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Solid-State Quantitative ^1H and ^{31}P MRI of Cortical Bone in Humans

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Abstract

Magnetic resonance imaging (MRI) plays a pivotal role for assessment of the musculoskeletal system. It is currently the clinical modality of choice for evaluation of soft tissues including cartilage, ligaments, tendons, muscle, and bone marrow. By comparison, the study of calcified tissue by MRI is still in its infancy. In this article we review the potential of the modality for assessment of cortical bone properties known to be affected in degenerative bone disease, with focus on parameters related to matrix and mineral densities, and porosity, by means of emerging solid-state ^1H and ^{31}P MRI techniques.

In contrast to soft tissues, the MRI signal in calcified tissues has very short lifetime, on the order of 100 μs to a few milliseconds, demanding customized imaging approaches that allow capture of the signal almost immediately after excitation. The technologies described are suited for quantitatively imaging human cortical bone in specimens as well as *in vivo* in patients on standard clinical imagers, yielding either concentrations in absolute units when measured against a reference standard, or more simply, in the form of surrogate biomarkers.

The two major water fractions in cortical bone are those of collagen-bound and pore water occurring at an approximately 3:1 ratio. Collagen-bound water density provides a direct quantitative measure of osteoid density. While at an earlier stage of development, quantification of mineral phosphorus by ^{31}P MRI yields mineral density, and together with knowledge of matrix density, should allow quantification of the degree of bone mineralization.

Compliance with Ethics Guidelines

Conflict of Interest

Alan C. Seifert and Felix W. Wehrli declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

The protocols for all Health Insurance Portability and Accountability Act (HIPAA)–compliant human studies were approved by the investigators' institutional review board (IRB), and written informed consent was obtained from the subjects. All animal research was performed in compliance with federal regulations and the guidelines of the Institution's Animal Care and Use Committee (IACUC).

Keywords

Solid-State MRI; Cortical Bone; UTE; ZTE; Bone Mineral Density; Bone Water

1. Introduction

In osteoporosis, bone remodeling increases in frequency, and bone resorption outpaces bone deposition^{1,2}. This condition is particularly prevalent in post-menopausal women, in whom the decrease in estrogen levels causes more frequent initiation of bone remodeling events^{3,4}, increased lifespan of bone-resorbing osteoclasts, and decreased lifespan of bone-depositing osteoblasts⁵. The result of this negative balance is thinning of the cortex and enlargement of cortical pores⁶. The increase in remodeling frequency also decreases the time available for secondary mineralization to occur, leading to a decrease in the degree of mineralization of bone (DMB), or mass of bone mineral per unit volume of bone matrix^{7,8}.

Although cortical bone responds more slowly in response to changes in loading than does trabecular bone, its importance must not be underestimated. Even at sites of predominantly trabecular bone, such as the femoral neck, half of the variance in bone's failure load is explained by the cross-sectional area and macroscopic mineral density of the cortical bone layer⁹. The mechanical properties of cortical bone are in turn strongly influenced by meso- and microstructural organization (i.e. porosity)¹⁰, tissue-level mineralization¹¹, and water content and compartmentalization^{12,13}.

Standard clinical measurement of bone density is typically performed by means of dual-energy x-ray absorptiometry (DXA). In this method, the contribution of soft tissue to total x-ray attenuation is removed, leaving only the attenuation of bone mineral. DXA, therefore, measures apparent areal (two-dimensional) bone mineral density (BMD), expressed in grams per cm². BMD obtained in this manner is 'apparent' in that it lacks sufficient spatial resolution to image individual pore spaces, and so the measured density represents mass of bone mineral per unit total bone area (including pore spaces) rather than per unit of matrix. DXA density is therefore affected both by changes in porosity (mesoscopic scale) and tissue mineralization (microscopic scale). Thus, the loss of total bone tissue in osteoporosis (and the concomitant loss in mineral) and the demineralization that occurs in osteomalacia would not be distinguishable with DXA.

Quantitative computed tomography (QCT) is less commonly used as a screening tool, but has one important advantage over DXA: it resolves bone structure in all three dimensions. By applying QCT to the limbs, resolution can be improved through use of greater x-ray exposure and a specialized high-resolution scanner. In-plane resolution of high-resolution peripheral QCT (HR-pQCT) is on the order of 100 μm , sufficient for visualization of large cortical pores, but still inadequate to quantify true tissue mineralization.

