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Original Article

A Feasibility Study on Quantifying Cortical Bone Free Water Longitudinal Relaxation Time Employing Short-TE MRI Technique at 3T

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ABSTRACT

Introduction– Aging is an important factor affecting bone quality, culminating in cortical bone thinning, increasing the number and size of the pores. As a consequence of these alterations, the free water molecules mobility augments and their longitudinal relaxation time (T_1) increases. An MRI with its sensitivity to capture signal from hydrogen proton would be the best candidate to assess the bone quality during aging. By employing an appropriate pulse sequence with a short TE which is capable of acquiring a signal from hydrogen molecules of cortical bone pores before decaying, valuable information about the bone structure was extracted.

Materials and Methods– Five healthy volunteers (3f/2m) were undergone a short TE MR imaging with dual-TR technique at 3T in order to calculate the cortical bone free water T_1. For T_1 calculation, the mean signal intensity of the whole cortical bone in long-TR image was divided by the short-TR image to acquire an 'r' ratio. This ratio value was used in an equation (described further) to calculate T_1 value. The process of cortical bone segmentation was performed manually due to the intense care that it needed for the discrimination of soft tissue from the bone tissue.

Results– The longitudinal relaxation time of human cortical bone free water was quantified using two Gradient Echo STE-MR images differing in TR values and the average of the obtained T_1 values was reported to be 589.32 ± 231.52 ms which was in a good agreement with previously reported values in the literature.

Conclusion– The result suggests a successful application of STE-MRI for an accurate quantification of cortical bone T_1-values, with the advantage of widespread clinical availability and a cost-effective procedure.

Key words:
Cortical Bone,
Short Time of Echo (TE),
Bone Water,
Relaxation Time.

1. Introduction

Recent advancements in the field of bone quality assessment show that the bone mineral density (BMD) as measured using a dual X-ray absorptiometry (DXA) is not a reliable indicator of bone strength [1]. There are more factors affecting bone strength which do not necessarily alter the bone mineral content. Vertebral fractures occurring in elderly people are a good example for this limitation as it is weakly associated with BMD

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[2]. Kanis *et al*. in 2001 reported a low correlation coefficient between BMD and bone strength [3]. Since decreasing the bone strength directly leads to increasing the risk of fracture is of high importance considering other risk determinants including bone microstructure, organic matrix, porosity, diffusion etc. [4]. Among these, a porosity assessment would provide valuable information regarding the bone quality [5]. Pores existing in cortical bone existed as Haversian canals, lacunae, and canaliculi, which are responsible for cortical age-related loss of bone strength during aging, are filled with fluids essentially water [6]. Bone water occurs in two different states namely bound water attached to the minerals and collagen matrix, and free water residing in cortical bone pores [7]. These two proton pools have an opposite effect on the bone mechanical strength in the sense that bound water decrease would reduce the bone strength, while an increase in the amount of free water would undermine the strength of bone [8]. In addition, bound and free water concentrations alter during aging by different trends. Therefore, the need to quantify free and bound water parameters separately is highlighted.

Since the surface interactions of these water protons are limited to the miniscule spaces of pores in the cortical bone, or even more limited about the bound water protons, they have very short relaxation times (T2* < 1 ms). This means that their nuclear magnetic resonance (NMR) signals are too fast-decaying to be detected. Therefore, conventional MRI methods certainly fail to image these short-T_2 components [9]. To capture the information embedded in the cortical bone water, we should consider a new family of pulse sequences with short/ultrashort TE (UTE), known as solid-state MR Imaging, which captures more signal from the cortical bone water using a lower time of echo (TE) values. Bound water protons attached to collagen matrix and mineral has very short T_2* in the range of microsecond and would not be detectable with clinical MR pulse sequences. Besides, during aging this concentration would decrease slightly [10]. However, this is the free water concentration that increases significantly due to aging since cortical pores thinning and pore enlargement is the consequences of aging. According to a physical concept, the spin-lattice relaxation times of the water protons occupying bone pores are proportional to surface to volume of pores ($1/T1 \propto s/v$) [11, 12]. This equation shows that as the surface to volume ratio of pores decreases by aging due to the increasing of the volume of the pores (V), cortical bone free water T_1 value increases consequently. So far, many studies have quantified cortical bone free water T_1 employing UTE pulse sequences (TE in the range of a few microsecond) [6, 12, 13]. Nonetheless, there are two shortcomings to this kind of research: firstly, they have reported a bulk value for cortical bone T_1. This T_1 value is the average of two water pools and this is not valuable as they have different trends with aging. Secondly, UTE MR Imaging is not a clinically applicable pulse sequence and needs a special hardware to apply. In the present work, we introduced Short Time of Echo (STE) MR Imaging pulse sequence with TE in the range of millisecond that was capable of capturing enough signal from cortical bone free water protons.

