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Water proton density in human cortical bone obtained from ultrashort echo time (UTE) MRI predicts bone microstructural properties

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Abstract

Purpose: To investigate the correlations between cortical bone microstructural properties and total water proton density (TWPd) obtained from three-dimensional ultrashort echo time Cones (3D-UTE-Cones) magnetic resonance imaging techniques.

Materials and Methods: 135 cortical bone samples were harvested from human tibial and femoral midshafts of 37 donors (61±24 years old). Samples were scanned using 3D-UTE-Cones sequences on a clinical 3T MRI and on a high-resolution micro-computed tomography (μCT) scanner. TWPd was measured using 3D-UTE-Cones MR images. Average bone porosity, pore size, and bone mineral density (BMD) were measured from μCT images at 9 μm voxel size. Pearson's correlation coefficients between TWPd and μCT-based measures were calculated.

Results: TWPd showed significant moderate correlation with both average bone porosity (R=0.66, p<0.01) and pore size (R=0.58, p<0.01). TWPd also showed significant strong correlation with BMD (R=0.71, p<0.01).

Conclusions: The presented 3D-UTE-Cones imaging technique allows assessment of TWPd in human cortical bone. This quick UTE-MRI-based technique was capable of predicting bone microstructure differences with significant correlations. Such correlations highlight the potential of UTE-MRI-based measurement of bone water proton density to assess bone microstructure.

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6. Conflict of interest statement

The authors have no conflicts of interest to declare.

Keywords

Cortical bone; MRI; Ultrashort echo time; total water proton density; porosity; bone mineral density

1. Introduction

Standard evaluation of cortical bone in clinics has been focused on x-ray-based techniques such as dual-energy X-ray absorptiometry (DEXA) and quantitative computed tomography (QCT) [1,2] to measure bone mineral density (BMD).

Magnetic resonance imaging (MRI)-based cortical bone evaluation has recently been increasing since MRI avoids the potential harm associated with x-ray-based techniques [1,3–5]. MRI-based bone evaluation may also provide excellent assessment of the surrounding soft tissue such as tendons [6] and muscles, a benefit which is not available in x-ray-based techniques. Notably, conventional MRI is not able to detect considerable signal of cortical bone because the apparent transverse relaxation time (T_2^*) of bone is very short. Among the recently developed MRI techniques, ultrashort echo time (UTE) MRI is capable of imaging cortical bone with high signal and can also offer quantitative measurements [3–5,7–9]. Specifically, the bone signal in UTE-MRI techniques can be acquired in less than a tenth of millisecond after radiofrequency (RF) excitation.

Total water proton density (TWPDP) in cortical bone can be estimated by comparing the UTE-MRI signals of bone and of an external reference with known water content [8,10–15]. A mixture of distilled water and heavy water (e.g., 20% H_2O and 80% D_2O) has been used routinely as the external reference [8,11,12,14,16]. It should be noted that any material with known apparent proton density and a range of MRI properties similar to bone, such as rubber, may be used as the external phantom. Bound and pore water proton densities (BWPD and PWPDP) in bone can be estimated using UTE-MRI techniques combined with different preparation techniques. Inversion recovery UTE-MRI (IR-UTE-MRI) signal in cortical bone compared with an external reference has been used to estimate BWPD [8,14–17]. PWPDP in cortical bone can be calculated indirectly by subtracting BWPD from TWPDP [11,16,18]. Alternatively, PWPDP can be estimated using a double adiabatic full passage pulse (DAFP) preparation to saturate the bound water signal followed by a UTE acquisition to selectively image pore water protons [8,14,19,20].

Gradual increase in the porosity of human bone due to aging or osteoporosis (OP) is hypothesized to return an increased PWPDP proton density in bone. If we assume that independent changes in the bone's organic matrix during normal bone aging and osteoporosis development are limited, alterations in PWPDP should be seen in TWPDP. Therefore, investigating only TWPDP in cortical bone, which merely requires a quick UTE-MRI scan, may be enough for initial bone evaluation. An earlier feasibility study on eight tibial cortical bone samples demonstrated significant correlations between cortical bone microstructural parameters and TWPDP [16]. Previous study was performed on a clinical MRI scanner using a standard eight channels knee coil and demonstrated that TWPDP technique can be potentially translated to clinical investigation. However, such correlations

have not been investigated in a large number of samples from a considerable number of donors, which is necessary before embarking on clinical translational studies.