Full resolution of small pores in bone is possible only with micro-computed tomography (μCT). Micro-CT uses spatial encoding principles similar to CT, but with much higher exposures necessary to achieve isotropic resolution finer than 10 μm . This method, therefore, can resolve the entire pore architecture in cortical bone, down to individual osteocyte

lacunae ¹⁴. Micro-CT is the gold-standard method for analysis of bone structure in specimens and small animals ^{15,16}, but is not applicable *in vivo* in humans. Accurate quantification of mineralization, in addition to high spatial resolution, also requires a monochromatic x-ray source to avoid beam-hardening artifacts; this can be achieved using a synchrotron x-ray source as reviewed recently by Peyrin *et al.* ¹⁴.

A method for *in vivo* measurement of DMB could be designed in two ways: a single high-resolution measurement to spatially differentiate bone matrix from pore spaces, or as the ratio of paired measurements of apparent bone mineral and matrix densities. X-ray-based measurements with high resolution involve large radiation dose, and are thus not applicable to human subjects. A paired-measurement method may therefore hold more promise for *in vivo* use.

Both ¹H (the most abundant isotope of hydrogen), present in bone water, and ³¹P (the sole naturally abundant isotope of phosphorus), a major component of bone mineral, have nuclear spin angular momentum ($I = 1/2$) and are thus NMR-active. Both components of a paired measurement of apparent bone mineral and matrix densities are therefore feasible using MRI ^{17,18}. Magnetic resonance can also provide valuable information on the concentrations and relative proportions of bound and pore bone water, which have important implications on the bone's mechanical competence ¹⁹.

2. Solid-State MRI

Fundamentals of MRI

In magnetic resonance imaging, nuclear spin magnetic moments are polarized by placing the sample or subject into a strong magnetic field. The resultant macroscopic magnetic moment (also called 'magnetization'), initially oriented along the direction of the polarizing field, is then manipulated in a spatially dependent manner by applied radiofrequency (RF) and magnetic gradient fields. As the magnetization vector precesses in a plane perpendicular to the polarizing magnetic field it induces a RF voltage in a receive coil. The resulting signal is then recorded and reconstructed into an image. Therefore, the three basic steps of an MRI imaging experiment, known as a pulse sequence, are to excite, encode, and acquire the nuclear magnetic resonance (NMR) signal.

After signal excitation, however, the NMR signal decays (approximately exponentially) with a time constant called the effective transverse relaxation time (T_2^*), essentially the lifetime of the signal. Among other effects, T_2^* depends on the homogeneity of the static magnetic field within the sample and the degree of molecular motion, which allows for averaging of the local magnetic field experienced by the spins over the course of the NMR experiment. The portion of this decay due to static field inhomogeneity, often represented by a time constant T_2' , can be removed using RF pulses to refocus spins in the transverse plane, thus isolating the true transverse relaxation time (T_2), which is related to T_2^* as $1/T_2^* = 1/T_2 + 1/T_2'$. Note that the reciprocals of the relaxation time constants, i.e., the decay rates, are additive.

MRI signal intensity is proportional to the density of the nucleus being imaged. It further depends on the longitudinal (T_1), transverse (T_2), and effective transverse (T_2^*) relaxation times and the transmit and receive radiofrequency fields (B_1). Once T_1 , T_2 , and T_2^* of the bone tissue are known, and the B_1 fields of transmit and receive coils are mapped, the image intensity can be corrected for these effects, and density can be quantified relative to a similarly corrected reference sample in the same image field of view ²⁰.

Solid-State MRI of Bone

One of the main difficulties facing MRI of bone is the extremely short lifetime of the MR signal. As a result of the highly inhomogeneous, motionally restricted environment characteristic of mineralized tissues ¹⁷, T_2^* of the detectable protons and ^{31}P nuclei is orders of magnitude shorter than those in soft tissue. The excited NMR signal, therefore, typically decays to below noise level before it can be sufficiently encoded and acquired by standard MRI pulse sequences (**Figure 1**). Bone, therefore, appears dark in standard magnetic resonance images. Magnetic resonance experiments on bone mineral ^{31}P are also hindered by its extremely long longitudinal relaxation time (T_1).

In order to image the fast decaying (i.e. short- T_2^*) ^1H and ^{31}P signal in bone, the time between signal excitation, encoding, and acquisition must be substantially reduced, relative to standard MRI pulse sequences. Three solid-state radial pulse sequences have emerged during the past two decades for imaging short- T_2^* tissues: ultrashort echo-time (UTE) ²¹, zero echo-time (ZTE) ²²⁻²⁴, and sweep imaging with Fourier transformation (SWIFT) ^{25,26}. As shown in **Figure 1**, these solid-state MRI (SS-MRI) pulse sequences can capture these rapidly-decaying signals.

