hopkins Univ

Assumptions for Hip Structure Analysis

estimating femoral geometry from 2D DXA

- Constant tissue mineral density
- Femoral neck & shaft : circular
- Fixed proportion of cortical and trabecular bone at each site
  Neck: 60% of mass is cortical
  Troch: 70% of mass is cortical
  Shaft: 100% of mass is cortical


Non-invasive Imaging Approaches

Geometry

DXA-based Hip Structural Analysis (HSA)

Quantitative computed tomography

3D geometry

Trabecular and cortical compartments
Age-Related Changes in vBMD and Geometry by 3D-QCT
(368 women, 320 men, aged 20-97 yrs; Riggs et al JBMR 2004)

% Change, ages 20-90 yrs

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total area</td>
<td>+14**</td>
<td>+15**</td>
</tr>
<tr>
<td>Trabecular vBMD</td>
<td>- 54**</td>
<td>- 47**</td>
</tr>
<tr>
<td>Femoral neck</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total area</td>
<td>+13**</td>
<td>+7*</td>
</tr>
<tr>
<td>Trabecular vBMD</td>
<td>- 56**</td>
<td>- 45**</td>
</tr>
<tr>
<td>Cortical vBMD</td>
<td>- 24**</td>
<td>- 13**</td>
</tr>
</tbody>
</table>

% Change, ages 20-90 yrs

F vs M (P-value)

<p>| | | |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>Total area</td>
<td>0.253</td>
<td></td>
</tr>
<tr>
<td>Trabecular vBMD</td>
<td>&lt;0.001</td>
<td></td>
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QCT of Femoral neck and hip fracture risk:
Multivariate analyses in MrOS
3358 men > 65 yrs, followed prospectively for frx, 40 hip frx
All models adjusted for age, BMI, race, clinic site

QCT

HR per SD
%
cortical volume 3.4 (2.3–4.9)
Min Fem Neck area (cm²) 1.6 (1.3–2.1)
Trab vBMD (g/cm³) 1.6 (1.1–2.3)

Black et al, JBMR 2008
QCT of Femoral neck and hip fracture risk: Multivariate analyses in MrOS

3358 men > 65 yrs, followed prospectively for frx, 40 hip frx
All models adjusted for age, BMI, race, clinic site

<table>
<thead>
<tr>
<th>QCT</th>
<th>QCT + DXA</th>
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<tbody>
<tr>
<td>% cortical volume</td>
<td>3.4 (2.3–4.9)</td>
</tr>
<tr>
<td>Min 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/cm³)</td>
<td>2.1 (1.1-3.9)</td>
</tr>
</tbody>
</table>

Black et al, JBMR 2008

QCT reveals asymmetry of cortical bone loss at femoral neck

Regional cortical thickness in femoral neck predicts 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>Women (88 frx, 187 ctrl)</th>
<th>Men (55 frx, 111 ctrl)</th>
</tr>
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<tbody>
<tr>
<td>Fem Neck Frx</td>
<td>Sup-Ant CtTh</td>
</tr>
<tr>
<td>FN aBMD</td>
<td>1.2 (0.7-2.0)</td>
</tr>
<tr>
<td>Troch Frx</td>
<td>Sup-Ant CtTh</td>
</tr>
<tr>
<td>Inf-Post CtTh</td>
<td>-</td>
</tr>
<tr>
<td>FN aBMD</td>
<td>1.5 (0.8-2.7)</td>
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</tbody>
</table>

Johannesdottir et al, Bone 2011

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

<table>
<thead>
<tr>
<th>aBMD by DXA</th>
<th>vBMD by QCT (Trabecular)</th>
</tr>
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<tbody>
<tr>
<td>Mean Change (%)</td>
<td></td>
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</table>

Black et al, NEJM, 2003
**Changes in proximal femur after teriparatide by DXA or QCT**

(52 postmenopausal women in EUROFORS trial)

<table>
<thead>
<tr>
<th>Change vs baseline (%)</th>
<th>12 mo</th>
<th>24 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck BMD DXA vBMD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trab vBMD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cort vBMD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cort Area QCT</td>
<td></td>
<td></td>
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</tbody>
</table>

