Predictions of Vertebral Strength using QCT and Intra-Vertebral Heterogeneity in Density vs. DXA

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Introduction
The density and architecture of trabecular bone are highly non-uniform throughout the vertebra. This intra-vertebral heterogeneity has often been proposed as a main reason why average measures of bone mineral density (BMD) explain only ~60% of the variance in vertebral strength [1] and do not discriminate well between fracture and non-fracture cohorts [2]. Using micro-computed tomography (µCT) imaging, we showed that accounting for intra-vertebral heterogeneity improved predictions of vertebral strength [3]. However, this has not been demonstrated yet with a clinical imaging modality. Given that spatial variations in trabecular density can be assessed non-invasively via quantitative computed tomography (QCT), the overall goal of this study was to determine the influence of the intra-vertebral heterogeneity in density, as quantified using QCT, on vertebral strength.

Specific Aims
- Compare heterogeneity measures from clinical QCT and µCT imaging.
- Assess the accuracy of predictions of vertebral strength made using:
  1) the intra-vertebral heterogeneity in density;
  2) estimates of areal BMD; and
  3) measures of the axial rigidity of the vertebra.

Materials and Methods

QCT Density Measures:
- Average Density – Average volumetric density (vBMD) and cross-sectional area of one voxel was calculated for the largest elliptical cylinder that was contained within the centrum (elliptical VOI, Figure 2).
- Intra-Vertebral Heterogeneity in Density – Inter-quartile range (IQRBMMD) was calculated from the average densities of contiguous 5mm cubes (Figure 2).
- Areal BMD – Average areal BMD (aBMD) was calculated to simulate lateral dual-energy X-ray absorptiometry (DXA) scan (Figure 3) [4].

µCT Density Measures:
- For the VOIs defined for QCT scans, average and inter-quartile range of bone volume fraction (BV/TV and IQRBV/TV) and apparent mineral density (ρapp and IQRapp) were calculated.

Axial Rigidities:
- The axial rigidity, or resistance to axial loading, was estimated for each transverse cross-section of the vertebra [5] as:
  \[ EA = \sum_{i=1}^{N} E_i \cdot dA; \]
  \[ N = \# \text{ voxels in the cross-section}; \]
  \[ dA = \text{ cross-sectional area of one voxel} \]
  \[ E_i = \text{ Young's modulus of voxel } i \]

where stiffness is estimated using [6]; \( E_i = -34.7 + 3230 \rho_{QCT} \). The minimum value of EA over all transverse cross-sections (EAmin) was identified.

Vertebral Strength:
- After preconditioning, the vertebrae were loaded to failure at a rate of 0.25 mm/sec.
- The ultimate force (Ful) was defined as the maximum force sustained by the vertebra.

Statistical Analyses:
- Linear regression analysis was used to determine the dependence of ultimate force on each of the following combinations of explanatory variables:
  1) vBMD*CSA;  2) vBMD*CSA and IQRBMD;  3) aBMD;  4) EAmin.
- Restricted vs. full F-tests were used to compare regression models 1 and 2.
- J-tests ranked the four regression models from best to worst predictive performance.

Conclusions
- Clinical QCT images can be used to quantify intra-vertebral heterogeneity in density. The QCT measures were highly correlated to those calculated for the same vertebrae using µCT images.
- Incorporating measures of the heterogeneous distribution of bone tissue throughout the centrum provided improved predictions of vertebral strength as compared to current clinical standards that use only average BMD from QCT or DXA.
- These findings show that non-invasive assessments of the intra-vertebral heterogeneity in density can have immediate bearing on current clinical approaches to estimating vertebral strength and fracture risk. The higher radiation dose incurred with QCT as compared to DXA may thus be acceptable for certain indications when seeking more accurate assessment of bone strength and fracture risk.

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References

Table 1. Correlations between density measures calculated from QCT and µCT images

<table>
<thead>
<tr>
<th>Voxel Density</th>
<th>Correlation Coefficient</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>vBMD</td>
<td>0.612</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>vBMD*CSA</td>
<td>0.656</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IQRBMD</td>
<td>0.814</td>
<td>&lt;0.001</td>
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<tr>
<td>IQRBMD*CSA</td>
<td>0.833</td>
<td>&lt;0.001</td>
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Table 2. Regressions of Fult against measures of density

<table>
<thead>
<tr>
<th>Model</th>
<th>Explanatory Variables</th>
<th>R²</th>
<th>RMSE (kN)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>vBMD*CSA, IQRBMD</td>
<td>0.59</td>
<td>0.36</td>
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<tr>
<td>1</td>
<td>vBMD*CSA</td>
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<tr>
<td>3</td>
<td>aBMD</td>
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<tr>
<td>4</td>
<td>EAmin</td>
<td>0.01</td>
<td>0.54</td>
<td>0.730</td>
</tr>
</tbody>
</table>

Table 3. Regression models ranked from best (top) to worst (bottom) predictions of vertebral strength as determined by J-test (RMSE: root mean square error)