In UTE, the time delay between the end of signal excitation and the beginning of encoding and acquisition (referred to as echo time, TE) is reduced by beginning signal encoding and acquisition simultaneously and immediately after the MRI system's transmit/receive (T/R) switching dead time (a hardware dependent parameter) has elapsed. This method is simple to implement, but may be complicated by inevitable deviations from the theoretical gradient waveform due to eddy currents, though these deviations can be measured and corrected for during reconstruction ²⁷.

The ZTE pulse sequence further reduces the delay between signal excitation and acquisition for each data point. In this method, signal encoding is begun simultaneously with excitation, but the time delay to signal acquisition is still dictated by the T/R dead time. This delay results in the loss of the first several data points in the acquisition window. Several methods exist to either recapture these lost data or reconstruct an image in their absence ²⁸⁻³⁰.

In SWIFT, the excitation, encoding, and acquisition steps are performed in a finely interleaved (gapped ²⁵) or fully simultaneous (continuous ²⁶) manner. This method, however, requires significant hardware modifications to completely eliminate the delay between excitation and acquisition for every k-space point. In vivo imaging of the teeth, whose T_2^* is even shorter than that of bone, has been achieved using SWIFT ³¹.

Wu and Ackerman first performed ^{31}P imaging of bone mineral in animal bone ex vivo in 1992²⁴, and in 2004, Robson et al.³² reported the first in vivo ^{31}P images of human bone. Cao *et al.* later measured a 22.1% decrease in bone mineral in cortical bone specimens from partially nephrectomized rat compared to controls by ^{31}P NMR³³ with separate determination of bone volume. Anumula *et al.* reported image-based quantification of ^{31}P in rabbit and rat bone specimens using experimental hardware^{20,34}. In ovariectomized rats, bone phosphorus density was found to be lower by 8.1% relative to controls, and a recovery of 14% was measured in response to treatment with alendronate. Seifert *et al.* measured a ^{31}P concentration of 6.7 ± 1.2 mol/L in human cortical bone specimens using a clinical scanner³⁵ (**Figure 2a**), and Wu published in vivo ^{31}P images of the human wrist³⁶ (**Figure 2c,d**).

3. ^1H Signal Components

While mineral is the only significant source of ^{31}P signal in bone, the ^1H signal arises from at least three major pools, distinguishable by their transverse relaxation times³⁷. Relatively free water within pores has the longest T_2 relaxation times, ranging from 1 ms to 1 s. Within this pool, water in small pores, which have greater surface-to-volume ratios, experiences greater surface relaxation and thus has shorter T_2 than water in larger pores³⁸. On the other hand, water hydrogen-bonded to bone matrix, is more tightly restricted in its movement, and its protons experience less motional averaging of their local magnetic environments. The ^1H signal from bound water has a shorter T_2 of approximately 300-400 μs ^{37,39,40}.

A third pool of ^1H signal with extremely short $T_2 < 100$ μs also exists⁴¹. This pool encompasses protons in matrix collagen, water within bone mineral crystals, and possibly other macromolecules. Clinical MRI equipment is unable to capture signal from this extremely short- T_2 pool, even using specialized solid-state pulse sequences.

The presence of multiple bone water pools presents a challenge and an opportunity: while bone matrix density is only moderately correlated with total bone water density^{39,42}, both matrix density and the bone's mechanical properties have been found to be more strongly positively correlated with bound water and collagen ^1H densities^{29,33,37,39,40,42-48}, and inversely proportional to pore water density^{39,40,42,45,46,49}. Meaningful studies of bone water by MRI must therefore involve discrimination between these bone water pools.

Various methods exist to isolate either the short- T_2 bound or longer- T_2 pore water fraction. These techniques belong to two general groups: bi-component fitting methods based on multi-exponential analysis of signal decays, and magnetization preparation using RF pulses applied prior to signal excitation.

Bi-Component Analysis

Bi-component analysis is based on the hypothesis that the temporal evolution of the ^1H signal in bone can be modeled as the amplitude-weighted sum of two or more decaying exponentials, each having a time constant corresponding to the transverse relaxation time of one of the signal pools discussed in the previous section. Hardware limitations of clinical scanners and potential hazards from tissue heating preclude application of pulse sequences

to study the T_2 components of the bone ^1H signal (though this is possible on spectroscopic and experimental systems ³⁷). T_2^* bi-component fitting of free induction decay (FID) data or a series of images collected at different TE s has been investigated as an alternative, due to its relative ease of implementation.

