Initial Results from Baseline Structural and Computational Biomechanics μMRI Study in Postmenopausal Women

Y. A. Bhagat[1], C. S. Rajapakse[1], J. F. Magland[1], M. J. Wald[1], T. M. Scattergood[2], P. J. Snyder[2], and F. W. Wehrli[1]
[1]Laboratory for Structural NMR Imaging, University of Pennsylvania, Philadelphia, PA, United States, [2]Division of Endocrinology, Diabetes and Metabolism, University of Pennsylvania, Philadelphia, PA, United States

INTRODUCTION: Osteoporosis is a disease of the remodeling imbalance between bone formation and resorption [1]. Accelerated bone resorption is believed to be a major pathogenic mechanism in postmenopausal bone loss. Antiresorptive and anabolic drugs hold the potential to return to the premenopausal range, the somewhat elevated levels of bone turnover found in such women. Bone mineral density (BMD) is a poor predictor of fracture risk and does not provide insights into bone quality, a secondary marker for elucidating changes in trabecular bone (TB) microarchitecture [2]. Furthermore, at present, remodeling induced changes upon treatment can only be observed by bone biopsy and there only in paired biopsies from different anatomic sites. High resolution μMRI-based virtual bone biopsy (VBB) techniques permit quantification of TB microarchitectural changes at peripheral skeletal sites such as the distal tibia [5]. Here, we present initial data from an ongoing longitudinal clinical study at 3T designed to evaluate the effectiveness of teriparatide (PTH) against zoledronic acid in 30 postmenopausal women with osteoporosis. A subset of the patients were also evaluated at 7T. We report some of the baseline data by examining inter-modality associations including finite-element (μFE) derived axial stiffness calculations and structural parameters and their relationships to densitometric variables as well as initial longitudinal data in a few subjects studied so far.

METHODS: The left distal tibiae of 30 postmenopausal women (ages, 58-84) with osteoporosis were scanned with a 4-channel receive array using 3D fast large angle spin echo (FLASE) [3] on a Siemens 3T Tim Trio system. The patients were then randomized to treatment by either PTH (N=15, 20 μg daily, s/.c) or zolendronic acid (N=15, 5 mg i.v. annually). A subset of these patients (N=5) were also scanned on a Siemens 7T whole body system with a shielded Helmholtz transmit coil with a decoupled 4-element phased array identical to the RF coil used at 3T. Data at 7T were acquired using a novel 3D fast spin echo with out-of-slab cancellation (FSE-OSC) sequence [4] as FLASE exceeds the acceptable specific absorption rate levels at 7T [4]. The 3D FLASE (3T) and 3D FSE-OSC (7T) acquisitions were performed according to previously published parameters [5, 6]. The baseline data from both, 3T and 7T, resulted after processing in a 3D grayscale image of 137x137x410 μm^3 voxel size with each voxel representing bone volume fraction (BVF, bone vol. (BV)/total vol. (TV)). Follow-up scans were performed once, at 12 months at 3T and twice, at 6 months and 12 months at 7T. An earlier follow-up scan was performed at 7T (6 months) as we expected to utilize the SNR increase at the higher field strength for enhanced detection sensitivity. Each baseline image was manually masked to isolate the tibial TB region. The full tibial cross-section masks were subjected to VBB processing [7] involving BVF mapping, skeletonization and digital topological analysis (DTA). Parameters quantifying scale and topology included BVF, surface/curve (S/C) ratio and erosion index (EI). FE analysis was performed on the full tibial TB mask with image voxels converted to hexahedral finite elements [8]. Young's modulus and Poisson's ratio of pure bone tissue were chosen as 15 GPa and 0.3, respectively, and the Young's modulus of each finite element was set proportional to the BVF of the corresponding voxels. Finally, compression loading was simulated along bone's axial direction by applying a strain (~0.1) to the proximal face of the FE model and keeping the distal face constrained. Axial stiffness was computed as the stress/strain ratio. Follow-up images were identically masked and full 3D transformations (3 rotations and 3 translations) were determined between baseline and follow-up images using a fast, rigid body registration algorithm [9]. Prior to application of the transformation, the follow-up images were upsampled in k-space by a factor of three and subsequently downsampled again after mapping the images to the grid of the baseline images. These images were accordingly subjected to VBB processing. The patients also underwent scanning by dual energy x-ray absorptiometry (hip, femoral neck and spine) and peripheral quantitative computed tomography (pQCT, distal tibia) for serial assessment of BMD.

