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Sodium relaxation times in the knee joint in vivo at 7T

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Abstract

The sodium concentration correlates directly with the concentration of proteoglycans (PG) in cartilage, the loss of which is an early signature of osteoarthritis (OA). As a result, quantitative sodium MRI is a promising technique for assessing the degradation of articular cartilage in patients with OA. Sodium relaxation times can also provide information on the degradation of cartilage: it has already been shown on bovine cartilage that T_1 and T_{2long} are longer and T_{2short} shorter when the PG concentration decreases. In this study, sodium T_1 , T_{2short}^* and T_{2long}^* relaxation maps were measured in vivo at 7T on 8 healthy volunteers and in 4 different regions of the cartilage in the knee joint. The patellar, femoro-tibial medial, lateral, and femoral condyle cartilage have an average $T_1 \sim 20$ ms, but different T_{2short}^* (from 0.5 ms to 1.4 ms) and T_{2long}^* (from 11.4 ms to 14.8 ms). Statistically significant differences in T_1 , T_{2short}^* and T_{2long}^* were observed between the different regions in cartilage ($p \ll 10^{-5}$). Statistical differences in T_1 were also observed between male and female data ($p \ll 10^{-5}$). These relaxation times measurements can further be applied as correction factors for sodium concentration maps in vivo and also be useful as complementary information to quantitative sodium MRI in the quest for detecting early OA. These measurements were done on low resolution sodium images in order to acquire sufficient quality data for fitting (5 images for T_1 and 9 images for T_2^*) while keeping the total time of acquisition of the data reasonable for the volunteer's comfort (1 h 15 min).

Keywords

Sodium MRI; articular cartilage; relaxation times; osteoarthritis

Introduction

Osteoarthritis (OA) is a degenerative articular cartilage disease that is characterized by joint pain, tenderness, limitation of movement, crepitus, effusion and local inflammation. It is a cause of chronic disability mainly in the elderly population and it is estimated that worldwide $\sim 10\%$ of men and $\sim 18\%$ of women aged >60 years are affected. It is more prevalent in Europe and USA, where $\sim 14\%$ of men and $\sim 23\%$ of women are affected.

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Because of the increase in life expectancy in developed and developing countries, OA is expected to be the fourth leading cause of disability by 2020 (1). To date, there is no cure for OA and the main treatments include physical therapy, lifestyle change (loss of weight, moderate exercise), use of pain relievers and ultimately surgery (joint replacement). It is therefore fundamental to detect early OA in order to adapt the treatment before the patient needs pain medication or surgery, and also to find a method to quantify the effects of new treatments under investigation.

Articular cartilage is a dense connective tissue that consists mainly of an extracellular matrix (ECM) composed of collagen (~ 20%), proteoglycans (PG, ~ 5%) and water (~ 75%) (2). From a biochemical point of view, OA is associated with a loss of PG, increase of water content and change in the arrangement of the collagen fibers. PG is a complex molecule of sulfate and carboxylate groups whose negative charge attracts free floating positive ions Na^+ mainly in the extracellular matrix (ECM). This process in turn leads to accumulation of water molecules in the ECM through osmotic pressure. It has been shown that the loss of PG is a signature of early OA and that the sodium concentration in the cartilage correlates with the PG concentration, therefore quantitative sodium (^{23}Na) magnetic resonance imaging (MRI) is a good candidate to assess early OA (3, 4, 5, 6, 7). An extensive review on the biochemical aspects of cartilage tissue, OA and sodium MRI is given in (2) and references herein. Moreover, it has been shown (on bovine cartilage samples) that not only the sodium concentration but also the ^{23}Na relaxation times vary with the trypsin degradation of bovine cartilage: T_1 and $T_{2\text{long}}$ are longer even for a small loss of PG in the ECM, while $T_{2\text{short}}$ is shorter but is detectable only for bigger changes in the PG content (8). One study has measured the sodium relaxation times in vivo on healthy human cartilage, using multiple quantum spectroscopy with a surface coil (9), T_1 was not measured, and the following results were found for the biexponential transverse relaxation times: $T_{2\text{short}} = 1 \pm 0.12$ ms and $T_{2\text{long}} = 12 \pm 0.75$ ms. A recent study (10) has measured a monoexponential $T_2^* \sim 8.5 - 20$ ms in the patella in vivo at 3T and 7T and presented a T_2^* map. In the present work, we measure the sodium relaxation times in vivo on 8 asymptomatic volunteers in 4 different locations of the articular cartilage in the knee joint using MRI at 7T. This method allows one therefore to get some spatial information on the relaxation times by calculating the sodium T_1 , $T_{2\text{short}}^*$ and $T_{2\text{long}}^*$ maps in selected regions of interest (ROI) in the cartilage and is expected, for future studies, to give more information of the cartilage degradation in early OA as a complement to the sodium concentration maps. The relaxation times were also measured in blood (artery) and muscle for comparison.