2. Subjects and Methods

2.1. Subject Recruitment

Five healthy volunteers (3 females and 2 males) ranging from 26 to 37 years old with BMI < 30 kg/m^2 were incorporated into our study. The healthiness criteria were insured using filled questioners by volunteers as follow: lacking any medical history of injury, surgical operation, renal osteodystrophy and other diseases that may affect the bone health. All subjects have filled the informed consent forms.

2.2. Data Acquisition

A ceMRA sequence on a 3T MR scanner (Siemens Tim Trio, Erlangen, Germany) at the imaging center of the Imam Khomeini hospital was used to perform STE-MR imaging technique so as to image cortical bone mid-shaft tibia. Imaging site was opted to be at 38% of the tibia length since cortical bone has the maximum thickness in this area making the analysis easier. Forty slices were acquired using dual-TR Imaging; twenty slices for each TR (TR=20ms and TR=60ms). A full-sinc radio frequency (RF) pulse with the duration of 2.5ms excited the spins for acquiring water proton signal. Imaging parameters are listed in Table 1.

Table 1. STE-MR imaging parameters.

Short TR	Long TR	Time of Echo	Field-of-View	Spatial Resolution	Slice Thickness	Flip Angle	Band Width	Total Scan Time
20 ms	60 ms	1.18 ms	267 mm^2×267	0.8 mm^2×0.8	4 mm	25°	651 Hz/Pix	20 min

As the main purpose of our proposed imaging protocol was to detect a signal from only free water protons, the most crucial imaging parameter was TE. It is the time we wait after the excitation till signal record, therefore it needs to be determined in such a way that the signal from cortical bone bound water has been completely decayed and the signal emanating from cortical bone free water has not decayed significantly. In this feasibility study, we examined three different TEs (1.01, 1.18, 3.78 ms). The one corresponded to the higher SNR values was considered as the most optimum TE.

Muscle and marrow long T_2^* signal suppression contributes to the acquisition of a brighter and sharper border of cortical bone, but at the same time it culminates in suppressing the signal from long T_2^* bone water component, exactly the one we aimed to detect.

2.3. Cortical Bone Segmentation

Cortical bone segmentation was done manually and boundaries of bone, marrow, and muscle were separated carefully. Automatic segmentation was accompanied with considerable errors, so a manual segmentation was preferred. In order to keep errors minimum, all images were segmented by a single user, and ROI was drawn five times for each slice of images. Then, the average value of these five measurements was reported as the signal intensity of the whole cortical bone. By averaging five measurements, the random errors posed by the manual segmentation were reduced.

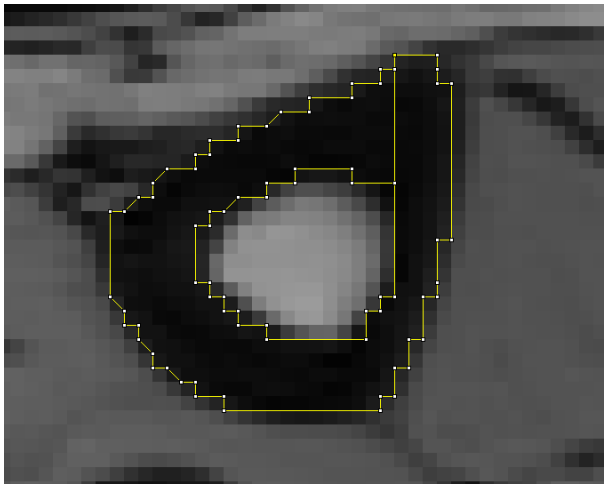


Figure 1. Manually segmented cortical bone of an axial image of a healthy 26 years old female volunteer.

