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Technical Note

Significant correlations between human cortical bone mineral density and quantitative susceptibility mapping (QSM) obtained with 3D Cones ultrashort echo time magnetic resonance imaging (UTE-MRI)

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ABSTRACT

Purpose: Quantitative susceptibility mapping (QSM) MRI is a tool that can characterize changes in susceptibility, an intrinsic property which is associated with compositional changes in the tissue. Current QSM estimation of cortical bone is challenging because conventional clinical MRI cannot acquire signal in cortical bone. This study aimed to implement Cones 3D ultrashort echo time MRI (UTE-MRI) for *ex vivo* QSM measurements in human tibial cortical bone, investigating the correlations of QSM with volumetric intracortical bone mineral density (BMD).

Materials and methods: Nine tibial midshaft cortical bone specimens (25 mm long specimens cut at the mid-point of tibial shaft, 67 ± 20 years old, 5 women and 4 men) were scanned on a clinical 3 T MRI scanner for QSM measurement. The specimens were also scanned on a high-resolution micro-computed tomography (μCT) scanner for volumetric BMD estimation. QSM and μCT results were compared at approximately nine regions of interest (ROIs) per specimen.

Results: Average 3D UTE-MRI QSM showed significantly strong correlation with volumetric BMD ($R = -0.82$, $P < 0.01$) and bone porosity ($R = 0.72$, $P < 0.01$). Combining all data points together (77 ROIs), QSM showed significant moderate to strong correlation with volumetric BMD after correction for interdependencies in specimens ($R = -0.70$, $P < 0.01$). The corrections were required because the data points were not independent in each specimen. Similarly, the correlation between QSM and porosity was significant ($R = 0.68$, $P < 0.01$).

Conclusions: These results suggest that the Cones 3D UTE-MRI QSM technique can potentially serve as a novel and accurate tool to assess intracortical bone mineral density whilst avoiding ionizing radiation.

1. Introduction

Current cortical bone assessment focuses mainly on the mineral compartment of bone, measuring variation of bone mineral density (BMD) in patients by employing ionizing radiation-based techniques, such as dual-energy X-ray absorptiometry (DEXA) and quantitative computed tomography (QCT) [1,2]. Employing magnetic resonance imaging (MRI) for bone quality assessment has become of great interest due to the relatively safe nature of MRI compared with x-ray based techniques [1,3–6]. Moreover, providing MRI-based bone assessment will enable a comprehensive assessment of bone and surrounding soft tissues in one MRI session that significantly benefits both patients and

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; MT, magnetization transfer; ROI, region of interest; TE, echo time; TR, repetition time; CT, computed tomography; μCT, micro-computed tomography; QSM, quantitative susceptibility mapping; FA, flip angle; BMD, bone mineral density; PBS, phosphate buffered saline; DEXA, dual-energy X-ray absorptiometry; IDEAL, iterative decomposition of water and fat with echo symmetry and least-squires estimation; CSSR, chemical shift species-specific R2* signal; PDF, Projection onto Dipole Fields

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physicians.

Among MRI techniques, quantitative susceptibility mapping (QSM) has recently received increased attention as a powerful tool to characterize pathophysiologic variation of magnetic susceptibility in tissues [7–17]. It is hypothesized that most diseases may affect tissue composition and chemical fractions. In bone tissue, any mineral variations caused by bone diseases may affect the magnetic susceptibility. QSM de-convolves magnetic susceptibility of the tissue based on the phase changes in the MR signal, where tissues with stronger magnetic susceptibility undergo faster evolution of phase [18,19]. Specifically for QSM calculation, gradient recalled echo (GRE) imaging is commonly performed, where MR images at multiple echo times (TEs) are typically acquired to measure the phase evolution accurately. Unfortunately, clinical MRI is not able to detect considerable signal of cortical bone for QSM applications because of bone's very short apparent transverse relaxation time (T2*) [1,3–5].