The goal of this study was to investigate the correlations between cortical bone microstructural properties and TWPDP obtained from a single UTE-MRI sequence performed ex vivo on a large number of human bone samples. This study highlights the potential applications of a quick UTE-MRI scan to assess human cortical bone.

2. Materials and methods

2.1. Cortical bone strips preparation

135 cortical bone samples were harvested from the femoral and tibial midshafts of 37 donors (61 ± 24 years old, 52 samples from 19 females, 83 samples from 18 males). Fresh frozen cadaver legs were obtained from a non-profit whole-body donation company (United Tissue Network, Phoenix, AZ, USA). The cortical bone midshafts were cut into 40 mm segments using a commercial band saw. Two approximately rectangular bone strips were harvested from each midshaft segment using a low-speed diamond saw (Isomet 1000, Buehler, IL, USA). The final size of the samples was approximately $4 \times 2 \times 40 \text{ mm}^3$. Samples were soaked in phosphate-buffered saline (PBS) solution overnight at room temperature before the MRI scans. Then, 15–20 samples were placed into 30-mL syringes (8 groups) filled with perfluoropolyether (Fomblin, Ausimont, Thorofare, NJ) to minimize susceptibility artifacts and to avoid sample dehydration. One rubber phantom with a known apparent proton density of 33 mol/L H^1 was placed in each syringe and scanned together with the bone strips. The rubber phantom proton density was measured previously by comparing the UTE-MRI signals with the signal of a water phantom (20% H_2O and 80% D_2O , 22 mol/L H).

2.2. UTE-MRI protocol

The UTE-MRI scans were performed on a 3T clinical scanner (GE Healthcare, Waukesha, WI, USA) using a transmit/receive birdcage coil (25.4 mm inner diameter). Two 3D-UTE-Cones MRI sequences were performed. First, to measure TWPDP, a single UTE sequence was performed with the following acquisition parameters: rectangular RF excitation pulse with a duration of 26 μs , repetition time (TR)=100 ms, echo time (TE)=0.032 ms, flip angle (FA)= 10° , field of view (FOV)= 40mm, matrix size=160 $\times$ 160, in-plane pixel size=0.25mm, slice thickness=2 mm, receiver bandwidth= ± 62.5 kHz. Second, a 30-mL syringe filled with pure water was imaged using the UTE-MRI protocol to generate the coil sensitivity map (η) over the selected FOV. The total scan time was approximately 7 minutes for UTE-MRI and coil sensitivity. The details of the 3D-UTE-Cones sequence have been given in the literature [21–23].

2.3. Calculating TWPDP in bone strips

Water proton density calculation in bone samples was performed by MRI signal comparison between bone samples and the rubber phantom with a known apparent proton density (33 mol/L H^1 , $T_2 \approx 1.3$ ms, T_1 equals to 280 ms) [3,8,14–17,20]. UTE MRI signal can be described using the Ernst equation, as presented in Eq.1 [11].

$$SI_{Bone}(TE) \propto \frac{1 - e^{-TR/T_1}}{1 - \cos\theta \times e^{-TR/T_1}} \times e^{-TE/T_2^*} \times TWPDP, \quad \text{Eq.1}$$

where TR, θ , and T_1 are repetition time, FA, and bone total water longitudinal relaxation time, respectively. A proton density-weighted UTE acquisition was used in this study to simplify the TWPDP calculation and minimize potential errors (e.g., a relatively long TR of 100 ms, a short TE of 32 μ s, and a low FA of 10° employing a short rectangular excitation pulse of 26 μ s). Since $T_2^*_{bone}$ and $T_2^*_{REF}$ are much higher than the ultrashort TE and the rectangular excitation pulse duration, the T_2^* and T_1 effects in Eq.1 can be neglected; thus, the TWPDP can be estimated by comparing the UTE signals of bone and external reference using Eq.2.

$$TWPDP \approx \frac{SI_{Bone}^{UTE}}{SI_{Rub}^{UTE}} \times \eta \times \rho_{Rub}, \quad \text{Eq.2}$$

where η and ρ_{Rub} are coil sensitivity and proton density in the rubber phantom, respectively. It should be noted that average signal intensity in each bone specimen was used for TWPDP calculation.

