Aging Augments the Suppression Ratio, A MRI Biomarker of Cortical Bone Porosity

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INTRODUCTION- The composition and microarchitecture of the cortical bone compartment are strong determinants of the overall mechanical competence of bone [1]. Ultra-short echo time (UTE) MR techniques can detect and quantify cortical bone water [2] comprising matrix water bound to collagen and mobile water residing in the lacuno-canalicular spaces and Haversian canals, respectively [3]. Of significant interest is the mobile water fraction as it scales with pore volume, which expands in senescence and particularly so in osteoporosis [4]. Although pores cannot be detected by high resolution imaging in vivo, the quantification of pore water would permit an indirect estimation of porosity. Here we present an alternate approach for a surrogate measure of porosity in the form of the suppression ratio (SR), i.e. a ratio of the unsuppressed to the soft tissue suppressed UTE signal intensity. The rationale driving this approach is that water in the larger pores possesses longer T2* values and will undergo a reduction in signal intensity by the suppression schemes employed to attenuate soft-tissue protons. Ex vivo SR data in concert with micro-CT-derived measures of porosity are provided to support in vivo results.

METHODS- Image Acquisition: The left mid-diaphyseal tibia (38% from the lateral malleolus) of 39 healthy females (24-81 years) was imaged at 3T (TIM Trio; Siemens Medical Solutions) using an 8-channel Tx-Rx knee coil. Preexisting bone water concentration (BWC) data were available from 32 subjects [5]. We used three soft tissue suppression schemes for UTE MRI to cancel and/or suppress signal from the long-T_2 species: 1) dual-echo UTE, 2) dual-band (DB)-UTE (saturation via dual band UTE pulses and 3) Inversion-recovery (IR)-UTE (inversion by adiabatic inversion pulses) as described previously [6, 7]. Imaging parameters common to all three sequences were: FOV= 180x180 mm^2, slice thickness= 5mm, TR/TE$_1$/TE$_2$= 300 ms/50µs/4.6ms, FA= 60°, sampling frequency BW= ±125 kHz, and 288 readout points for each half radial projection that resulted in a reconstructed matrix size of 512 x 512 and in-plane resolution = 0.35x0.35 mm^2. DB-UTE used an optimized dual-band saturation pulse (length=15ms, flip order=300, FA(water/fat)= 100°/110°, Suppression BW= 120 Hz on resonance, 320 Hz at fat resonance centered at 430 Hz (3T) and ripple values of 0.5%). IR-UTE employed an optimized hyperbolic secant pulse (Pulse BW/duration= 1kHz/20ms, 270 Hz frequency shift towards the lipid peak, 30% B1 variation and TI=100ms). Each sequence was of 5 min 12s in duration. The subjects were scanned by peripheral quantitative computed tomography (pQCT) for the assessment of cortical bone mineral density (BMD) at the same anatomical site.

Ex vivo Study: Thirteen whole-section 37mm long bone specimens were cut from tibiae obtained from human donors (9F, 4M, 27-97 years) at locations similar to the in vivo portion of this study. Bone specimens were housed in plastic tubes containing phosphate-buffered saline, stabilized with PVC pipes at either end and centrifuged to eliminate air bubbles. Imaging was performed with an elliptical Tx-Rx birdcage coil (3T) using the same protocol as detailed above for the in vivo scans. Micro-computed tomography (µCT, Skyscan, Kontich, Belgium) was performed using an isotropic spatial resolution of 9 µm to quantify porosity (pore volume/total volume) by segmentation in a single 2D slice.

Reconstruction and Analysis: Steps are shown in **Figure 1** and described elsewhere [7] in detail. Suppression ratio (SR) maps were computed as a ratio of the dual-echo UTE images (TE=50 µs) to the corresponding images (TE=50 µs) of both, IR and DB techniques. Manual segmentation of the periosteal and endosteal cortical boundaries was performed followed by extraction of mean IR and DB SR values as global cortical parameters [7]. Geometric parameters (Cortical thickness and normalized bone area (cortical area/total bone area)) were measured from GRE images [8] (**Figure 1**).

