Bone Quality by QCT and HR-pQCT: Translation to Multicenter Clinical Research

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Introduction

- QCT and HR-pQCT are X-ray based imaging techniques used to assess bone quality at a macro-scale (mm) and micro-scale (µm).
- From images, we calculate bone structure, density and strength.
- Bone measurements used to evaluate bone quality, investigate age-, sex, and race-related differences, monitor drug therapies, and assess fracture risk.
- Currently, QCT and HR-pQCT lack of some degrees of standardization, which prevents them to be used clinically.
  - Cross-scanner calibration (QCT)
  - Acquisition procedures (HR-pQCT)
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Scanner Cross-Calibration
Quantitative Computed Tomography (QCT)

- Pad phantom positioned under the patient allows transformation from Hounsfield Units to bone mineral density (mg/cm$^3$HA)

- Volumetric quantification of bone mineral density and geometry separately for cortical and trabecular bone

- Assessment of bone strength through finite element models (geometry and mechanical properties directly derived from images)

Adams 2009; Lang 2010
Why Do We Need Cross-Scanner Calibration?

- Inter-scanner acquisitions
  - Multicenter studies, longitudinal studies with scanner substitution
  - Inter-scanner differences are systematic (hardware and software) and patient-specific (beam hardening effect)
Beam Hardening Effect and Patient’s Size

- Attenuation of X-rays depends on energy of emitted photons, body tissue and size, and location of the region of interest

Hsieh 2009; Levi 1982
Aim of Cross-Calibration

- To create **correction equations** that allows us to reduce *inter*-scanner errors to *intra*-scanner precision errors

- Different anthropomorphic phantoms are used to cross-calibrate

- Equations are calculated regressing bone mineral density from images acquired on different scanners

- Inter-scanner differences remain and body size has an effect

- There is no current standard solution for QCT scanner cross-calibration

Birnbaum 2014, Carpenter 2014
Anthropomorphic Hip Phantom (AHP)

- Simulates the anatomy and the beam-hardening environment of the pelvis
- Calibration hip to calculate cross-calibration regression
- Test hip inserts to assess the quality of the regression for old and young subjects
- Three body circumferences simulating normal, medium-sized and obese subjects
Experiment

- Anthropomorphic hip phantom scanned on 4 scanners
  - GE VCT 64 System and Siemens Biograph/Definition Flash at UCSF and Mayo Clinic
- Different configuration of age (old/young) and size (no/small/large)

- Cross-calibration procedure
  - Calculated regression line on BMD of phantom calibration hip
  - Tested regression line on BMD of phantom test hip
  - Applied regression line to BMD of 16 women (age: 64±3 yrs) scanned on GE and Siemens scanners at UCSF
Calculating BMD For Phantom Images

- Same region segmented in all images using affine registration
- One reference image semi-automatically segmented avoiding partial volume effect voxels
Calculating BMD and Body Size For Subjects

- Calculation of BMD (threshold-driven region growing)

- Calculation of body size (morphologic operators and Hough transform)

Lang 2010, Carpenter 2014
Calculating Inter-Scanner Corrections

- Regression lines for BMD of images from different scanners

Regression line applied to:
- test hip
- human subjects
Results – Calibration Hip BMD and Inter-Scanner Corrections

- The most stable scanner with respect to body size was the Siemens at UCSF → reference scanner
- For the other scanners, *intra*-scanner differences of BMD were larger for large body size

- *Inter*-scanner differences of BMD were larger
  - For phantom with large girdle
  - For cortical bone

- In *inter*-scanner regressions, slopes and intercepts were larger for large ring and GE system
- For subjects, we used inter-scanner regression calculated from phantom with old test hip and no girdle

\[ \text{BMD}_{\text{GEcrosscal}} = 0.998 \times \text{BMD}_{\text{GE}} - 17.126 \]
Results – Testing Corrections on Test Hip and Subjects

- Before correction, inter-scanner differences were significant in all compartments, both for old and young test hip.

- After correction, differences reduced considerably, although not significantly.

- Mean differences between BMDs decreased after correction, but standard deviation remained the same.

