Combined implications of bone′s structural and material impairment following renal transplantation assessed by μMRI based finite-element modeling

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INTRODUCTION: High-resolution magnetic resonance imaging (μMRI) based micro-finite-element (μFE) modeling at peripheral sites is emerging as an attractive means to assess short-term alterations in bone's mechanical competence caused by disease or in response to intervention [1, 2]. In this approach, subject-specific bone's 3D micro-architecture derived from *in-vivo* μMRI is taken as input to a finite-element model. Ordinarily, bone tissue is assumed to have a constant elastic modulus (~15 GPa) because μMRI-based *in-vivo* measures of bone mineralization are not yet available. As a consequence, μMRI-based μFE analysis is not sensitive to possible changes in bone-mineral density (BMD) observed in patient populations such as those with end-stage renal disease (ESRD) following renal transplantation (RTxp) [3]. On the other hand, BMD alone correlates poorly with fracture risk [4, 5], which is markedly greater in ESRD than in general population [6, 7]. The purpose of this study is to examine the feasibility of generating μMRI-based μFE models with subject-specific tissue modulus by incorporating peripheral quantitative computed tomography (pQCT)-derived cortical and trabecular bone BMD measures, thereby making the approach suitable for capturing the temporal variations in bone's mechanical competence resulting from simultaneous structural and material alterations. 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 modeling with subject-specific tissue modulus 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 FLASE pulse sequence [8] on a 1.5-T (Siemens Sonata) scanner at 137 × 137 × 410-μm^3 voxel size with the third dimension being along the axial direction. Volumetric trabecualr and cortical BMD were also measured at the metaphysis (centered at the μMRI site) and diaphysis (site of thickest cortex), via pQCT.
Image processing: First, the raw μMR data were corrected for involuntary subject motion during the scan [9, 10]. Image intensity variations across the volume produced by inhomogeneous sensitivity of the MR receiver coil were then corrected using a local thresholding algorithm [11]. 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 [12]. 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 [13].
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 (BVF) map with individual voxel values representing the fraction of the voxel occupied by bone (i.e. BV/TV). Next, each voxel in the BVF map was directly converted to a hexahedral finite element with dimensions equal to the voxel size. Two sets of μFE models were generated using (1) generic tissue modulus (GTM model) and (2) *subject-specific* tissue modulus (SSTM model). For the GTM model, empirically determined tissue modulus of 15 GPa was assumed [2]. For the SSTM model, finite elements representing cortical and trabecular bone were assigned different tissue moduli using the linear relationship with corresponding BMD (first derived by Guo et al. [14] and extended to volumetric BMD by Diamant et al. [15]). Here, trabecular BMD was first normalized by the μMR-derived BV/TV of the trabecular bone compartment before computing the tissue modulus to account for the modulation of BMD by the spatial distribution of the trabecular network during pQCT scanning, while measured cortical BMD was directly used because pQCT-derived cortical BMD measures are highly accurate if the cortex is thicker than the full width at half maximum of the scanner's point-spread function [16, 17]. Finally, tissue moduli of all models at each finite element were linearly modulated by the BVF value of the corresponding voxel to account for partial volume effects in the limited spatial resolution regime of *in vivo* μMRI. The Poisson's ratio was kept constant at 0.3 for all models.
Computation of stiffness: To estimate the axial stiffness of the cortical bone (K_{CB}), trabecular bone (K_{TB}), and whole bone (K_{WB}) section (i.e. CB and TB jointly), compressive loading was simulated in the linear elastic regime along bone's longitudinal axis by applying a constant displacement (~1% strain) to the proximal face of the μFE model while keeping the distal face constrained. The axial stiffness was obtained as the ratio of the stress on the proximal face to the applied strain.

RESULTS: The three regions of the tibial metaphysis subjected to 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. GTM-model-derived WB and TB stiffness showed a relative reduction of 6.47% (p=0.001) and 9.45% (p=0.004), respectively, between the baseline and 6-month follow-up while the relative change in CB stiffness was not significant. SSTM-model-derived axial stiffness showed 10.7% (p=0.0001) and 16.3% (p=0.0005) decline in WB and TB regions between the RTxp and 6-month follow-up, while the reduction in CB stiffness failed to reach statistical significance. Between the two time points, pQCT-derived trabecular and cortical BMD declined by 2.08 % (p<0.0001) and 0.262 % (p=0.02), respectively, while no significant changes were observed in BV/TV, trabecular bone thickness (Tb.Th) and cortical bone thickness (Cb.Th).

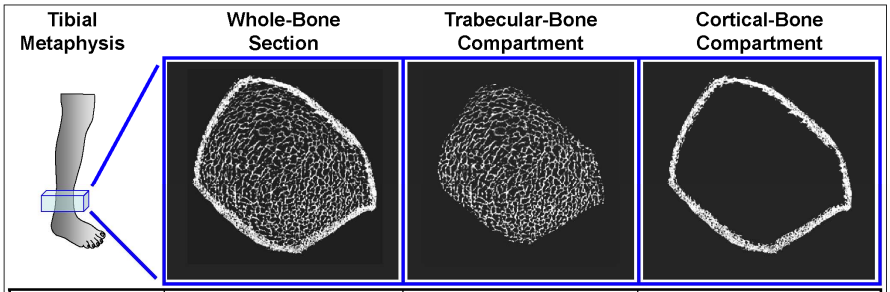

Figure 1: BVF maps of different regions of tibial metaphysis analyzed via μFE modeling with detected mean change in stiffness between the baseline and 6-months following RTxp indicated.

CONCLUSIONS: As a consequence of the heightened steroid usage and time required to restore the renal function of the new kidney, RTxp recipients are expected 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—BV/TV, Tb.Th, CB.Th, etc.—proved not to be useful in detecting the hypothesized short-term changes during the first 6 months following RTxp. Incorporation of the temporal variations in BMD, albeit small, into the μFE model improved the detection sensitivity of the FE approach by capturing both the architectural and material alterations in the ESRD population. Further, since BV/TV did not change during the study period, the decrease in BMD is likely due to decreased mineralization density. Finally, the μFE approach detailed here has promise for a much needed technique to assess the mechanical implications following RTxp and in other bone diseases.

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