Longitudinal Characterization of Trabecular Bone Microstructure and Computational Biomechanics for Determining Treatment Effects in Postmenopausal Women

Yusuf A Bhagat[1], Maite Aznarez-Sanato[1], Jeremy F Magland[1], Theresa M Scattergood[2], Peter J Snyder[2], and Felix 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 linked to the remodeling imbalance between bone formation and resorption [1]. Accelerated bone resorption has been identified as a major pathogenic mechanism in postmenopausal bone loss. Antiresorptive and anabolic drugs hold the potential to arrest or reverse bone loss. 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]. High resolution µMRI-based virtual bone biopsy (VBB) techniques permit quantification of TB microarchitectural changes at peripheral skeletal sites such as the distal tibia. Here, we present data from an ongoing longitudinal translational patient study at 3T and 7T designed to evaluate the effectiveness of drug intervention in postmenopausal women with osteoporosis. A subset of the patients were also evaluated at 7T.

METHODS: The left distal tibiae of 15 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=9, 20 µg daily, s/.c) or zoledronic acid (N=6, 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 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 1 year at 3T and twice, at 6 months and 1 year 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. 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, compressive 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 (E_{zz}) was computed as the stress/strain ratio. Follow-up images were identically masked and registered using a fast 3D rigid body registration algorithm [9]. 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 and DISCUSSION: BVF derived from baseline 3T-based 3D FLASE data was significantly correlated with trabecular density as measured by pQCT (R^2 =0.54, p=0.002). The association between these parameters was strong despite the fact that BVF derived from µMRI does not take into account changes in mineralization captured by pQCT. Co-registered baseline FLASE and FSE-OSC data sets in patients scanned at 3T and 7T yielded strong associations between parameters of scale, topology and mechanics (R^2=0.80-0.95, p<0.03). Following 1 year of treatment, no significant changes in trabecular BMD were observed. **Table 1** provides 3T-based 3D FLASE derived mean (±SD) values relaying serial changes in structure (BVF (BV/TV)), topology (S/C and EI) and mechanics (axial stiffness, E_{zz}) over one year post treatment. Increases of 3-9% were seen in S/C and axial stiffness suggesting that topology and mechanics are stronger determinants of treatment-induced changes in trabecular microarchitecture compared to BVF. **Figure 1** displays representative images from a 73-year old patient randomized to zoledronic 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 17.1 ± 1.1 and 31.9 ± 0.9 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 ellipses) 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 the VBB-derived parameters of 13-28% at 1-year relative to baseline. The use of the novel 3D FSE-OSC sequence combined with the factor of ~2 higher SNR at 7T demonstrates more plate-like topology as evident in the coregistered virtual cores.

CONCLUSION: Data in 15 women from this ongoing treatment study show an improvement in bone microstructural parameters over a 1-year period. Increases in SNR at ultra-high field or 7T may enable enhanced sensitivity which can be translated to earlier detection of therapy-induced remodeling changes as seen in some patients. At present, the blind has not been broken which is why we cannot distinguish the treatment arms and we report the intermediary data pooled.

REFERENCES: [1] Riggs. J Bone Miner Res 20:177 (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 31:1157 (2010). [6] Bhagat. JMRI 33:372 (2010). [7] Magland. Acad Radiol 15:1482 (2008). [8] Rajapakse. J Orthop Res 27:1263 (2009). [9] Magland. JMRI 29:118 (2009).
A**CKNOWLEDGEMENTS:** Eli Lilly for PTH (Forteo™), Novartis for Zoledronic acid (Reclast®), and NIH Grants RO1 AR53156 and ROI DK75648.

Figure 1: Representative co-registered axial images and virtual bone biopsy cores of a 73-year old patient (Zoledronic acid).

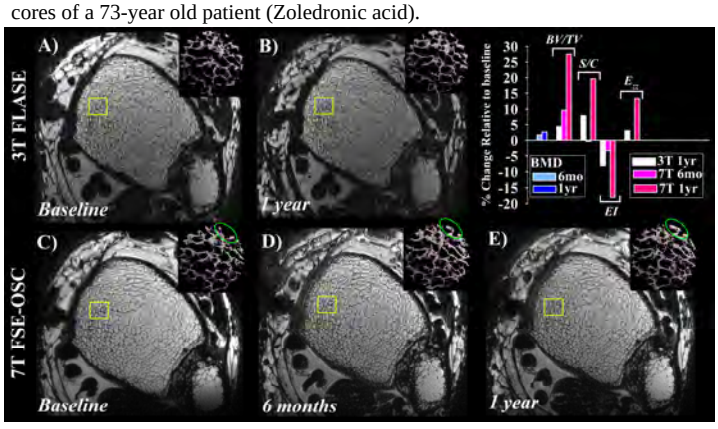

Table 1: Mean ± SD values (N=15, 3T) for parameters of scale, topology and biomechanics in baseline and 1-year follow-up 3T scans (*, p<0.05, paired *t*-tests).

Parameter	Baseline	1 year	%Diff	p-value
BV/TV (%)	8.80 ± 0.01	8.95 ± 0.01	1.79	0.073
S/C	6.53 ± 1.23	7.13 ± 1.37	9.26	0.002*
EI	0.74 ± 0.15	0.67 ± 0.12	-9.12	0.008*
E_{zz}	0.91 ± 0.14	0.94 ± 0.14	3.03	0.028*