<table>
<thead>
<tr>
<th></th>
<th>Ct. BMD</th>
<th>Tb. BMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Correction</td>
<td>17.95±17.50</td>
<td>14.42±5.96</td>
</tr>
<tr>
<td>After Correction</td>
<td>-5.81±14.35</td>
<td>-3.76±6.67</td>
</tr>
</tbody>
</table>
Discussion

- Novel anthropomorphic hip phantom simulates anatomy and beam hardening effect of the pelvis to calculate cross-scanner corrections
- Intra- and inter-scanner BMD measurement differences increase when body size increases and are larger for cortical bone
- Cross-scanner correction removed systematic inter-scanner differences, but patient specific differences are still present
Next Steps

- Linear regression does not reduce patient-specific errors in cross-scanner calibration → different approach to the problem

- Currently testing combined cross calibration on 120 patients scanned at UCSF and Mayo Clinic on 4 different scanners
Publications


Acknowledgments

- **PI**
  - Thomas Lang
- **Mayo Clinic**
  - L. Yu, M. Bruesewitz, S. Khosla
- **Clinical coordinators**
  - I. Saeed (UCSF), L. McCready (Mayo Clinic)
- **Colleagues**
  - D. Carpenter, J. Carballido-Gamio
- **Funding**
  - NIH/NIAMS 5R01AR060700
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Standardization of Acquisition – Operator Precision in Reference Line Positioning
High-Resolution Peripheral Quantitative Computed Tomography (HR-pQCT)

- High resolution (82µm) *in-vivo* acquisition of distal radius and tibia with low radiation dose (3µSv)

- Morphometric measurements

- Bone density measurements
  - Tt.BMD, Ct.BMD, Tb.BMD

- Biomechanical measurements
  - L_{failure}, Ct.LF_{prox}, Ct.LF_{dist}
Operator Determines Region to Be Scanned

- Operator positions a reference line at a defined landmark on scout view image
- Scanned region is at a fixed distance from reference line
- Morphometric and densitometric measurements change considerably along bone axis
- Effects on data comparability in cross-sectional studies, in particular multicenter studies
- → Precise positioning of reference line

Modified from Boyd, 2008
Previous Literature and Aim

- Scan/rescan total precision errors are smaller
  - For tibia (<5.2%) than for radius (<6.3%)
  - For densitometric (<1.5%) than for structural (<4.5%) measurements

- No study has systematically evaluated the role of HR-pQCT operators in reference line positioning

- To analyze the role of operator precision in a multicenter HR-pQCT setting
  - Variability of reference line positioning
  - Consequent effects on bone measurements

Operators and Imaging

- Operators from eight imaging centers
  - University of Calgary
  - University of British Columbia
  - UCSF
  - Mayo Clinic
  - Columbia University
  - Harvard
  - Université de Lyon
  - University of Melbourne

- Image acquisition
  - 2 operators at UCSF and Mayo Clinic
  - 56 male and female subjects (71±4 yrs)
  - Double-length stacks (220 slices)

- Simulation outcome measures
  - Reference line positioning
  - Effect on bone parameters
Simulation and Experiment

- Software reproducing acquisition software GUI

- Short-term intra-operator precision
  - Same scout images randomly repeated 3 times
  - 45 images for radius and 48 images for tibia

- Inter-operator precision
  - 50 images for radius and 55 images for tibia
### Results - Positioning Precision

<table>
<thead>
<tr>
<th>POSITIONING PRECISION ERROR</th>
<th>Intra-operator $SD_{RMS}[mm]$</th>
<th>Inter-operator $SD_{RMS}[mm]$</th>
</tr>
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<tbody>
<tr>
<td>Radius</td>
<td>0.24</td>
<td>0.68</td>
</tr>
<tr>
<td>Tibia</td>
<td>0.13</td>
<td>0.30</td>
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- Positioning precision error for radius was double then for tibia
- Inter-operator positioning precision was double than inter-operator positioning precision
### Results – Bone Parameter Measurements