Strong correlations between QSM and BMD in trabecular bone of spine or ankle have been reported with the use of clinical MRI sequences [20,21]. Since clinical MRI is not capable of imaging bone with considerable signal, Dimov et al. [6] developed the 3D radial ultrashort echo time (UTE)-MRI QSM technique for potential detection of BMD variation in porcine hoof and human distal femur. The capability of UTE-MRI for quantitative bone imaging has been discussed by various research groups [22–33]. More specifically, UTE-MRI can acquire signal several microseconds after radiofrequency (RF) excitation before the rapid transverse magnetization decay of cortical bone [3,4].

Dimov et al. [6] reported significant correlations between computed tomography (CT) Hounsfield unit and radial 3D UTE-MRI QSM values in a combined set of ROIs covering tendon, trabecular bone, and cortical bone. Cones 3D UTE-MRI imaging [34–36] has recently emerged as a way to achieve a faster acquisition speed compared with the radial 3D UTE-MRI techniques. Cones 3D UTE-MRI generally utilizes a short rectangular excitation pulse followed by an efficient spiral trajectory data readout with a minimal nominal TE of 32 μs (a minimal TE of 8 μs can be achieved with the addition of a fast transmit/receive switch) [34–36]. The Cones trajectories are more time-efficient than radial trajectories in covering 3D k-space [37] and resolve the limitations associated with 2D UTE sequences, namely, sensitivity to eddy currents [38]. Furthermore, the 3D UTE Cones sequence allows anisotropic fields of view (FOVs) and spatial resolution, resulting in vastly reduced scan times [39–41]. Lu et al. [42] combined the Cones 3D UTE-MRI and QSM techniques to detect the variation of iron concentration in phantoms. Later, Lu et al. [43] showed that the Cones 3D UTE-MRI technique results in similar QSM values, but faster scanning process, compared with radial 3D UTE-MRI technique. Jang et al. [44] demonstrated that Cones 3D UTE-MRI and 3D single point UTE-MRI QSM measurements are feasible in cortical bone specimens. However, the correlation of Cones 3D UTE-MRI QSM and BMD in cortical bone has not been investigated. Such *ex vivo* correlation studies are required before investigating the clinical utility of Cones 3D UTE-MRI QSM for *in vivo* cortical bone assessment.

This study aimed to determine the correlations of 3D Cones UTE-MRI QSM with μCT-based volumetric BMD and bone porosity in human cortical bone specimens. This study complements earlier feasibility studies and provides additional understanding of the technique's sensitivity before translation of the 3D Cones UTE-MRI QSM method to clinical *in vivo* studies.

2. Materials and methods

2.1. Sample preparation

Nine cortical bone specimens were harvested from freshly frozen human tibial midshafts (67 ± 20 years old, 5 women and 4 men). These tibial midshafts were provided by a nonprofit whole-body donation company (United Tissue Network, Phoenix, AZ). Bone specimens were cut to 25 mm in length roughly at the mid-point of the tibial shaft using a Delta ShopMaster band saw (Delta Machinery, Tennessee, USA), then immersed in phosphate-buffered saline (PBS) for four hours at room temperature before the MRI scans. Loose marrow which was not trapped in pores was removed with a scalpel. The bone samples were embedded in 1% weight/volume agarose gel in a cylindrical plastic container (160 mm diameter and 200 mm length). Bone samples were scanned in 3 groups (2, 3, and 4 specimens in each container).

2.2. UTE-MR protocol

The UTE-MRI scans were performed on a 3 T clinical scanner (MR750, GE Healthcare Technologies, Waukesha, WI) using an eight-channel knee coil for both RF transmission and signal reception. The UTE-MRI scans involved six Cones 3D UTE-MRI sequences with the following TEs: 0.032, 0.2, 0.4, 1.2, 1.8, 2.4 ms. Details of the Cones 3D UTE sequence are given in previous studies [34–36]. Other scanning parameters were as follows: sampling bandwidth (BW) = 83.3 kHz, flip angle = 10°, TR = 30 ms, matrix size = 256 × 256 × 30, voxel size = 0.5 × 0.5 × 2 mm^3.