* p<0.05, ** p<0.01 vs BL

Borggrete et al, JBMR 2010

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**Imaging Approaches**

**Macroarchitecture / Bone Geometry**

**Microarchitecture**

High-res peripheral computed tomography (HR-pQCT)

Magnetic resonance imaging (MRI)

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**High Resolution pQCT**

(X-treme CT, Scanco Medical AG)

- ~ 82 µm³ voxel size
- ~ 3 min scan time, < 4 µSv

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

Peripheral skeleton only

Specialized equipment

* Boutroy, et al, JCEM 2005
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)

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

DXA HR-pQCT

* P <0.05
* P < 0.05 UDR adj

Rozental et al, JBJS (submitted)

Osteopenic by DXA BMD (70 yr old woman)

Images courtesy of S. Boutroy & P. Delmas, Inserm U831, Lyon
hr-pQCT shows increased cortical porosity in postmenopausal women

- Cortical porosity 2 to 4-fold higher in postmenopausal vs premenopausal women

Nishiyama et al, JBMR 2010
Burghardt et al, JBMR 2010

Cortical porosity and pathophysiology of fragility in Type II Diabetes?

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

Burghardt et al, J Clin Endo Metab (2010)

Non-invasive Imaging Approaches

Geometry
- DXA-based Hip Structural Analysis (HSA)
- Quantitative Computed Tomography (QCT)

Microarchitecture
- High-res peripheral computed tomography (hr-pQCT)
- High-res magnetic resonance imaging (MRI)

MRI Assessment of Trabecular Bone Architecture

- Features / Advantages of MRI
  - Nonionizing radiation
  - 3-D
  - Clinical scanners
  - Images depict marrow, whereas bone has no signal
  - 150 x 150 x 300 µm

- Disadvantages
  - Technically demanding
  - Expensive, time consuming
  - Precision
  - Problem for claustrophobics!
What does the future hold for MRI?

- Axial skeleton and hip
- Better signal-to-noise ratio
- Shorter imaging time
- Less motion artifact
- Higher resolution

Images courtesy of Sharmila Majumdar, UCSF

Non-invasive Imaging Approaches

**Geometry**
- DXA-based Hip Structural Analysis (HSA)
- Quantitative Computed Tomography (QCT)

**Microarchitecture**
- High-res peripheral computed tomography (hr-pQCT)
- High-res magnetic resonance imaging (MRI)

**Bone strength**
- Finite element analysis (FEA)

3D QCT ➔ Geometry + vBMD ➔ Prediction of bone strength

Prediction of Bone Strength Using Finite Element Analysis (FEA)

- Standard engineering approach to evaluate mechanical behavior of complex structures
  - Integrates material and structural information from 3D QCT and hr-pQCT
  - Can provide multiple strength metrics
- Cadaver studies show that FEA predicts femoral and vertebral strength better than BMD (Cody 1998; Pistoia 2002; Crawford 2004)
- Has been used in vivo to study effect of treatment on bone strength and predict fracture risk

Approach: QCT-based Finite Element Model

3D geometry ➔ material properties ➔ Ultimate Strength ➔ QCT Density

Crawford, et al., Bone 2003
QCT-based FEA models of proximal femur

Intertroch Fx
Fem Neck Fx

FEA and femoral strength

FEA-predicted strength strongly correlated with experimentally measured femoral strength in sideways fall configuration (sideways fall configuration, 73 femurs, aged 55 to 98 yrs)

\[ r^2 = 0.78 \]
\[ p < 0.001 \]

Femoral strength declines more than femoral BMD (~ 50 M and W per decade, Mayo cohort)

Keaveny, et al, JBMR 2010
**QCT-based FEA and clinical vertebral frx in men**

63 Clin Fx, 242 No Frx Controls: Hazard ratios per SD reduction
All models adjusted for age, BMI, race

- **HR per SD**
  - DXA - L Spine BMD: 3.4 (2.4–4.7)
  - DXA - Fem Neck BMD: 2.1 (1.5–3.0)
  - QCT - Integral vBMD: 5.8 (3.9–8.7)
  - FEA - Vert Strength: 7.3 (4.6-11.4)