In bi-component fitting methods, signal can be acquired at several TE s and fitted to a sum of two weighted exponential functions.

$$f(t) = M_S \exp\left(\frac{-t}{T_{2S}^*}\right) + M_L \exp\left(\frac{-t}{T_{2L}^*}\right) + n$$

The weights of these exponential decays, M_S and M_L , have been hypothesized to represent bound and pore water pool signal amplitudes ^{44,45,48,50}. Using this method, Diaz et al. measured a bound water fraction of 76% in bovine cortical bone ⁴⁴, and Biswas et al. observed that gravimetrically-validated air-drying of bovine cortical bone resulted in reduction of the long- T_2^* fraction representative of pore water ⁴⁵. The bi-component method requires acquisition of 10 to 34 images at multiple delay times, with each image taking several minutes to acquire ⁵⁰. A time-saving variation on this method, also based on differences in T_2^* relaxation, involves subtraction of an image acquired at a long TE (for example, equal to an integer multiple of the inverse of the difference between fat and water frequencies, e.g. 4.6 ms, to cause methylene and water signal to be in phase ⁵¹) from a matched image acquired with very short TE . To further reduce scan time, the long- TE image can be acquired in the same excitation as a gradient echo after the short- TE image.

In a variation of the bi-component method, a ‘porosity index’ ⁵² is computed from two echoes, by dividing long- TE image ($TE \sim 2\text{--}4\text{ms}$) by a UTE image ($TE_{\min} \sim 50\mu\text{s}$). The resulting index is a surrogate for long- T_2^* pore water content and, therefore, porosity. The authors show that the porosity index is strongly positively correlated with μCT -derived porosity. The advantage of this abbreviated approach is that the two echoes can be collected in a single scan. However, the porosity index is sensitive to the choice of the second echo.

One possible complication of bi-component analysis and related methods is that T_2^* of pore water is shortened due to strong internal magnetic field gradients arising from the difference in magnetic susceptibility between water and bone tissue ($\chi \sim 2.5 \text{ ppm SI}$) ⁵³. The reduced separation between bound and pore water T_2^* values complicates separation via bi-component fitting, which, as a form of inverse Laplace transformation, is an ill-posed problem ⁵⁴. Because the strength of the induced magnetic fields increases linearly with field strength, this effect becomes more severe at higher field strengths ⁵⁵.

Water- and Fat-Suppressed Proton Projection Imaging (WASPI)

An alternative method, also exploiting differences in T_2^* between bound and pore water, makes use of the T_2^* selectivity of RF pulses determined by pulse bandwidth ⁵⁶. In spectroscopic terms, signal with short T_2^* has a broad spectral bandwidth, while signal with long T_2^* has a narrow bandwidth. Similarly, RF pulses with short duration have broad bandwidth, and those with long duration have narrow bandwidth. A short RF pulse, with its

broad bandwidth, covers both the broad-band short- T_2^* signal and narrow-band long- T_2^* signal. A long RF pulse (i.e., orders of magnitude longer than the short T_2^*) with its narrow bandwidth, however, fully covers only the narrow-band long- T_2^* signal, while less strongly affecting the broad-band short- T_2^* signal.

The T_2^* -selectivity of RF pulses was exploited to selectively image bound bone water by Wu and Ackerman in 2003²⁹. By applying a preparatory saturation (90-degree) RF pulse with a duration orders of magnitude longer than the short T_2^* but less than or on the order of the long T_2^* , the spins of the long- T_2^* signal are effectively saturated (i.e., they yield no signal), while the short- T_2^* signal is preserved. Immediately after such preparation, an imaging pulse sequence will acquire signal from short- T_2^* bound water. Cao et al. reported in 2008 that WASPI image intensity in porcine cortical and trabecular bone specimens is highly correlated ($R^2 = 0.98$) with bone matrix density measured using a gold-standard gravimetric method⁴³.

Pore Water-Suppressed Imaging

As previously discussed, T_2^* may be less suited for differentiating bound and pore water than is T_2 . Pore water signal has a long T_2 , but is also distributed across a broad band of resonance frequencies due to susceptibility-induced magnetic field perturbations⁵⁷ and, therefore, could have T_2^* similar to that of bound water. Both bi-exponential analysis and WASPI, which rely on T_2^* to distinguish bound and pore water signal, may therefore misclassify water in small pores as bound water due to similarities in their T_2^* values.