Each Cones 3D UTE acquisition was reconstructed into both magnitude and phase images using a re-gridding algorithm, which interpolates the measured signal from Cones spokes onto a Cartesian grid. Nominal TEs were used for QSM calculation. Due to the non-uniform sampling density in 3D Cones trajectory (spiral trajectory on conical surfaces), density compensation was applied to the measured signal prior to re-gridding. The six single echo MRI acquisitions were combined to form a 4D complex matrix with an increasing order of TEs.

For the calculation of susceptibilities in bone specimens, a chemical shift species-specific R2* signal model-based UTE QSM (CSSR UTE QSM) reconstruction was applied offline on the generated 4D UTE matrix [6]. The region outside of the cylindrical phantom container (*i.e.*, air) was masked out from the 4D UTE matrix. The B_0 direction was calculated from localization information in the MRI dataset and as the input for the QSM reconstruction protocol. The first three echoes of each dataset (TE = 0.032, 0.2, and 0.4 ms) were used for estimating frequency shift in an iterative fashion. Specifically, the phase wrapping phenomena at the three first TEs were negligible. Then, a region growing-based phase unwrapping algorithm [45] was implemented to obtain the global frequency shift (f0).

Better frequency shift map (fm) and R2* were estimated using a graph-cut-based iterative decomposition of water and fat with echo symmetry and least-squares estimation (IDEAL)-based algorithm at each slice of the data [46–48]. Then, the corrected frequency shift map (f_correct) map was obtained by fitting the complex 4D UTE matrix to a species-specific R2* signal model-based iterative least squares estimation with a multi-peak model [6]. Specifically, the Projection onto Dipole Fields (PDF) algorithm was used to remove the background from the corrected frequency shift map and mask [49]. Then, dipole inversion of the local susceptibility distribution was achieved using an iterative Bayesian regulation method [18]. For all datasets, the regularization parameter and the radius for the spherical mean value operator were set as 500 and 5, respectively, for calculating the QSM map. The steps of QSM measurement process are shown as a flowchart in Fig. 1.

The average QSM values were calculated in one slice (2 mm thick) at the middle of the specimens within nine regions of interest (ROIs) per specimen. ROIs were selected at different cortical bone layers and anatomical sites on the UTE images to provide an adequate range of BMD. Fig. 2 illustrates the schematics of selected ROIs in one representative bone specimen. ROIs were drawn in four different bone sites: anterior, mid-lateral, mid-medial, and posterior.

2.3. Micro-computed tomography (μCT)

To measure volumetric bone mineral density (BMD), all bone

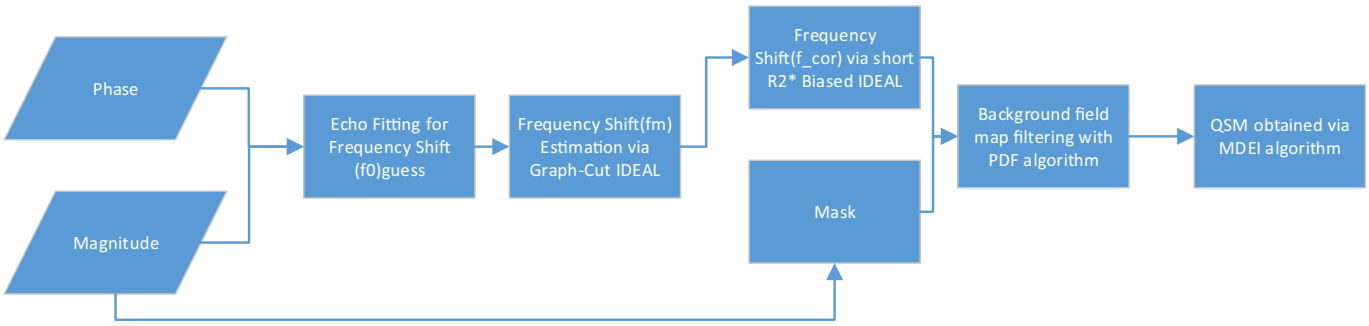

Fig. 1. QSM measurement flowchart using the magnitude and phase images.