RESULTS and DISCUSSION- In Vivo: Both, IR and DB methods demonstrated an increase in SR with age (R^2=0.47-0.51, p<0.001; **Figure 2A**), suggesting the presence of larger pores with long T2* values in older individuals. Mean SR was 35% higher (p<0.001) in the older (N=18, 61-81 years) relative to the younger group (N=9, 24-38 years). Similarly, a significant difference (26%, p<0.001) in SR was observed between middle-aged (N=13, 40-56 years) and older individuals. The association between SR and age was stronger than that found between BWC and age (R^2=0.24, p=0.004, **Figure 2B**), given that BWC comprises both, bound and pore water fractions, and in the young, a higher proportion of bone water is collagen-bound [3]. Consequently, the association between BWC and SR is weaker (R^2=0.25-0.27, p<0.01). Cortical BMD was inversely associated with SR (R^2=0.44-0.46, p<0.001) suggestive of the notion that increased porosity is an outcome of osteoid loss, which in the case of constant mineralization density scales with volumetric BMD. Inverse associations (p<0.001) were seen between SR vs. cortical thickness (R^2=0.43) and SR vs. normalized bone area (R^2=0.51-0.53).

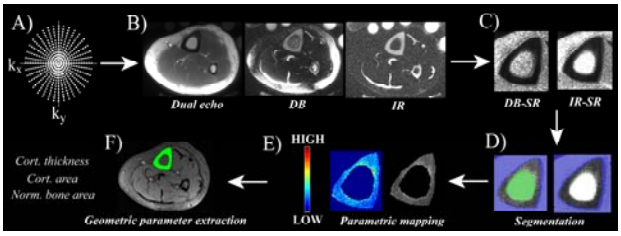

Figure 1: Steps showing k-space re-mapping (A), magnitude image reconstruction (B), SR mapping (C), segmentation (D), parametric mapping and analysis (E) and extraction of geometric parameters (F).

Ex vivo: Results from bone specimen scans corroborated the in vivo findings, i.e. a strong association between SR and age (R^2=0.76-0.82, p<0.001). Furthermore, we noted visual evidence of increases in SR with age that parallel those of µCT-derived porosity (**Figure 3**) and observed a significant correlation between measures from the two modalities (R^2=0.44-52, p<0.01). Increased SR is likely the result of a greater proportion of large pores (>100 µm) associated with longer T_2* values expected in mobile water pools. Endocortical resorption and decreases in periosteal bone formation are factors assumed to promote cortical porosity and increase fracture risk [9]. Recent in vitro [10, 11] studies have shown the presence of short and long T_2* components in cortical bone.

CONCLUSION- Preliminary results from the in vivo component of our study suggest that the UTE suppression ratio may serve as a surrogate marker of cortical bone porosity. These data are supported by results from the ex vivo study showing SR is associated with µCT-derived porosity, augmented by aging. Future work would entail evaluating the role of SR in a serial treatment intervention study within an osteoporosis cohort.

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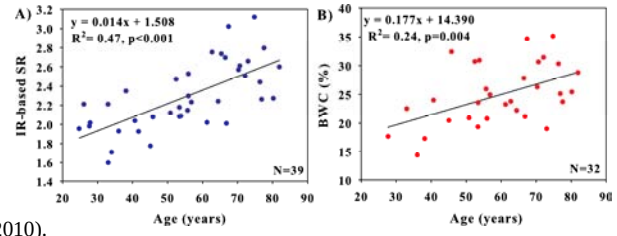

Figure 2: Plots of A) Age vs. mean IR-based Suppression ratio and B) Age vs. BWC.

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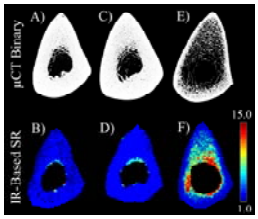

Figure 3: Mid-tibia µCT binary images and IR-based SR color maps from young (A-B,27y.o.), middle-aged (C-D,53y.o.) and elderly (E-F,83y.o.) female donors.