Cortical Bone Porosity: A Novel MRI-Based Clinical Biomarker to Assess Cortical Bone Quality In Vivo

Shahrokh Abbasi Rad[1,2], Atena Akbari[1], Niloofar Tondro[3], Mohsen Shojaee-Moghaddam[3], and Hamidreza Saligheh Rad[1,2]

[1]*Quantitative MR Imaging and Spectroscopy Group, Research Center for Molecular and Cellular Imaging, Tehran University of Medical Sciences, Tehran, Iran,* [2]*Medical Physics and Biomedical Engineering Department, Tehran University of Medical Sciences, Tehran, Iran,* [3]*Imaging Center, Payambaran Hospital, Tehran, Iran*

Target Audience: Researchers, scientists, clinicians and students who work in the field of quantifying cortical bone using MRI techniques

Purpose: Assessment of human bone quality is a dilemma which has been baffling scientists and researchers for many years. One of the most important determinants of bone quality is its porosity. In this study we aim to assess cortical bone porosity using an MR-based approach *in vivo*. Cortical bone water is a pivotal concept for any MR-based technique in investigation of the bone tissue. Recent studies have revealed that there exist three different proton pools in the cortical bone each representing a specific characteristic of the bone. First water pool is tightly bonded to the mineral phase, another one is loosely bonded to the collagen matrix, and the last one (mobile water) resides in pores of the cortical bone such as Haversian canals (typical diameters > 30 μm), lacunae (~ 10 μm), and canaliculi (~ 0.5 μm) **[1-3]**. It can be concluded that mobile water may give us comprehensive information about cortical bone porosity. Magnetic Resonance Imaging (MRI), due to its sensitivity to the hydrogen nuclei, is able to quantify water concentration. The surface interaction of the molecules of water residing in the pores is limited to the miniscule spaces of those pores, therefore the lifetime of their signal is too short for the conventional MRI techniques to capture **[3]**. Short Echo Time (STE) pulse sequence has the most efficient value of TE in order to capture signal only from the mobile water. Among the three water pools existing in the cortical bone (tightly bound water: $T_2 \sim 60$ μs, loosely bound water: $T_2 \sim 400$μs, and mobile water: $T_2 \sim 1ms$-$1s$), only mobile water can be detected by STE-MRI **[4]**. So we hypothesized that Bone Water Concentration (BWC) acquired by STE-MRI can provide us with an exhaustive information of cortical bone porosity. Since the cortical bone porosity increases with age, a good correlation between the acquired quantity (STE-MR Derived bone water concentration) and age would be a strong verification of the proposed method.

Materials and Methods: In order to pursue the study, 12 healthy volunteers (6 males and 6 females) with the age ranging from 20 to 70 have been incorporated. The imaging site is chosen to be at the 38% of the tibia length, known to be the site of maximum cortical thickness, measured from the medial malleolus. *Image acquisition*: Mid-tibia images were acquired using STE pulse sequence with two different *TR* values on a 1.5T MR scanner (Siemens, Magnetom Avanto 18 channel) **[5, 6].** The imaging parameters are selected to be: $TR_1/TR_2/TE$ = 20/60/1.29*m*sec, field-of-view (FOV) = 267×267*m*m^2, spatial resolution = 0.8×0.8*m*m^2, slice thickness = 5*m*m, flip angle = 20°, total scan time of about 20 minutes, using an 8-channel Tx/Rx knee coil (an example is shown in **Fig. 1**). A reference sample (20% H_2O in D_2O doped with 27mM $MnCl_2$, yielding $T_1 \sim 15$ ms and $T_2^* \sim 320$ μs) with NMR properties similar to the NMR properties of cortical bone was adhered to the volunteer's leg during imaging. This reference sample has a key role in bone water quantification process which will be explained later. *T_1 Quantification*: Steps of this quantification are as follows: (1) manual segmentation of the whole cortical bone at each of the two images with different *TR*s , shown in **Fig. 2**; (2) computation of the ratio value (*r*), as in **Eq. 1**, by dividing the mean signal intensities of the segmented cortical bone acquired from long-*TR* (TR_2) and short-*TR* (TR_1) images, respectively; (3) calculation of cortical bone T_1-value at each imaging slice by solving **Eq. 1** using nonlinear solver in MATLAB 7.14 (The MathWorks); and (4) calculation of the average T_1-values for each subject and from ten different slices. As quantification of T_1-values are very sensitive to f_z (a parameter which characterizes the longitudinal magnetization as a function of pulse duration to the tissue T_2^* (τ/T_2^*) **[7]**), it must be carefully determined based on Bloch equation simulation employing T_2^* value of the cortical bone extracted from the literature at 1.5T, and parameters of the actual excitation pulse such as pulse shape and flip angle.