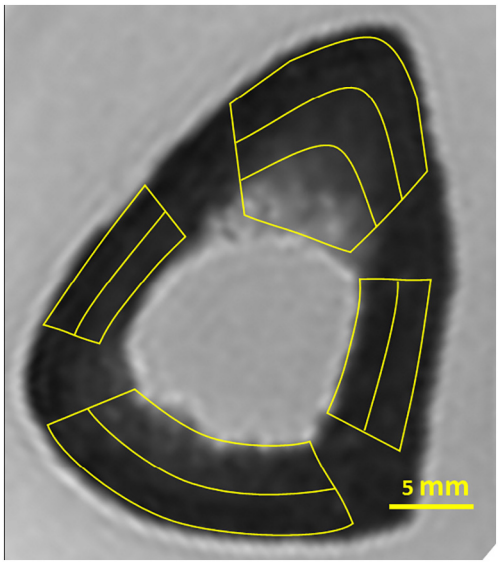

Fig. 2. Schematics of nine selected ROIs on Cones 3D UTE-MRI (TE = 0.032 ms) image (0.5 × 0.5 × 2 mm voxel size) of a representative tibial midshaft cortical bone (45-year-old female).

specimens were taken out of the agarose gel and scanned using a Skyscan 1076 (Kontich, Belgium) μCT scanner at 9 μm isotropic voxel size. Specimens were scanned in the presence of two hydroxyapatite phantoms (0.25 and 0.5 g/cm^3), which enabled deriving a linear function of image gray level to volumetric BMD values in bone specimens. Other scanning parameters were as follows: a 0.05 mm aluminum plus a 0.038 mm copper filter, 100 kV, 100 mA, 0.4° rotation step, 5 frame-averaging, and 5 h scan time.

A single gray level threshold was used for μCT image segmentation of the bone voxels from void voxels or pores. The gray level threshold was selected for each set of μCT data by investigating the gray level histograms and pore interfaces in raw images. Thresholding resulted in a stack of binary images which were used only for porosity assessment. A local volumetric BMD value was calculated for each voxel of the μCT raw images using a linear function of the voxel's gray level, which was determined based on gray levels of hydroxyapatite phantoms. The average volumetric BMD value was calculated using local BMD values of all voxels within the selected ROIs in 222 consecutive μCT slices which corresponded to a 2 mm MRI slice. Average bone porosity in each ROIs was the number of pore voxels to total voxels. Porosity pixel map corresponding to the middle MRI image of each specimen was generated by superimposing the 222 consecutive segmented (binarized) μCT images (*i.e.*, sum of matrices divided by the number of slices). Affine image registration was used to propagate ROIs selected on UTE MRI images (Fig. 2) onto the μCT data. Image registration was performed manually by an image processing expert in MATLAB by selecting four identical points in images from MRI and μCT. Regions affected by μCT ring artifact were excluded from the study.

2.4. Statistical analysis

Average and standard deviation of Cones 3D UTE-MRI QSM and μCT-based volumetric BMD and porosity values were calculated for each bone specimen. Pearson's correlations were calculated between average QSM values in specimens and their average μCT-based measures (volumetric BMD and porosity). Pearson's correlations were also calculated using all selected ROIs combined together to examine the capability of UTE-MRI QSM in detecting the differences of volumetric BMD regardless of intracortical bone location. Because of the variable-length repeated measurements per specimen, the significance levels for all correlations were assessed using non-parametric bootstrap (with resampling by specimen, 1000 replicates per analysis) to adjust for within-specimen dependence. To understand the independent impact of BMD on QSM measures, the correlation coefficient between QSM and BMD was also calculated by adjusting for porosity variations. All the data analyses were performed in MATLAB (version 2017, The Mathworks Inc., Natick, MA, USA). Statistical analyses were performed using a statistical programming language (R, version 3.2.5, R Development Core Team, Vienna, Austria).