Materials and Methods

MRI acquisition

All sodium images were acquired on a 7T whole-body Siemens scanner (Siemens Medical Solution, Erlangen, Germany) using a single tuned quadrature birdcage RF coil (Rapid MR International, Columbus, OH, USA) of length 27 cm and inner diameter 21 cm, tuned to 78.6 MHz. The data were acquired with a 3D ultrashort TE (UTE) radial sequence (11) written with SequenceTree 4.2.2 (12) and compiled with the Siemens pulse development environment IDEA VB15A. The common acquisition parameters for T_1 and T_2^* measurements were: number of projections $N_{\text{proj}} = 3500$, with a RF pulse duration of 500 μs , a maximum of 128 points of acquisition for each radial projection, dwell time = 80 μs , field of view $\text{FOV} = 200 \times 200 \times 200 \text{ mm}^3$. Note that there is no echo in this 3D radial sequence, therefore the conventional term “TE” represents here the delay calculated from the end of the RF pulse to the beginning of the data acquisition, in accordance with standard practice in UTE literature. Prior to data acquisition, 100 projections were acquired with $\text{FA} = 0^\circ$ for noise measurements, followed by 30 projections for reaching the steady state.

Eight healthy volunteers (4 females, 4 males) were scanned, with an average age of 30.3 ± 5.1 years, an average weight of 64 ± 15 Kg and average height of 175 ± 20 cm (Females: average age of 28.3 ± 5.7 years, weight of 48 ± 4 Kg and height of 161 ± 10 cm; Males: average age of 32.3 ± 4.3 years, weight of 75 ± 4 Kg and height of 178 ± 10 cm). The study was approved by the institutional review board (IRB) and all volunteers signed an informed consent form prior to the experiments. One tube filled with PBS (154 mM of NaCl) and 5 tubes filled with Agar 4% and NaCl concentrations of 100, 150, 200, 250 and 300 mM were placed within the field-of-view (FOV) as well. The gel and PBS relaxation times were also measured. The signals from these tubes can be used as calibration phantoms for sodium concentration map calculations.

For T_1 measurements, 5 acquisitions were obtained with a flip angle $FA = 90^\circ$ and echo time $TE = 0.15$ ms and 5 different repetition times $TR = 30, 60, 100, 150$ and 250 ms. The acquisition times were therefore 1:50, 3:30, 5:50, 9:00 and 15:00 min. For T_2^* measurements, 9 acquisitions were obtained with flip angle $FA = 70^\circ$ and $TR = 70$ ms and 9 different $TE = 0.15, 0.55, 0.95, 1.55, 2.75, 4.75, 9.75, 24.75$ and 39.75 ms. The acquisition time was 4:10 min. The total time of acquisition for each relaxation time was therefore $\sim 35 - 40$ min. Prior to imaging the volunteers, the reference voltage of the coil, corresponding to a 180° pulse of 1 ms duration, was calibrated manually on gel phantoms and knees in vivo, using 2D and 3D sequences, with a $TR = 200$ ms. This reference voltage was then used by the scanner to calculate the optimum voltage corresponding to a rectangular 90° or 70° RF pulse of $500 \mu s$.