While duration and bandwidth are inversely proportional in non-adiabatic pulses, they are less strictly linked in adiabatic RF pulses. Such a pulse can therefore simultaneously possess a long duration and broad bandwidth. The long duration allows it to saturate short- T_2 signal while inverting long- T_2 signal, and the broad bandwidth encompasses the broad frequency distribution of pore water within the complex internal magnetic field environment of bone pores. The inverted long- T_2 magnetization will subsequently recover by longitudinal relaxation, passing through zero at some time, while the saturated short- T_2 signal will recover from zero to positive values. If the signal is read out at the time the long- T_2 magnetization passes through zero, long- T_2 pore-water signal will be virtually absent from the resulting image.

Several groups have incorporated such RF pulses and a judiciously-chosen inversion-recovery time (TI) to selectively image bound water^{12,35,42,46,58,59}. Larson et al.⁵⁸ first demonstrated the T_2 selectivity of adiabatic pulses in vivo by summing two images: one with adiabatic preparation and no delay, and one without the inversion pulse. Du et al.⁵⁹ implemented the adiabatic RF pulse and TI to null long- T_2 signal in a single image and quantified bound water. Li et al.¹² introduced the ‘suppression ratio’, in which an image acquired without long- T_2 suppression is divided by an image with long- T_2 suppression by adiabatic inversion recovery (**Figure 3a,b**). The rationale underlying this concept is that with increased porosity, pores increase in size, causing prolonged water T_2 relaxation times (as a result of decreased surface-to-volume ratio⁶⁰). The authors found the suppression ratio to be positively correlated with independently measured porosity. While not providing absolute

water concentrations, the suppression ratio is a potentially useful biomarker, not requiring calibration against an external concentration standard.

Horch et al.⁴² found that bound water measured in specimens of human cortical bone by long T_2 -suppressed UTE were strongly correlated with mechanical testing results and T_2 relaxation NMR spectroscopy. Manhard et al.⁶¹ proved the reproducibility of this method by reporting a bound water ^1H concentration of 27.9 ± 2.0 mol/L in 15 measurements across 5 subjects (**Figure 3c,d**). The same group of investigators also introduced a double adiabatic full passage (DAFP) method to isolate and image pore water^{42,46}; two successive adiabatic pulses invert and immediately restore long- T_2 pore water magnetization, while saturating short- T_2 bound water. The authors found pore water to be negatively correlated with peak stress ($R^2 = 0.69$,⁴²), consistent with the notion that increased porosity weakens the bone. In another study using the same technology, bound and pore water measured at 3 T on a clinical scanner were positively correlated with values measured by gold-standard T_2 relaxation spectroscopy ($R^2 = 0.76$ and 0.41 , respectively⁴⁶). In other recent studies, Seifert et al. also found bound water density measured ex vivo in human tibial cortical bone to be correlated positively with gravimetric matrix density ($R^2 = 0.74$,⁶²) and ^{31}P concentration ($R^2 = 0.59$, **Figure 2b**³⁵) and negatively with porosity ($R^2 = 0.81$,³⁵). These observations support the utility of T_2 -selective magnetization preparation for estimation of bound and pore water density. The results are consistent with the known roles bound and pore water play in determining bone mechanical properties.

4. Conclusions

Limitations of SS-MRI

Spatial resolution, signal to noise ratio (SNR), and scan time are the key current limitations of solid-state MRI. The achievable spatial resolution in an MR image is determined by the strength of the spatial-encoding magnetic field gradients, and by T_2^* (over which we have no control); stronger gradients yield finer resolution, while short T_2^* increases image blurring. The maximum gradient amplitude available on most standard clinical scanners is approximately 40 mT/m, from which one calculates an intrinsic resolution limit of 0.48 mm for bound water ^1H ($T_2^* \sim 400$ μs) and 2.44 mm for bone mineral ^{31}P ($T_2^* \sim 120$ μs). Since T_2^* is an intrinsic property of bone, resolution can only be improved by increasing gradient strength, which is limited by instrumental and safety concerns. Recently, Frey, et al.⁶³ combined a spectroscopic line-narrowing technique with spatial encoding gradients to improve image resolution, but the high RF power used in this method is not compatible with current clinical hardware.