3. Results

Magnitude images and phase images of three representative scanned bone specimens for different TEs are shown in Supplemental Fig. 1 and Supplemental Fig. 2, respectively. Fig. 3a illustrates the Cones UTE-MRI QSM map for a representative tibial bone specimen (45-year-old female). Fig. 3b shows one representative μCT slice of the same specimen scanned at 9 μm voxel size. The typical nine selected ROIs are shown schematically on the μCT slice, where they were propagated from drawn ROIs on UTE MRI through image registration process. Figs. 2c and d illustrate the bone porosity and volumetric BMD maps, respectively, for the same specimen. Local maxima in the QSM map qualitatively correspond to the regions of high BMD and low porosity in μCT-based maps.

The average and standard deviation of QSM, BMD, and bone porosity values for each of the nine studied bone specimens are presented in Table 1. Four ROIs affected by μCT ring artifact were excluded from all statistical measurements in this study.

Scatter plots and linear regressions of average UTE-MRI QSM values on average volumetric BMD and bone porosity are shown in Figs. 3a and b, respectively. Average QSM showed significantly strong correlations with volumetric BMD (R = -0.82, $P < 0.01$) and bone porosity ($R = 0.72$, $P < 0.01$).

Pearson's correlations, with 95% significant intervals, and p values between UTE-MRI QSM and μCT-based results (volumetric BMD and porosity) are presented in Table 2 considering all selected ROIs combined together. Correlation coefficients became lower when combining

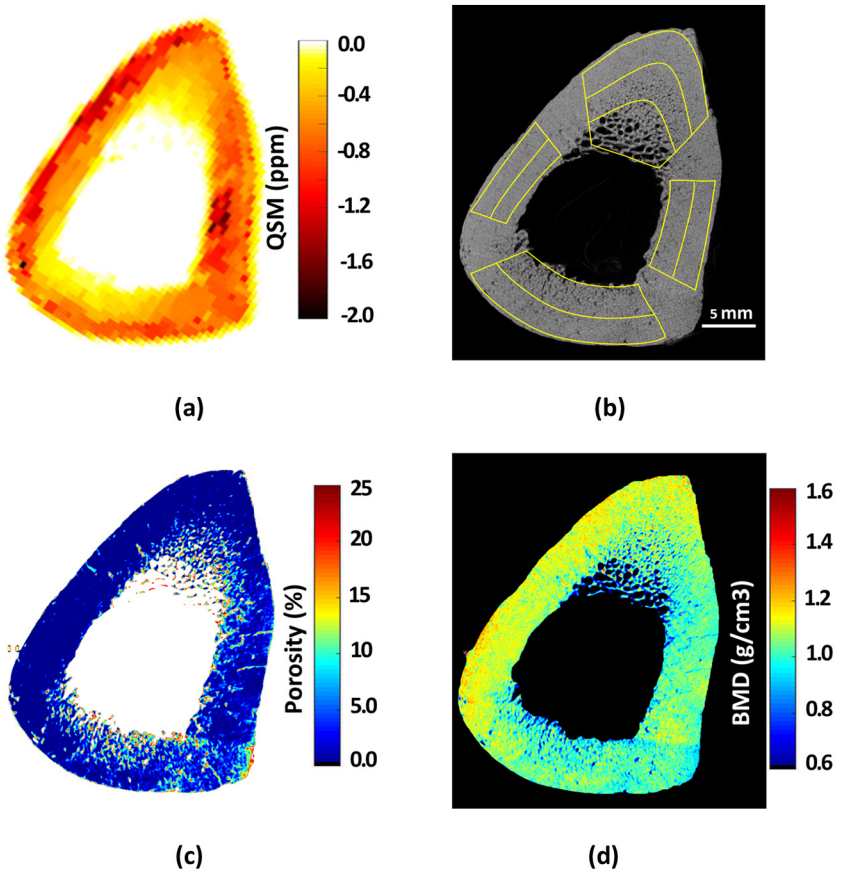

Fig. 3. (a) Quantitative susceptibility map (QSM) using Cones 3D UTE-MRI scans (0.5 × 0.5 × 2 mm voxel size) of a representative tibial midshaft cortical bone (45-year-old female), (b) one representative μCT slice at 9 μm isotropic voxel size, (c) μCT-based porosity, and (d) bone mineral density (BMD) maps of the same representative tibial bone specimen. Local maxima in the QSM map clearly correspond to the regions of high BMD and low porosity in μCT-based maps.