2.4. T1 Quantification

T1 values were computed by calculating the r ratio and solving equation 1 using "trust-region-dogleg" algorithm in MATLAB. The r ratio was obtained by dividing the mean signal intensity of the whole cortical bone in long TR image by the short TR image. T_1 values were quantified for all slices and the average was reported as the cortical bone free water longitudinal relaxation time.

$$r = \frac{1-\exp(-TR_1/T_1)}{1-f_z\exp(-TR_1/T_1)} \Big/ \frac{1-\exp(-TR_2/T_1)}{1-f_z\exp(-TR_2/T_1)} \quad (1)$$

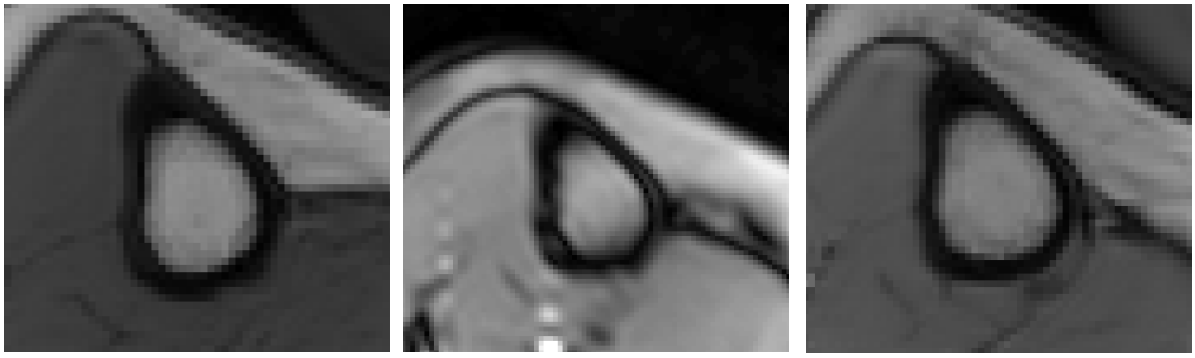
One must note that f_z is a function of τ/T_2^* (ratio of pulse duration to T_2^* relaxation time of cortical bone) defining a correction parameter for relaxation (during RF excitation) [14]. Although for rectangular RF pulses analytical expressions have been derived for $f_z(\tau/T_2^*)$ [12], this parameter must be calculated numerically for shaped pulses

(as full sinc pulse applied in our study). Hence, this value has been rigorously determined based on Bloch equation simulation employing T_2^*-value of the cortical bone free water extracted from the literature at 3T [11, 14], as well as actual parameters of the employed RF excitation pulse such as the pulse shape and flip angle.

Establishing a balance between the spatial resolution and Signal-to-Noise Ratio (SNR) was a challenge in cortical bone imaging. Selecting a proper value for echo time, a trade off was made in the way that spatial resolution was kept in the order of 0.87×0.87 mm^2, while SNR (measured by dividing the intensities of cortical bone to intensities of background noise) was maintained higher than 15.

3. Results

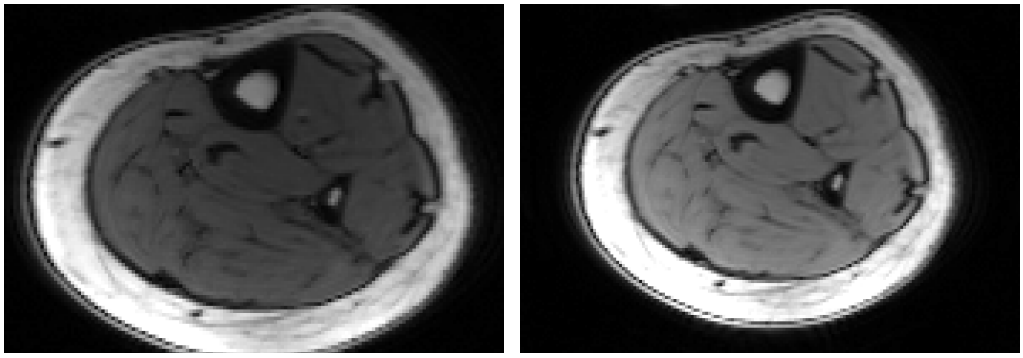
Cortical bone images with different TEs and the same TR (TR = 20ms) are shown in Figure 2. The results show that from the aspect of SNR value, the most optimum TE for our protocol is TE = 1.18 ms.



a b c

Figure 2. Cortical bone images using clinically available ceMRA sequence at 3T with the same TR (20 ms) and different TE values a) TE=1.18 ms, SNR = 16, b) TE=3.78 ms, SNR = 3.5, and c) TE=1.01 ms, SNR = 11.