Using the simplified Eq.2 instead of Eq.1 may result in some errors in calculation of TWPDP. Based on our earlier measurements, T_1 of TW bone is 350 ms and T_1 of the rubber phantom is 280 ms. Therefore, the T_1 correction term in Eq.1 equals 0.957 and 0.966 for TW bone and rubber phantom, respectively, when TR=100ms and FA=10°. This may lead to an error of less than 1% in TWPDP calculation. The main difference between the rubber phantom and bone will be in their T_2^* values. Based on our earlier measurements, T_2^* of TW bone is 0.4 ms and T_2^* of the rubber phantom is 1.3 ms, which results in the T_2^* correction terms of 0.975 and 0.923, respectively. This may lead to an error of around 5% in TWPDP calculation. Consequently, the total combined potential error in TWPDP estimation will average 6 % when neglecting the T_1 and T_2^* terms in Eq.1. The expected errors would be slightly different if separate contributions of PW and BW pools were assumed in the calculations. Based on our earlier measurements, T_1 of PW is 500 ms and T_2^* of PW is 3 ms, which results in the correction terms of 0.9357 and 0.989, respectively. Comparing these correction values with those of the rubber phantom leads to an error of 5% in PWPDP calculation. On the other hand, T_1 of BW is 150 ms and T_2^* of BW is 0.3 ms, which results in the correction terms of 0.985 and 0.898, respectively. Comparing these correction values with those of the rubber phantom leads to an error of 6% in BWPDP calculation. Therefore, the maximum expected error for measured water proton density can reach up to 6%.

2.4. Bone microstructure with μ CT

A Skyscan 1076 (Kontich, Belgium) μ CT scanner at 9 μ m isotropic voxel size was used to scan the bone strips. The μ CT scan time was approximately 12 hours. Two cylindrical hydroxyapatite phantoms (0.25 and 0.75 g/cm³) were placed in the field of view enabling BMD measurements. A 0.05-mm aluminum filter in addition to a 0.038-mm copper filter

were utilized in the μ CT scans. Other scanning parameters were as follows: 100 kV, 100 mA, 0.3° rotation step, and 5 frame-averaging.

The μ CT images were segmented using a gray intensity threshold. Gray intensity histograms were used to select the gray intensity threshold for the segmentation process. Intracortical bone porosity was estimated as the number of voxels in pores divided by the total number of voxels covering each bone sample. The pore size at each pore voxel was defined as the diameter of the largest covering sphere. Local BMD value at each voxel was assumed as a linear function of its gray intensity, which was derived from the average gray intensities of the scanned hydroxyapatite phantoms. Finally, the average BMD for each sample was calculated by averaging the local BMD values over all corresponding voxels.

2.5. Statistical correlations

Pearson's correlation coefficients were calculated between TWPD and μ CT-based measures including porosity, pore size, and BMD. Correlations with p-values below 0.05 were considered significant. All image processing and statistical analyses were performed using MATLAB (version 2018, The Mathworks Inc., Natick, MA, USA) codes developed in-house.

3. Results

Figure 1a shows the UTE-MRI image ($TE=0.032$ ms) of a set of bone samples in the 30-ml syringe scanned in axial plane, showing the average $4\text{mm} \times 2\text{mm}$ cross sections of samples. The rubber phantom with the known proton density placed in the syringe for TWPD measurement is indicated with a yellow arrow in the UTE-MRI image. Figure 1b shows the μ CT image of the same set of samples at 9-micron isometric voxel size.

Figures 2a, 2b, and 2c demonstrate the scatter plots and linear regressions of TWPD on μ CT-based average bone porosity, pore size, and average BMD, respectively. TWPD demonstrated significant moderate correlation with both average bone porosity ($R=0.66$, $p<0.01$) and pore size ($R=0.58$, $p<0.01$). TWPD demonstrated significant strong with BMD ($R=0.71$, $p<0.01$).