Table 1
Donor information, average, and standard deviation values of QSM, BMD, and bone porosity measures in nine studied bone specimens.

	Gender	Age	Porosity (%)	BMD (g/cm3)	QSM (ppm)
Sample 1	F	86	20.4 ± 6.1	0.95 ± 0.08	−0.59 ± 0.41
Sample 2	F	95	18.7 ± 10.7	0.96 ± 0.08	−0.65 ± 0.34
Sample 3	F	90	12.5 ± 10.3	0.99 ± 0.11	−0.73 ± 0.32
Sample 4	M	73	7.2 ± 8.4	1.11 ± 0.11	−1.09 ± 0.44
Sample 5	M	71	13.5 ± 8.3	1.05 ± 0.08	−0.62 ± 0.42
Sample 6	M	53	20.3 ± 14.4	1.00 ± 0.14	−0.63 ± 0.49
Sample 7	F	49	9.1 ± 8.6	1.14 ± 0.11	−0.85 ± 0.47
Sample 8	F	45	8.2 ± 9.1	1.07 ± 0.08	−0.99 ± 0.36
Sample 9	F	38	15.5 ± 8.8	1.15 ± 0.06	−1.04 ± 0.29

Table 2
Pearson's correlations (indicated with bold figures), 95% significant intervals, and *p* values between UTE-MRI QSM and μCT-based results (BMD and porosity) when considering all data points together (77 ROIs). Significance for all correlations was assessed using non-parametric bootstrap (with resampling by specimen) to adjust for within-specimen dependence.

	BMD	Bone porosity
QSM	**−0.70** [−0.80, −0.54] p < 0.01	**0.68** [0.50, 0.76] p < 0.01

all data points together compared with correlations obtained using average values (Fig. 4). QSM showed significant moderate to strong correlations with volumetric BMD (R = -0.70 [−0.80,-0.54], $P < 0.01$). The correlation between QSM and porosity was significant and in a similar range ($R = 0.68$, $P < 0.01$). The correlation between QSM and BMD after adjusting for porosity variations was poor, but still significant (P = -0.32, $P < 0.01$).

Scatter plots and linear regressions of UTE-MRI QSM values on volumetric BMD and bone porosity are shown in Figs. 4a and b, respectively. As mentioned in Table 2, QSM demonstrated slightly higher correlations with volumetric BMD compared with bone porosity. Data points of different bone sites (Fig. 2) are illustrated with markers where no obvious differences were found between bone sites. Scatter plot and linear regression of UTE-MRI QSM values on R2* is shown in Supplemental Fig. 3 where the correlation was significant, but poor ($R = 0.38$, $p < 0.01$).

4. Discussion

This study was the first to investigate the correlations of 3D Cones UTE-MRI QSM with μCT-based volumetric BMD and bone porosity in human cortical bone specimens. This study complements earlier feasibility studies employing 3D Cones UTE-MRI QSM to assess volumetric BMD differences in human cortical bone.

Chen et al. [20] previously studied the QSM technique's capability in detecting QCT-derived volumetric BMD variation *in vivo* at trabecular bone regions of lumber vertebrae. They observed significant strong correlations between QSM and age, as well as between QSM and volumetric BMD. Diefenbach et al. [21] investigated QSM for measuring trabecular bone density in ankle using GRE-based sequences. They found a significant strong correlation between QSM and trabecular bone density. Additionally, Rochefort et al. [50] used a phantom-based validated QSM technique to assess the human forearm. They reported QSM values in soft-tissue, cortical bone, and bone marrow consistent with values in the literature.