<table>
<thead>
<tr>
<th>BONE PARAMETERS ERRORS</th>
<th>Intra-operator CV&lt;sub&gt;RMS&lt;/sub&gt;[%]</th>
<th>Inter-operator CV&lt;sub&gt;RMS&lt;/sub&gt;[%]</th>
<th>Scan-rescan CV&lt;sub&gt;RMS&lt;/sub&gt;[%]</th>
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<tr>
<td>Tt.BMD</td>
<td>1.39</td>
<td>3.69</td>
<td>0.89</td>
</tr>
<tr>
<td>Ct.Th</td>
<td>3.17</td>
<td>8.40</td>
<td>2.10</td>
</tr>
<tr>
<td>Ct.FL&lt;sub&gt;dist&lt;/sub&gt;</td>
<td>2.65</td>
<td>6.37</td>
<td>4.31</td>
</tr>
<tr>
<td>Tibia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tt.BMD</td>
<td>0.26</td>
<td>0.61</td>
<td>0.43</td>
</tr>
<tr>
<td>Ct.Th</td>
<td>0.94</td>
<td>1.97</td>
<td>1.25</td>
</tr>
<tr>
<td>Ct.FL&lt;sub&gt;dist&lt;/sub&gt;</td>
<td>0.92</td>
<td>2.02</td>
<td>4.01</td>
</tr>
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- Precision errors for bone parameters followed the trend of positioning precision errors (radius>tibia, inter-op>intra-op)
- Ct.Th had the highest variation for the radius
- Errors due to reference line positioning are equivalent too, or exceed, the in-vivo precision error (scan/rescan)
Discussion and Second Step

- Operator variability in reference line positioning is a major component of in-vivo precision error, for both radius and tibia.
- Inter-operator variability is significantly greater than intra-operator variability, for both radius and tibia.

- How can we reduce inter-operator variability?
Reference Line – Training and Evaluation

- Standard platform for operator training and certification

- Precise guidelines for reference line positioning
Operators and Experiments

- Six operators involved in the MrOS study with no previous experience with HR-pQCT
- MrOS operators trained on Reference Line – Training and Evaluation and obtained certification
- After certification, operators took part in the same experiments as the experienced operators (intra- and inter-reproducibility)
## Results - Positioning Precision

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<tr>
<td>Tibia</td>
<td>0.13/0.11</td>
<td>0.30/0.16</td>
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Experienced operators/New operators

- Intra-operator errors for new operators were similar errors of experienced operators
- Inter-operator positioning errors for new operators approached intra-operator precision errors
## Results – Bone Parameter Measurements

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<td>0.89</td>
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<tr>
<td>Ct.Th</td>
<td>3.17/3.46</td>
<td>8.40/4.90</td>
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<tr>
<td>Ct.FL$_{dist}$</td>
<td>2.65/3.03</td>
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<td>Ct.FL$_{dist}$</td>
<td>0.92/0.75</td>
<td>2.02/1.32</td>
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Experienced operators/New operators

- Precision errors for bone parameters followed the trend of positioning precision errors (radius>tibia, inter-op~intra-op)
Discussion and Third Step

- Inter-operator positioning precision errors were half for operators who used our training software to learn standard positioning procedures.

- Our training platform could be a useful tool to homogenize operator positioning, especially for multicenter studies.

- How can we make the tool available for the HR-pQCT community?
Reference Line – Training and Evaluation

Web Application

webapps.radiology.ucsf.edu/refline
Next Steps and Related Works

- Add modules to webapp for hand and knee (OA), and pediatric subjects
- Change radius anatomical landmarks to decrease precision errors
- Anatomically standardized positioning of the region to be scanned (%limb length)
- Detection and correction of patient motion in images, especially radius
- Development of pediatric protocol
- Scanner cross-calibration
Publications


Acknowledgments

- **PI**
  - Andrew Burghardt

- **Experienced HR-pQCT Operators and PIs**

- **MrOS operators**
  - D. Cusick, S. Hanson, K. Jacobson, K. Kent, P. Miller, N. Webb

- **Webapp**
  - Caroline Mai Chan

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  - I. Saeed (UCSF), L. McCready (Mayo Clinic)

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  - J. Peterson (Mayo Clinic)

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