RESULTS: BVF derived from 3T data was moderately correlated with BMD ($p<0.001$, hip ($R^2=0.38$) and femoral neck ($R^2=0.24$)). **Figure 1** shows a plot comparing BVF and trabecular density as measured by pQCT in 30 patients scanned at 3T using 3D FLASE. A moderate correlation was observed between the measures reflecting that 38% of the variability in trabecular BMD can be attributed to the variation in BVF. **Figure 2** highlights a comparison of BVF and axial stiffness at 3T (**A**) and 7T (**B**). Despite the lower number of patients at 7T, a strong correlation between the two parameters was observed, as demonstrated previously at lower fields such as 1.5T [8]. **Figure 3** displays representative images from a 67-year old patient randomized to zolendronic acid. The 3T 12 month follow-up image and 7T baseline, 6 month and 12 month images were co-registered to the patient's 3T baseline image. The mean SNR values were 14.1 ± 0.14 and 34.6 ± 0.3 at 3T and 7T, respectively. The co-registered images and the 3D rendered VBB cores (23x23x68 μm^3 voxels) highlight the level of reproducibility achievable across the time series (color coding: surface interior – gray, surface edges – red, curves – blue). While most structural features are replicated in repeat VBBs, some remodeling changes are clearly detectable manifesting as small plate perforations (green arrows) observed at baseline, diminishing and filling in over the course of the treatment. The visual changes are also apparent when inspecting the quantitative measures as increases in BVF (up to 17%), S/C (up to 28%) and reductions in EI (down to 21%) were observed. The use of the novel 3D FSE-OSC sequence combined with higher SNR levels at 7T demonstrates more plate-like topology as evident in the co-registered virtual cores.

CONCLUSION: The data in this ongoing treatment study show internal consistency between structural, mechanical and densitometric measures and suggest that the hypothesized changes in these parameters can be quantified.

REFERENCES: [1] Riggs. J Bone Miner Res 20(2):177 (2005). [2] Griffith. Ann NY Acad Sci 1192:45 (2010). [3] Ma. *MRM* 35:903 (1996). [4] Magland. MRM 63(3):719 (2010). [5] Wald. JMRI 31(5):1157 (2010). [6] Bhagat. 18th ISMRM:787 (2010). [7] Magland. Acad Radiol 15:1482 (2008). [8] Rajapakse. J Orthop Res 27:1263 (2009). [9] Magland. JMRI 29:118 (2009).
ACKNOWLEDGEMENTS: Eli Lilly for Forteo™, Novartis for Reclast®, and NIH Grants RO1 AR53156 and ROI DK75648.

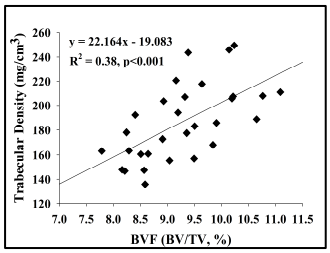

Figure 1: Comparison of BVF (3T FLASE) and BMD measurements (pQCT) at the distal tibia in 30 patients.

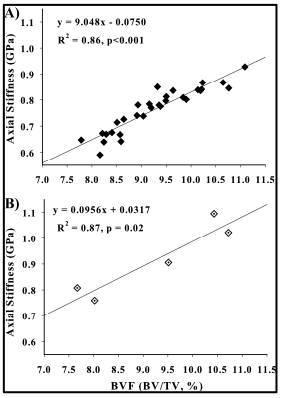

Figure 2: Comparison of BVF and TB axial stiffness in baseline data within 30 patients at 3T using 3D FLASE (**A**) and 5 patients at 7T with 3D FSE-OSC (**B**).

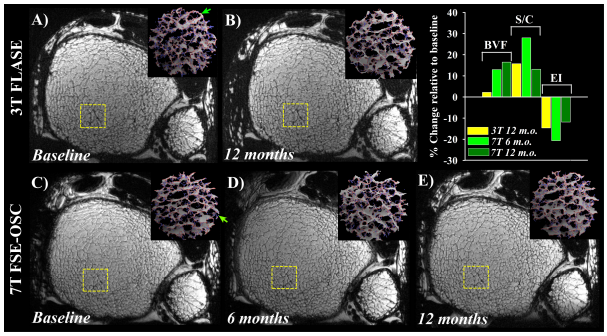

Figure 3: Representative co-registered axial images and cores of a 67-year old patient randomized to Zoledronic acid acquired with 3D FLASE at 3T (**A**, **B**) and 3D FSE-OSC at 7T (**C-E**).