Image reconstruction

Images were reconstructed offline using a combination of MATLAB (Mathworks, Natick, MA, USA) and FORTRAN code. The image $\rho(\mathbf{x})$ was estimated by solving the linear system arising from the discretized imaging equation:

$$s(\mathbf{k}_j) = \sum_p \rho(\mathbf{x}_p) e^{i\mathbf{k}_j \cdot \mathbf{x}_p}, \quad (1)$$

where $s(\mathbf{k})$ is the signal in k-space expressed as the Fourier transform of the image. Here, $\mathbf{x}$ represents the spatial coordinates in real space and $\mathbf{k}$ the spatial frequency coordinates in k-space. Briefly, optimal density compensation weights w_i were calculated according to the following formula (13):

$$w_i = \frac{1}{\sum_j \text{sinc}^2(\mathbf{k}_i - \mathbf{k}_j)}, \quad (2)$$

and used as a diagonal pre-conditioner in an iterative least-squares algorithm similar to (14). The Fast Sinc Squared Transform (15) and the Non-Uniform Fast Fourier Transform (NUFFT) (16) algorithms were used to accelerate the computations.

The image $\rho(\mathbf{x})$ can only be estimated up to a resolution determined by the Nyquist criterion (11):

$$k_{\max} = \sqrt{\frac{N_{\text{proj}}}{4\pi}}. \quad (3)$$

For $N_{\text{proj}} = 3500$ projections, $k_{\text{max}} = 17$ (in unit of $\frac{1}{FOV}$) and for a field of view $FOV = 200$ mm, images have therefore an isotropic Nyquist resolution $\Delta r = \frac{FOV}{2k_{\text{max}}} = 5.9$ mm. As a regridding algorithm is included in the NUFFT method, we choose to reconstruct the images as $80 \times 80 \times 80$ matrices, therefore the nominal resolution (pixel size) of the 3D output images is 2.5 mm. Taking into account the fact that the data is also acquired during the ramp up time of the gradient, the acquisition time used in the reconstruction algorithm is $T_{\text{acq}} = 1.6$ ms (20 points).

Point Spread Function

The point spread function (PSF) of the 3D sequence was calculated using the equations given in (17) for an average $T_2^* = 9$ ms (corresponding to an average weighted T_2^* of the cartilage composed of 34% $T_{2\text{short}}^* \sim 0.9$ ms and 66% $T_{2\text{long}}^* \sim 13.3$ ms, see Results section). The full width at half maximum (FWHM) of the PSF is then measured to be ~ 3.7 pixels. This means that the images are quite blurred and some partial volume averaging will affect the accuracy of the relaxation times measurements, mainly due to the presence of synovial fluid around the cartilage that can therefore affect the signal of the pixels within the cartilage.

Relaxation parameter fitting and mapping

The relaxation time constants T_1 and T_2^* were measured pixel by pixel for each volunteer in the following ROIs:

- in the patellar cartilage, in the gels, in the PBS tube and in the artery (blood) over 4 consecutive transverse slices.
- in the femoro-tibial (FT) lateral and FT medial cartilage and in muscle over 4 consecutive coronal slices.
- in the femoral (F) condyle cartilage over 4 consecutive sagittal slices.

For the relaxation time mapping, the signal from each pixel of every ROI in all slices was fitted in Matlab with a monoexponential function for T_1 of the form $y = y_0 + A [1 - \exp(-TR/T_1)]$, and a biexponential function for T_2^* of the form

$y = y_0 + A_{\text{short}} \cdot \exp(-TE/T_{2\text{short}}^*) + A_{\text{long}} \cdot \exp(-TE/T_{2\text{long}}^*)$ using a nonlinear regression algorithm. The term y_0 was forced to be the average noise level: for each volunteer, the average noise signal was measured from the noise signal of 3 slices where no other signal could be detected (first coronal slice, first transverse slice and first sagittal slice) on images acquired with $TE = 40$ ms, as with this TE , all signal from muscle and cartilage was below the noise level. The terms A , A_{short} and A_{long} are the amplitudes of the exponential terms. For the biexponential fitting, the respective percentage parts of the signal from $T_{2\text{short}}^*$ and $T_{2\text{long}}^*$ were calculated as follows:

