Impairment of Bone Following Renal Transplantation Assessed by MRI and pQCT based Finite-Element Modeling

INTRODUCTION
Although bone fractures among patients with end-stage renal disease (ESRD) are markedly greater than in the general population [1, 2], the short-term mechanical effects of renal transplantation (RTxp) remain uncharacterized. Currently, the non-invasive assessment of bone in ESRD is mostly based on bone-mineral density (BMD), which correlates poorly with fracture risk [3, 4]. High-resolution magnetic resonance imaging (μMRI) in conjunction with micro-finite-element (μFE) analysis has shown great potential in estimating mechanical properties of bone at peripheral sites in response to intervention in vivo [5, 6]. However, since μMRI-based in-vivo measures of bone mineralization are not yet available, bone tissue is assumed to have a constant elastic modulus (~15 GPa) when generating μFE models. The purpose of this study is to examine the utility of incorporating peripheral quantitative computed tomography (pQCT) based trabecular BMD measures into the μMRI-based μFE model, thereby making the approach suitable for capturing the temporal variations in bone’s mechanical competence even when trabecular bone volume fraction does not change following RTxp. Towards this goal, we computed the cortical and trabecular bone stiffness of the distal tibia in RTxp recipients as part of an ongoing longitudinal study via a μMRI-based μFE model incorporating BMD and compared the results to those obtained when a constant tissue modulus is assumed.

METHODS
This study consisted of ESRD patients (22 female and 17 male, 20-61 yr of age) who underwent RTxp to restore their renal function.

Image acquisition: The tibial metaphysis was imaged within two weeks (baseline) and at six months after RTxp using μMRI with a custom-designed receive coil and 3D spin-echo pulse sequence [7] on a 1.5-T scanner at 137 × 137 × 410-μm³ voxel size. Volumetric BMD was also measured at the same anatomic site for similar time points using pQCT.

Image processing: First, the raw μMR data were corrected for in-vivo subject motion during the scan [8, 9]. Image intensity variations across the volume produced by inhomogeneous sensitivity of the MR receiver coil were then corrected using a local thresholding algorithm [10]. Subsequently, co-registered trans-axial slabs of 5 mm thickness were extracted from the 3D image dataset at the two time points for each subject [11]. Finally, three sets of 3D volumes, referred to as whole-bone (WB) section, trabecular-bone (TB) compartment, and cortical-bone (CB) compartment, were extracted from each image by delineating the endosteal and periosteal boundaries using a custom-developed operator-guided segmentation algorithm [12].

FE-model generation: First, the grayscale values of the images were linearly scaled to cover the range from 0 to 100%, with pure marrow and pure bone having minimum and maximum values, respectively. We refer to the resulting 3D array as the bone-volume fraction (BV/TV) map with individual voxel values representing the fraction of the voxel occupied by bone (i.e. BV/TV). Next, each voxel in the BV/TV map was directly converted to a hexahedral finite element with dimensions equal to the voxel size. The bone tissue was assumed to be isotropic and linearly elastic. For the BMD-scaled model, each element’s Young’s modulus (YM) was set linearly proportional to the BVF at each voxel and pQCT-derived normalized BMD such that YM = (15 GPa) × (BVF) × (BMD/μBMD) where BMD is a constant representing the typical BMD in an age-matched healthy adult (BMD = 1000 mg/cm³) for all nodes in the proximal face of the μFE model while keeping those in the distal face constrained. The axial stiffness was obtained as the ratio of the stress on the proximal face to the applied strain.

Computation of stiffness: To estimate the axial stiffness of the cortical bone (KCB), trabecular bone (KTB), and whole bone (KWB) section (i.e. CB and TB jointly), compressive loading was simulated along bone’s longitudinal axis by applying a constant displacement (~1% strain) to all nodes in the proximal face of the μFE model while keeping those in the distal face constrained. The axial stiffness was obtained as the ratio of the stress on the proximal face to the applied strain.

Computation of morphological parameters: To quantify the structural changes in the tibial metaphysis following the RTxp, TB volume fraction (BV/TV), TB thickness (Tb.Th), and CB thickness (Cb.Th) were computed on the basis of segmented BVF maps.

RESULTS
The three regions of the tibial metaphysis subjected to the μFE analysis are illustrated in Figure 1 together with the estimated mean temporal changes in axial stiffness between the RTxp and 6-month follow-up. Table 1 summarizes the observed temporal variations in surrogate parameters of bone strength measured at the tibial metaphysis. Neither TB nor CB thickness showed significant change between the two time points. Similarly, BV/TV was unable to detect any temporal changes. The relative reduction in BMD at the same site was small (2.1%), albeit highly significant (p=0.0002). Since BV/TV does not change, the decrease in CBF must be due to decrease in mineralization.

Table 1: Relative changes in commonly used markers of bone quality between the baseline and 6-month follow-up at the tibial metaphysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>% Change</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trabecular bone thickness (Tb.Th)</td>
<td>-0.23</td>
<td>0.36</td>
</tr>
<tr>
<td>Cortical bone thickness (Cb.Th)</td>
<td>-1.2</td>
<td>0.37</td>
</tr>
<tr>
<td>Trabecular bone volume fraction (BV/TV)</td>
<td>1.7</td>
<td>0.23</td>
</tr>
<tr>
<td>Bone mineral density (BMD)</td>
<td>-2.1</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

DISCUSSION
As a result of the heightened steroid usage and time required to restore the renal function of the new kidney, RTxp recipients are hypothesized to lose bone mass during the first few months following the RTxp. In this work, we have provided compelling evidence for μMRI-based in-vivo μFE analysis for detecting expected short-term changes in bone’s axial stiffness at the tibial metaphysis following RTxp. Surrogate markers of bone strength—Tb.Th, CB.Th, BV/TV, etc.—were not very useful in detecting the hypothesized short-term changes during the first 6 months following RTxp. Incorporation of the temporal variations in BMD, albeit small (2.1%), into the μFE model, improved the sensitivity of the FE approach. Finally, the μFE approach detailed here has promise for a much-needed technique to assess the mechanical implications of RTxp in patients with ESRD and other bone diseases.

REFERENCES