Image SNR is also related to scan time via NMR relaxation times. As T_2^* becomes shorter, the signal decays more quickly, and data must be acquired more quickly as a result. As a general rule, SNR is proportional to the square root of data acquisition time; therefore, the short T_2^* of bone water ^1H and mineral ^{31}P limits the achievable SNR. Some SNR can be recovered by increasing voxel size, that is, at the expense of resolution, or by signal averaging, which increases total scan time. Due to the fully 3D nature of UTE and ZTE, spatial encoding takes longer, which in turn prolongs scan times: a fully sampled ^1H IR-ZTE

or ^{31}P ZTE image can be acquired in approximately 20-30 minutes. Therefore, acquiring both types of images in a single scan session may exceed patient tolerance.

Fortunately, several opportunities exist to improve SNR and reduce scan time without undue trade-offs. For instance, the long bones of the appendicular skeleton are relatively featureless along their axis. This presents the opportunity to anisotropically lower the resolution along this direction (i.e., increase voxel size along the bone's shaft), which increases SNR proportionally for a fixed image acquisition time. Scan time can also be further reduced by strategically undersampling during image acquisition. While undersampling results in distracting and disruptive aliasing artifacts in standard Cartesian sampling methods, it results in much more tolerable incoherent streaking or noise-like features in radial imaging methods.

Establishment of Clinical Potential

A solid-state bone MRI pulse sequence with clinically practical scan time must be rigorously evaluated in the context of established methods, including DXA and QCT. Studies should include healthy control subjects, as well as patients with established osteoporosis, examined before and after intervention. An important question to be addressed is whether the MRI-based methods for the assessment of cortical bone predict fracture risk better than established X-ray based methods at sites with significant cortical bone content, such as the femoral neck and shaft. Specifically, such studies would establish the utility of ^{31}P and bound- and pore-water discriminated ^1H imaging to quantify bone mineral and matrix densities, porosity, and mineralization, and the role these measures play as determinants of cortical bone mechanical properties. Lastly, the methods must be sensitive enough to detect changes of the measured parameters in response to intervention.

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Figure 1.

Plot of the signal decay curves for several tissue types. Both ^1H and ^{31}P signal from bone tissue decay extremely rapidly and, consequently, standard gradient-echo and spin-echo MRI pulse sequences are unable to acquire signal from bone. Solid-state MRI (SS-MRI) pulse sequences, including UTE, ZTE, and SWIFT, are able to capture these extremely short-lived signals before they decay below the noise level.

Figure 2.

Parametric maps of ^{31}P (a) and bound water ^1H (b) concentrations (mol/L) in human tibial cortical bone acquired ex vivo at 3 T and 7 T, respectively (reproduced from ³⁵). ^{31}P and bound water ^1H were correlated ($R^2 = 0.59$) in these data from non-osteomalacic donors. (c,d) In vivo images of cortical bone ^{31}P in the human wrist (reproduced from ³⁶).

Figure 3.

Parametric maps of the Suppression Ratio (SR) obtained with and without long- T_2 suppression in six subjects (a), along with the corresponding histograms (b). As SR values increase, histograms become increasingly asymmetric with long tails toward high SR values, commensurate with the notion of elevated T_2 of the water in larger pores (reproduced from ¹²). Maps of bound (c) and pore (d) water concentration, measured by adiabatic

inversion-recovery and double adiabatic full passage UTE MRI, respectively (reproduced from ⁶¹).

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Table 1Various measures of bone matrix and water obtained by ¹H MRI, micro-CT, and gravimetry.