It should be noted that a set of inversion recovery (IR) UTE sequences were performed to measure BWPDP and consequently PWPDP of the studied bone specimens using the described equations in an earlier study [16]. Since the focus of this article was employing a relatively fast MRI scan for TWPD estimation to be used for bone microstructural assessment, the correlations of PWPDP and BWPDP versus microstructural parameters are presented in Supplementary Data, Figure 1. PWPDP correlations with microstructural parameters were slightly higher than the TWPD correlations with bone microstructure. BWPDP did not show significant correlations with microstructural parameters.

4. Discussion

We have measured TWPD in cortical bone and investigated its correlations with cortical bone microstructure in a large number of bone samples (i.e., 135) from a considerable

number of donors (i.e., 37). Earlier feasibility studies on TWPD and bone microstructure correlations were performed on a limited number of tibial bone samples [16]. UTE-MRI-based techniques for bone assessment can be considered non-invasive and readily translatable to in vivo studies. Moreover, the bone MRI-based assessment can provide invaluable evaluation of the surrounding soft tissues such as tendons and muscles, which can improve diagnostic procedures.

For accurate estimation of bone water protons we must consider: i) the difference between relaxation times of cortical bone and the rubber phantom, ii) the spatial variation of coil sensitivity in scanned FOV, and iii) the duration of RF pulse and its inhomogeneity (or actual flip angles) [11]. Due to short T_1 in cortical bone and due to the use of a relatively low FA and relatively high TR in the PD-weighted 3D-UTE-Cones sequence, the T_1 effect on the TWPD calculation could be neglected in this study. The actual FA is a function of RF transmit field (B_1). Since FA used in this study has been relatively low ($FA=10^\circ$), a regular B_1 variation within the studied tissue (e.g., $\approx 5\%$) may not lead to considerable errors in TWPD calculation. Since the T_2^* s of the rubber phantom and bone were significantly higher than ultrashort TE of $32\mu s$, the T_2^* term in the proton density measurement could also be neglected in this study (Eq. 1).

To validate the correlations between the TWPD values and the bone microstructural properties, μCT was employed for bone porosity and BMD measurements. TWPD showed significant moderate correlation with bone porosity and pore size ($R=0.66$ and 0.57 , respectively, $p<0.01$, Fig.2). TWPD also showed significant strong correlation with BMD ($R=0.71$, $p<0.01$, Fig.2). Presented correlations were in the range of previously reported correlations for eight tibial bone cross-sections imaged in clinically used knee coils [16]. This study complements the earlier feasibility study and validates earlier obtained correlations. As presented in the supplementary figure, PWPB correlations with microstructural parameters were higher compared with TWPD correlations. However, BWPD did not show significant correlations with microstructural parameters in this study for three potential reasons. First, the range of BWPD was relatively restricted, potentially limiting the results of the regression analysis. Second, because of the cadaveric bone specimens used in this study, BW restoration may not have completely occurred in some specimens even after overnight soaking in PBS. Third, the rubber phantom used in this study was not pure short T_2 material and contained some impurity which make it improper for BWPD measurement.

In addition to TWPD estimation [8,10–16], other UTE-MRI techniques have also demonstrated significant correlations with intracortical bone porosity. Bicomponent T_2^* fitting technique [7,24] can estimate short- T_2^* (i.e., BW pool) and long- T_2^* (PW pool) proton fractions and their average T_2^* values in cortical bone [7,24,25]. Estimated BW and PW fractions can predict bone microstructure indirectly [7,24,25]. Tricomponent T_2^* fitting technique [9,25] improves bicomponent analysis by estimating the fat proton fraction in addition to the water proton fractions. Tricomponent fitting avoids the common BW overestimation by bicomponent analysis in endosteal side of cortex [9,25]. Bi- and tricomponent T_2^* fitting techniques do not estimate absolute water proton contents. Such techniques need a series of MRI images with differing TEs which can extend the scanning