Dimov et al. [6] proposed estimating bone QSM in porcine hoof and human distal femur based on acquired bone images using 3D radial UTE-MRI technique. They reported significant correlations between computed tomography (CT) in Hounsfield units and QSM values within

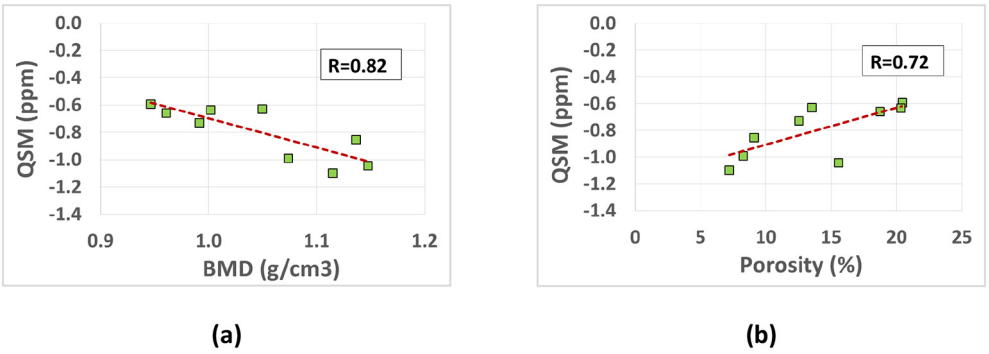

Fig. 4. Scatter plot and linear regressions of average quantitative susceptibility mapping (QSM) of the nine studied bone specimens on their (a) bone mineral density, BMD, and on (b) bone porosity.

a combined set of ROIs covering tendon, trabecular bone, and cortical bone of porcine hoof. However, this QSM validation process for cortical BMD assessment was limited since they considered various tissues for correlation analysis. Lu et al. [42] used 3D Cones UTE-MRI [34–36] combined with a QSM technique to detect the variation of iron concentration in phantoms. Employing 3D Cones in UTE imaging has helped to reduce the scan time and also to decrease image artifacts, such as blurring, in cortical bone scans. It has also been shown that QSM values obtained from different sampling trajectories are similar with no significant differences [43].

The current study validated the capability of the 3D Cones UTE-MRI QSM technique to detect human cortical bone volumetric BMD differences *ex vivo,* particularly between specimens. The QSM measurement from UTE images was similar to previous studies [6,42,44]. For the nine studied human tibial cortical bone specimens, average QSM values demonstrated significantly strong correlations with average BMD and cortical porosity (Fig. 4). Considering all analyzed ROIs in the nine studied specimens combined together, QSM values demonstrated significant moderate to strong correlations with BMD and cortical porosity (Table 2, Fig. 5). Lower correlation coefficients for combined data sets might be due to minor image registration errors between two modalities or due to lower intraspecimen sensitivity of the QSM technique. These need to be investigated in future studies with a larger number of specimens or subjects. Since the μCT scans were performed in high resolution and with 9 μm voxel size, volumetric BMD was highly correlated with bone porosity. Therefore, the QSM correlation with porosity was in the range of QSM and BMD correlation, though lower. Correlation between QSM and BMD after adjusting for porosity variations was found to be lower ($R = -0.70$ *versus* $R = -0.32$), but still significant ($P < 0.01$), indicating QSM as an independent predictor of BMD.

Results in this study suggest that the 3D Cones UTE-MRI QSM technique has the potential to be examined as a sensitive tool for diagnosing bone diseases which can detect mineral level changes in human cortical bone without exposing patients to ionizing radiation. However, a separate sensitivity study is required to understand the sensitivity level of the presented QSM technique. Bone stress injuries [51,52] may also lead to QSM variation due to microfractures, though this hypothesis requires a future well-designed investigation.

MRI-based cortical bone assessment has also been investigated with the use of other UTE-MRI techniques which investigate the water proton pools. Such UTE-MRI techniques include bi-component T2* fitting [53], tri-component T2* analysis through modeling the fat signal [54], dual-echo UTE imaging (*i.e.*, porosity index) [22], direct pore water imaging after nulling bound water [55–57], T1-based decomposition of total water signal [33,58], and magnetization transfer (MT) techniques [51,59–6165].