Keaveny et al, ASBMR 2010

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**FEA and Clinical Vertebral Fracture in Men**

63 Clin Fx, 242 No Frx Controls: Hazard ratios per SD reduction
All models adjusted for age, BMI, race

- **HR per SD**
  - DXA - L Spine BMD: 3.4 (2.4–4.7)
  - DXA - Fem Neck BMD: 2.1 (1.5–3.0)
  - QCT - Integral vBMD: 5.8 (3.9–8.7)
  - FEA - Vert Strength: 7.3 (4.6-11.4)

- **Adj LS BMD**
  - DXA - L Spine BMD: 2.1 (0.6 - 1.4)
  - QCT - Integral vBMD: 9.4 (5.1-17.4)
  - FEA - Vert Strength: 8.5 (4.5-16.2)

Keaveny et al, ASBMR 2010

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**QCT-based finite element analysis of hip vs femoral BMD for prediction of hip fracture**

- **Hazard Ratio (95% CI)**
  - Older men (Mr OS)
    - 40 hip fx vs 210 controls: 4.4 (2.4-9.1) 6.5 (2.3-18.3)
  - Men and women (AGES)
    - 199 hip fx vs 724 control: 3.3 (2.8-4.1) 4.1 (3.4 - 5.2)

* Adjusted for age, BMI, race

1 Orwoll et al, JBMR 2009; 2 Kopperdahl et al, ASBMR 2010

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**VFx Case**

Str = 4656 N

**Control**

Str = 6095 N

Melton et al, JBMR 2008
QCT-based FEA — Effect of ibandronate treatment on femoral strength
(~ 40 postmenopausal women / group, 12 mo tmt, mean ± 95% CI)

Lewiecki, et al JCEM 2009

% Change at 12 mo in femoral strength vs BL

* p<0.05 vs baseline

QCT-based FEA — Effect of denosumab on femoral strength
(48 PBO, 51 denosumab, 36 mo tmt, mean ± 95% CI)

Keaveny et al, ASBMR 2010

* p<0.05 vs baseline

QCT-based Finite Element Analysis:
Effect of denosumab on femoral and vertebral strength
(48 PBO, 51 denosumab, 36 mo tmt, mean ± 95% CI)

Keaveny et al, ASBMR 2010

* p<0.05 vs baseline

Discrimination of wrist fx subjects by FEA

Boutroy et al, JBMR 2008

-15% FX CON

Estimated failure load

Fracture Control

distal
proximal

0 MPa 20

0 1000 2000 3000 4000

CON FX
Considerations for applying FEA to clinical studies

- Loading conditions?
  - Falls are variable
  - Activities that cause vertebral fx largely unknown
  - Role of intervertebral disk degeneration?

- Assume relationship between QCT-density and tissue mechanical properties

- Clinical QCT does not reflect sub-mm trabecular architecture or cortical porosity

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

Several techniques show promise for non-invasive assessment of bone microarchitecture and strength.

- For clinical research -- YES!
  - Pathophysiology

- For clinical trials -- YES!
  - Differentiate mechanism of action

- For routine clinical practice -- NOT YET!
  - Need standardization, reference data, prospective studies

Beyond BMD...what is the hope for new non-invasive imaging tools?

- Gain insight into pathophysiology of disease and effects of treatments

- Enhance identification of those at greatest risk for fracture

- Improve monitoring of treatment response

- Serve as endpoints for fractures in clinical trials

Understanding Fracture Risk: Today and Tomorrow

QCT, MRI, HRCT → FEA

BMD → Bone Mass Distribution

Micro-Architecture

SKELETAL FRAGILITY

Prev Frx Age → Bone Turnover

Damage → Collagen

Mineralization

Bone Turnover
Thank you for your attention

Acknowledgements
Sharmila Majumdar
Andrew Burghardt
Tony Keaveny
David Kopperdahl

Femoral neck cortical thickness varies around neck circumference

Cortical porosity and trabecularization of the endocortical surface with age

Prior studies have likely underestimated cortical bone loss

Zebaze et al, Lancet 2010