Reference		Magnetic Field/Technique	Anatomic Location/Species	Parameter Measured	Measured Value	Specimens/Subjects
C. Li	12	3T UTE MRI	Human Tibial Cortical Bone (In Vivo)	Total Water (% vol.)	24.8 % ± 4.7 %	72
Rad	64	3T UTE MRI	Human Tibial Cortical Bone (In Vivo)	Total Water (% vol.)	21.80%	10
Rad	64	3T UTE MRI	Lamb Tibial Cortical Bone	Total Water (% vol.)	26.5 % ± 1.6 %	6
Techawiboon wong	65	3T UTE MRI	Human Tibial Cortical Bone (In Vivo Healthy Control)	Total Water (% vol.)	17.4 % ± 2.2 %	5
Techawiboon wong	65	3T UTE MRI	Human Tibial Cortical Bone (In Vivo Post-Menopausal)	Total Water (% vol.)	28.7 % ± 1.3 %	5
Techawiboon wong	65	3T UTE MRI	Human Tibial Cortical Bone (In Vivo Renal Osteodystrophy)	Total Water (% vol.)	41.1 % ± 9.6 %	6
Techawiboon wong	66	3T UTE MRI	Human Tibial Cortical Bone (In Vivo)	Total Water (% vol.)	19.6 % ± 1.5 %	4
Anumula	34	9.4T 1H UTE MRI	Rat Femoral Cortical Bone (Ex Vivo)	Total Water (% wt.)	14.6 % ± 1.4 %	15
Anumula	67	9.4T 1H UTE MRI	Rabbit Tibial Cortical Bone (Ex Vivo)	Total Water (% wt.)	14.4 % ± 1.1 %	5
Anumula	67	9.4T 2H-Exchange 1H NMR	Rabbit Tibial Cortical Bone (Ex Vivo)	Total Water (% wt.)	17.4 % ± 1.2 %	5
Anumula	67	Gravimetry	Rabbit Tibial Cortical Bone (Ex Vivo)	Total Water (% wt.)	15.4 % ± 0.8 %	5
Fernandez-Seara	68	9.4T 2H-Exchange 1H NMR	Rabbit Tibial Cortical Bone (Ex Vivo)	Total Water (% wt.)	15.4 % ± 0.6 %	6
Seifert	62	9.4T ZTE MRI	Human Tibial Cortical Bone (Ex Vivo)	Total Water [1H]	32.7 ± 3.2 M	15
Seifert	62	Gravimetry	Human Tibial Cortical Bone (Ex Vivo)	Water Density	326.2 ± 48.4 mg/cc	15
Seifert	62	9.4T IR-ZTE MRI	Human Tibial Cortical Bone (Ex Vivo)	Bound Water [1H]	32.9 ± 3.9 M	15
Manhard	61	3T IR-UTE MRI	Human Tibial Cortical Bone (In Vivo)	Bound Water [1H]	27.86 ± 2.00 M	5 (3 ROIs each)
Manhard	61	3T IR-UTE MRI	Human Radial Cortical Bone (In Vivo)	Bound Water [1H]	34.86 ± 2.59 M	5 (2 ROIs each)
Seifert	35	3T IR-ZTE MRI	Human Tibial Cortical Bone (Ex Vivo)	Bound Water [1H]	31.3 ± 4.2 M	16
Horch	37	4.7T NMR w/ T2 Bicomponent Analysis	Human Femoral Cortical Bone (Ex Vivo)	Bound Water [1H]	24.8 ± 5.8 M	6
Seifert	62	Gravimetry	Human Tibial Cortical Bone (Ex Vivo)	Matrix Density	503.7 ± 24.3 mg/cc	15
Cao	33	4.7T 1H ZTE MRI	Rat Femoral Cortical Bone (Ex Vivo)	Matrix Density	0.45 ± 0.04 g/cc	10
Manhard	61	3T DAFP-UTE MRI	Human Tibial Cortical Bone (In Vivo)	Pore Water [1H]	7.32 ± 1.15 M	5 (3 ROIs each)
Manhard	61	3T DAFP-UTE MRI	Human Radial Cortical Bone (In Vivo)	Pore Water [1H]	6.14 ± 1.97 M	5 (2 ROIs each)
Horch	37	4.7T NMR w/ T2 Bicomponent Analysis	Human Femoral Cortical Bone (Ex Vivo)	Pore Water [1H]	9.2 ± 2.3 M	6
Rajapakse	52	3T UTE MRI w/ T2* Bicomponent Analysis	Human Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	18 % ± 7 %	16