This study had several limitations. First, this study was performed on *ex vivo* cortical bone specimens where low bone marrow and no surrounding muscles were present. Future well-designed *in vivo* studies should examine if the correlations between the Cones 3D UTE-MRI QSM and volumetric BMD are still apparent. In addition to the impact of other tissues on bone signal *in vivo*, the difference between body and room temperatures may introduce some MRI differences [62,63]. Additional cross-sectional *in vivo* studies are required to compare BMD and MRI-QSM between healthy volunteers and osteoporotic patients to clarify the relevance of QSM and osteoporosis. Moreover, future longitudinal *in vivo* studies are needed to assess sensitivity of the QSM technique to BMD variations in patients. Second, QSM correlations with BMD may not imply good correlation between QSM and mechanical properties of cortical bone, which is critical in evaluating patient fracture risk. A well-designed specimen study is required to investigate the correlations between QSM and bone mechanical properties measured using bending tests applied on cortical bone strips. Third, the total scan time for Cones 3D UTE-MRI QSM was around 20 min, which is more than the clinical MRI sequences. Additional investigations are required to accelerate the Cones 3D UTE-MRI QSM technique for

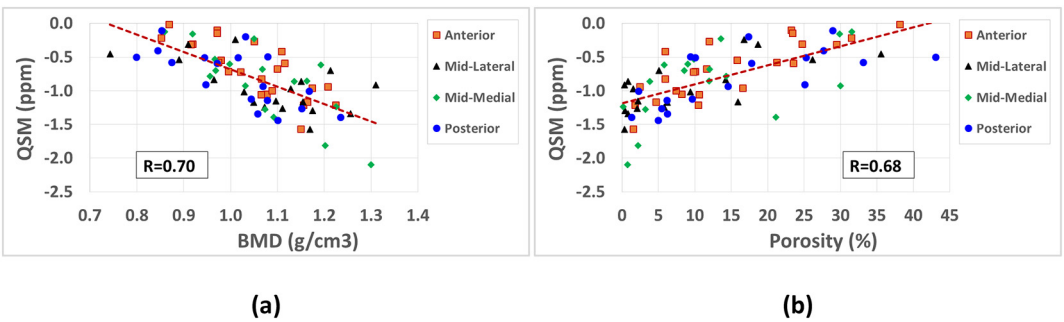

Fig. 5. Scatter plot and linear regressions of QSM on (a) BMD, and on (b) bone porosity. Correlation coefficients were lower when combining all data points together. Significance levels for these correlations were below 0.01, as measured using non-parametric bootstrap (with resampling by specimen) to adjust for within-specimen dependence. Anterior, mid-lateral, mid-medial, and posterior data points are illustrated with markers, where no obvious differences were found between bone sites in the limited number of studied specimens.

clinical applications. This can be achieved by stretching the spiral trajectories, while reducing the number of readouts [64]. Fourth, nowadays, x-ray-based techniques are quite appropriate for BMD measurement at proximities with limited radiation dosage and at a low cost. However, peripheral MRI scanners may be available in the near future that result in affordable costs similar to those of HR-pQCTs. Moreover, other MRI techniques to assess water protons in the bone and its organic matrix are progressing in parallel. Therefore, having a combination of MRI techniques to assess water and organic matrix, plus bone minerals, would be very appealing. Such techniques will enable a comprehensive assessment of bone and surrounding soft tissues in one MRI session that significantly benefits both patients and physicians.

5. Conclusion

Cones 3D UTE-MRI QSM was employed for the first time to investigate the correlation of QSM with BMD in human tibial cortical bone specimens. Cones 3D UTE-MRI previously demonstrated a faster scanning process compared with other 3D UTE-QSM methods. Presented average Cones 3D UTE-MRI QSM values in bone specimens showed significantly strong correlations with their average BMD and porosity. When combining all datasets together, QSM estimations showed significant moderate to strong correlation with BMD, likely indicating lower intraspecimen correlation between QSM and BMD. This study highlighted Cones 3D UTE-MRI QSM technique as a useful method to assess intracortical BMD, which may be used in future clinical studies to avoid ionizing radiation.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mri.2019.06.016.

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