process over 30 mins. Quantitative susceptibility mapping (QSM) [26] is another method to indirectly estimate bone mineral content as an index for bone microstructure. The larger the QSM, the higher the mineral content. QSM requires a set of MRI images with various TRs and TEs that can lead to scan times over 30 mins. Dual-echo UTE imaging [27] is faster technique (can be performed in 7 minutes) that calculates the signal ratio between two MRI images, one with $TE < 0.05\text{ms}$ and one with $TE \approx 2\text{ms}$. Although, this technique does not estimate the absolute water proton contents, it can estimate porosity indirectly. Direct pore water imaging after nulling bound water [8,14,19,20] is another relatively fast MRI scan that can estimate the PTPD. This technique requires an excellent nulling of bound water signal which can be challenging. Magnetization transfer modeling technique [7,16,28,29] has been also reported for bone microstructural assessment. This technique can estimate bone's macromolecular proton fraction (MPF) relative to water fraction using a series of MT pulse saturation powers and frequency offsets. MPF is an index related to bone's collagen matrix which can be used to detect bone stress injuries [30]. MT modeling technique may require approximately 15 mins scan time for the setup used in this study.

This study was performed *ex vivo* on bone samples cut from pure cortical bone layers of femoral and tibial midshafts where there was negligible bone marrow and no surrounding muscle. The samples were scanned in fMRI using a small coil that resulted in high SNR. In the light of the abovementioned facts, the performance of the presented technique will likely drop when translated to *in vivo* studies due to the presence of soft tissues, lower spatial resolutions, lower SNR, temperature differences [31], and subject motion during scan. Thus, further *in vivo* studies are still necessary to compare cortical bone PTPD and its measurable microstructural parameters. Human cortical bone often has considerable amount of fat due to the bone marrow infiltration into intracortical pores. The fat presence in cortical bone results in an increased UTE-MRI signal (Figure 2a) which eventually lead to PTPD overestimation. Such PTPD overestimations can be reduced by employing lower FAs (e.g., $FA \approx 2^\circ$). Employing tricomponent $T2^*$ fitting model has been proposed in previous studies for accurate measurement of water proton fraction by considering the fat-water chemical shift contribution in UTE-MRI signal [9,25]. Nevertheless, tricomponent $T2^*$ modeling will require a relatively long scan time which is not aligned with the main objective of this study; proposing a relatively fast UTE-MRI technique for bone microstructural assessment.

5. Conclusion

A quick 3D-Cones-UTE MRI technique was presented to measure total water proton density in a large number of cortical bone samples. Water proton density showed significant moderate to strong correlations with bone microstructural properties, as measured with high resolution μCT . Such significant correlations demonstrated the potential of UTE-MRI-based measurement of bone water proton density to assess bone microstructure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

MR	magnetic resonance
MRI	magnetic resonance imaging
3D	three-dimensional
3D-UTE	three-dimensional ultrashort echo time imaging
RF	radio frequency
FOV	field of view
ROI	region of interest
TE	echo time
TR	repetition time
CT	computed tomography
μCT	micro-computed tomography
FA	flip angle
TWPD	total water proton density
PWPD	pore water proton density
BWPD	bound water proton density
BMD	bone mineral density
PBS	phosphate-buffered saline
DEXA	dual-energy X-ray absorptiometry
QCT	quantitative computed tomography
HR-pQCT	peripheral quantitative computed tomography

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Figure 1:

UTE-MRI image and μ CT image of a set of twenty cortical bone strips harvested from different donors possessing different levels of porosity. (a) UTE-MRI ($TE=0.032\text{ms}$) image of a set of twenty cortical bone strips harvested from different donors with $4\times 2\text{ mm}^2$ cross-sections ($250\text{ }\mu\text{m}$ in plane pixel size) soaked in fomblin, which has no signal in MRI. UTE scans of the samples were performed in the presence of a rubber phantom with known proton density (33 mol/L). (b) μ CT image of the same set of bone samples at $9\text{ }\mu\text{m}$ voxel size.

Figure 2:

Scatter plots and linear regression analyses with significant correlations ($p<0.01$) of total water proton density (TWPd) on μCT -based microstructural properties. TWPd versus (a) porosity, (b) average pore size, and (c) bone mineral density (BMD).