Reference		Magnetic Field/Technique	Anatomic Location/Species	Parameter Measured	Measured Value	Specimens/Subjects
Seifert	62	9.4T NMR w/ T1-T2 Bicomponent Analysis	Human Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	23.0% $\pm$ 9.3 %	15
Chang	69	3T UTE MRI w/ T2* Bicomponent Analysis	Human Femoral and Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	20%	122 (from 38 donors)
Seifert	55	9.4T 2H IR NMR	Human Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	37.4 % $\pm$ 9.56 %	15
Seifert	55	9.4T NMR w/ T2* Bicomponent Analysis	Human Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	30.4 % $\pm$ 12.7 %	15
Seifert	55	7T NMR w/ T2* Bicomponent Analysis	Human Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	31.9 % $\pm$ 21.9 %	15
Seifert	55	3T NMR w/ T2* Bicomponent Analysis	Human Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	17.7 % $\pm$ 14.0 %	15
Seifert	55	1.5T NMR w/ T2* Bicomponent Analysis	Human Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	44.9 % $\pm$ 28.7 %	15
S. Li	70	1.5T UTE MRI w/ T2* Bicomponent Analysis	Bovine Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	31.5%	6
S. Li	70	1.5T UTE MRI w/ T2* Bicomponent Analysis	Human Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	25.6%	9
S. Li	70	3T UTE MRI w/ T2* Bicomponent Analysis	Bovine Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	31.0%	6
S. Li	70	3T UTE MRI w/ T2* Bicomponent Analysis	Human Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	24.1%	9
Du	47	3T UTE MRI w/ T2* Bicomponent Analysis	Human Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	22.4 % $\pm$ 4.9 %	8
Biswas	45	3T UTE MRI w/ T2* Bicomponent Analysis	Bovine Femoral and Tibial Cortical Bone (Ex Vivo)	Pore Water Fraction	11.40%	14 (from 4 animals)
Horch	42	4.7T NMR w/ T2 Bicomponent Analysis	Human Femoral Cortical Bone (Ex Vivo)	Pore Water Fraction	29 % $\pm$ 10 %	14
Horch	42	4.7T UTE MRI w/ T2* Bicomponent Analysis	Human Femoral Cortical Bone (Ex Vivo)	Pore Water Fraction	10 % $\pm$ 6 %	14
Du	50	3T UTE MRI w/ T2* Bicomponent Analysis	Bovine Cortical Bone (Ex Vivo)	Pore Water Fraction	21.8 % $\pm$ 3.6 %	5
Diaz	44	3T UTE MRI w/ T2* Bicomponent Analysis	Bovine Cortical Bone (Ex Vivo)	Pore Water Fraction	24.30%	1
Seifert	62	Micro-CT	Human Tibial Cortical Bone (Ex Vivo)	Pore Volume Fraction	8.96 % $\pm$ 8.61 %	15
Biswas	45	Micro-CT	Bovine Femoral and Tibial Cortical Bone (Ex Vivo)	Pore Volume Fraction	0.89 % $\pm$ 0.57 %	14 (from 4 animals)
Horch	37	Micro-CT	Human Femoral Cortical Bone (Ex Vivo)	Pore Volume Fraction	4.0 % $\pm$ 1.0 %	6
C. Li	12	3T IR-UTE MRI	Human Tibial Cortical Bone (In Vivo)	IR Suppression Ratio	2.32 $\pm$ 0.42	40
Rajapakse	52	3T UTE MRI Porosity Index	Human Tibial Cortical Bone (In Vivo)	Porosity Index	20 % $\pm$ 3.8 %	5

Table 2Measures of bone mineral content by ^{31}P MRI and gravimetry.

Reference		Magnetic Field/Technique	Anatomic Location/Species	Parameter Measured	Measured Value	Specimens/Subjects
Seifert	35	7T ^{31}P ZTE MRI	Human Tibial Cortical Bone (Ex Vivo)	Mineral [^{31}P]	6.74 ± 1.22 M	16
Seifert	62	Gravimetry	Human Tibial Cortical Bone (Ex Vivo)	Mineral Density	1118 ± 130 mg/cc	15
Cao	33	4.7T ^{31}P ZTE MRI	Rat Femoral Cortical Bone (Ex Vivo)	Mineral Density	1270 ± 100 mg/cc	10
Anumula	34	9.4T ^{31}P UTE MRI	Rat Femoral Cortical Bone (Ex Vivo)	Mineral Density (% wt.)	$12.4 \% \pm 0.8 \%$	15
Anumula	34	9.4T ^{31}P Solution-State NMR	Rat Femoral Cortical Bone (Ex Vivo)	Mineral Density (% wt.)	$13.3 \% \pm 0.8 \%$	15
Anumula	67	9.4T ^{31}P UTE MRI	Rabbit Tibial Cortical Bone (Ex Vivo)	Mineral Density (% wt.)	$11.1 \% \pm 0.3 \%$	5
Anumula	20	9.4T ^{31}P UTE MRI	Rabbit Tibial Cortical Bone (Ex Vivo)	Mineral Density (% wt.)	$11.14 \% \pm 0.31 \%$	5
Anumula	20	9.4T ^{31}P Solution-State NMR	Rabbit Tibial Cortical Bone (Ex Vivo)	Mineral Density (% wt.)	$12.94 \% \pm 0.85 \%$	5
Fernandez-Seara	68	9.4T ^{31}P Solution-State NMR	Rabbit Tibial Cortical Bone (Ex Vivo)	Mineral Density (% wt.)	$13.8 \% \pm 0.5 \%$	6
Fernandez-Seara	68	Gravimetry	Rabbit Tibial Cortical Bone (Ex Vivo)	Mineral Density (% wt.)	$20.5 \% \pm 0.6 \%$	6