STE-MR images with short and long TRs (TR = 20/60ms) are shown in Figure 3. These figures show the image quality acquired by STE-MR imaging. Mean and standard deviation of cortical bone free water T_1 values acquired by employing STE-MRI on five healthy volunteers are presented in Table 1. The average value of cortical bone free water T1 for all five healthy volunteers was computed as 589.32 ms at 3T. Mean SNR values are also reported which are all higher than 15 indicating enough signal intensities for the purpose of quantification.



a **b**

Figure 3. STE-MR images of axial human mid-shaft tibia of a 24 years old female a) TR=20 ms, b) TR=60 ms.

Table 2. Cortical bone free water T1 values of five healthy volunteers acquired using dual-TR STE-MRI technique.

Row	Gender	Age (yrs.)	T_1 (millisecond)
1	F	27	308.65
2	F	28	576.34
3	F	25	670.53
4	M	26	464.95
5	M	37	926.11
Mean age = 28.6 years ±4.8			Mean T_1= 589.32 ± 231.52 ms

4. Discussion

Cortical bone free water T_1 values were calculated in five healthy volunteers using the proposed STE-MRI technique as a feasibility study. Dual-TR MR imaging was introduced in the previous study [11], making possible T_1 quantification by dividing two gradient echo signal intensities (the long TR over the short TR).

Among different TE values, we are sure that we have no contamination of bound water in our signals for all three imaging protocols since all TE values are larger than five times of the T2* relaxation of bound water at 3T (T2* = 0.28 ms at 3T [15]). This indicates that any signal originating from cortical bone bound water has decayed completely before signal detection.

The values reported in this study were in a good agreement with the literature [7, 16, 17]. To date, a few researches have been done in order to calculate the values of cortical bone free and bound water longitudinal relaxation time separately. Horch *et al.* in 2010 quantified and discriminated cortical bone free and bound water proton pools at 4.7 T by the use of Carr-Purcell-Meiboom-Gill sequence (CPMG) and reported the value of 1000 ms for free water T1[18]. Chen *et al*. in 2015 reported the mean value of free water T_1 to be 527+28 ms for bovine cortical bone samples at 3T using 2D saturation recovery (SR) UTE, and inversion recovery (IR) UTE [19]. Seifert *et al.* reported a mean free water T_1 of about 880 ± 281 ms by the use of suppression ratio technique and CPMG at 3T [20]. In a recent study carried out by Akbari *et al.* the values of cortical bone free water T_1 was quantified in thirty healthy volunteers reported in the range of 111 – 243 ms employing STE-MRI at 1.5T [11, 21, 22].

According to the governing physical theories, longitudinal relaxation time of a tissue augments by increasing the strength of the main magnetic field and there is a linear relationship between T_1 and B_0. The Larmor frequency is directly proportional to field strength (B_0), so if we increase B_0, the Larmor frequency increases. Shifting the magnetic field to higher values may significantly decrease the fraction of protons able to interact at the new (higher) Larmor frequency and the T_1 time is lengthened. Our reported T1 values in this study are higher than values reported at 1.5T and lower than the values reported at 4.7 T.

The limitations of our study can be recited as: 1) Subject's motion; though a lot of efforts were made to keep the subject's leg stable during the imaging time, but a little movement was truly inevitable, which led to an image degradation and thus affecting the T1 quantification process. 2) No long-T_2 suppression was done due to capture the signal of long-T_2 water protons of cortical pores as much as possible; this posed some difficulty in the segmentation process. Accurate detection of boundaries and separation of the bone marrow, muscle and cortical bone pixels was tricky and needed a careful ROI drawing by the user. All images were analyzed by a single user trying to keep the errors minimum.

The feasibility of quantifying cortical bone free water with a clinically applicable pulse sequence (STE-MRI) was examined and the results were

in a good agreement with the literature. Cortical bone free water assessment regarding aging may provide a new insight into the bone quality with complementary role of DXA and quantitative computer tomography (QCT) as clinical tools for assessing BMD.

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