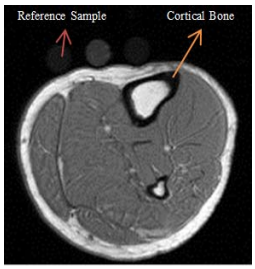
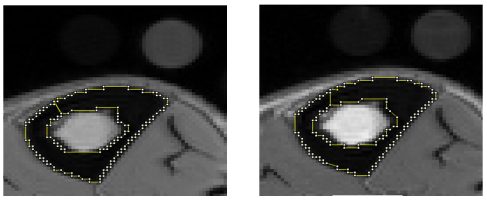


Fig. 1 A sample image of the mid-tibia acquired by the STE pulse sequence

$$r = \frac{1-\exp(-TR_1/T_1)}{1-f_z\exp(-TR_1/T_1)} \Big/ \frac{1-\exp(-TR_2/T_1)}{1-f_z\exp(-TR_2/T_1)} \qquad \textbf{Eq. 1}$$

RF coil inhomogeneity correction: Quantification process of the cortical bone water is based on the comparison of signal intensities between the bony tissue and of a reference sample. Therefore, even minor inhomogeneities of the RF field may incur large systematic errors. The effects from an inhomogeneous reception profile were corrected by creating a mask with the aid of a homogeneous phantom and dividing the bone intensity image by the mask, pixel by pixel. *Bone Water Concentration Quantification*: Steps of this quantification process are as follows: (1) manual segmentation of the whole cortical bone at STE image with *TR* = 20 and calculate the mean signal intensity of the obtained segment (I_{bone}); (2) placing an ROI on the phantom in the inhomogeneity-corrected image with *TR* = 20 *ms* and calculate the mean signal intensity (I_{ref}); (3) calculation of bone water concentration using **Eq. 2** where ρ_{bone}, $\rho_{ref.}$, I_{bone} and I_{ref} are proton densities and signal intensities of cortical bone and reference sample respectively. *TE* is echo time, $R_2^* = 1/T_2^*$ is the effective transverse relaxation rate and the factor F represents a fraction of the available magnetization when the duration of the radiofrequency pulse, is comparable to or longer than T_2^*; (4) calculation of the average BWC values for each subject and from ten different slices.

$$\rho_{bone} = \rho_{ref}\,(I_{bone}.F_{ref})/(I_{ref}.F_{bone}).\exp(-TE_{eff}(R^*_{2ref} - R^*_{2bone})) \qquad \textbf{Eq. 2}$$



(a) (b)

Fig.2 Manual segmentation of the cortical bone for image with TR = 20 (a) and image with TR = 60 (b). The segmentation process was done by manually placing the polygons, covering the area between periosteal and endosteal boundaries, with the exclusion of boundary pixels, with ImageJ (National Institutes of Health, Bethesda, Md).

Results: Measurements were performed for both genders at 1.5T and shown in **Fig. 3**, proposing a significant correlation ($r^2 = 0.71$, $\rho < 0.0001$) between STE-derived BWC and age. Considering the fact that the porosity of human cortical bone increases with age, such a significant correlation was expectable – demonstrating the capability of BWC to be a clinical biomarker of cortical bone porosity.

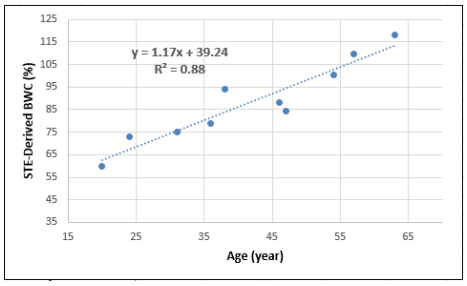


Fig. 3 Correlation between STE-Derived BWC and Age in 12 healthy volunteers ($p < 0.0001$)

Discussions and Conclusions: Regarding the values of T_2 of different water pools in the cortical bone and the TE value of 1.29 *ms* employed in the applied pulse sequence, the acquisition technique captures the signal emanating only from mobile water **[5]** which is proved to be a reliable determinant of porosity. Therefore, this study introduces STE pulse sequence to be a clinically available and applicable protocol to assess human cortical bone porosity *in vivo.* The STE-derived BWC can be considered as a clinical biomarker to assess cortical bone porosity *in vivo*, with which consequently the bone quality can be evaluated. Also, the proposed method has the advantages of being cost benefit, clinically available, and fast (in comparison with other available techniques).

References: **[1]** Horch RA. *et al*, PLoS ONE, 6:(1), (2011) **[2]** Nyman JS. *et al,* Bone, 42:193-199, (2008) **[3]** Horch RA. *et al*, Magn Reson Med, 64:680-687, (2010) **[4]** Akbari A. *et al*, *ISMRM 22* (2014) **[5]** Akbari A. *et al*, *ESMRMB 30* (2013) **[6]** Saligheh Rad H. *et al*, *NMR Biomed*, 23: 1-11 (2011) **[7]** Sussman M. *et al*, *MRM*, 40:890-899 (1998)