$Part_{\text{short}}^{\%} = 100 \times \frac{A_{\text{short}}}{A_{\text{short}} + A_{\text{long}}}$ and $Part_{\text{long}}^{\%} = 100 \times \frac{A_{\text{long}}}{A_{\text{short}} + A_{\text{long}}}$. For a more accurate and consistent T_1 fitting and mapping, a sixth point corresponding to $TR = 0$ was added to the 5 acquired data points: the signal was taken as the measured average noise y_0 . For T_1 fitting, a biexponential function was also tested but the results were similar to a monoexponential function ($T_{1\text{short}} \sim T_{1\text{long}}$). For the biexponential T_2^* mapping, outlier values ($T_2^* > 60$ ms) were excluded from the final map. These outliers were due to the low signal-to-noise ratio (SNR) of the images and to the relatively small number of data points (9) for 4 fitting parameters.

When the T_2^* fitting results yielded $T_{2\text{long}}^* - T_{2\text{short}}^* < 4$ ms, the results were considered to be

more suitably represented by a monoexponential fit, and these points were also excluded from the final map. This latter restriction allows one therefore to exclude the voxels that include too much fluid from the relaxation map and highly reduces the partial volume effect in the T_2^* measurements in cartilage. The SNR was measured as the mean value of the signal intensity in the regions of interest divided by the standard deviation of the noise (measured on the same images from which the average noise level term y_0 was determined).

Coefficient of determination

The coefficients of determination R^2 and adjusted R^2 (R_{adj}^2) were calculated for each fit (18):

$$R_{adj}^2 = 1 - (1 - R^2) \frac{N - 1}{N - P - 1} \quad (4)$$

where N is the number of points to fit (9 for T_2^* and 6 for T_1) and P is the number of fitting coefficients (not counting the constant term y_0 , that is 2 terms for monoexponential and 4 terms for biexponential fitting). Average values of T_1 and T_2^* in the 4 different cartilage regions, blood, muscle, gels and PBS were then calculated over all the relaxation maps for each volunteer.

Sodium B_0 maps

3D sodium B_0 maps (in Hz) were calculated by using the phase difference between two images with different TEs ($TE_1 = 0.15$ ms and $TE_2 = 2.75$ ms) (19):

$$\Delta B_0(x, y, z) [\text{Hz}] = \frac{\phi_1(x, y, z) - \phi_2(x, y, z)}{2\pi (TE_1 - TE_2)}, \quad (5)$$

where ϕ_1 and ϕ_2 are the phase of the images acquired with TE_1 and TE_2 respectively.

Statistical analysis

The non-parametric statistical Wilcoxon rank-sum test (20, 21) was applied on all the values (T_1 , T_{2short}^* and T_{2long}^*) from all the pixels of all the maps in order to assess the significance of the difference in relaxation times between male and female volunteers, and also between the different regions in cartilage (patellar, FT medial, FT lateral, F condyle).

Results

SNR

The measured SNR was on the order of 40 in articular cartilage, 20 in skeletal muscle and 50 in blood.

Relaxation time maps

Representative examples of monoexponential T_1 and biexponential T_2^* fittings from one pixel in the FT lateral cartilage of one volunteer are presented in Figure 1. In these examples, $T_1 = 14$ ms, $T_{2short}^* = 0.7$ ms and $T_{2long}^* = 16$ ms.

Examples of T_1 maps are shown in Figure 2 and of T_{2short}^* and T_{2long}^* maps are shown in Figure 3. The different regions in the cartilage are described in Figure 2.

Longitudinal relaxation times

Table 1 shows the average T_1 in the Agar gels, PBS, patellar, FT medial and lateral, F condyle cartilage, artery and muscle over all volunteers (locations of the ROIs in cartilage are shown on Figure 2). It can be seen that the T_1 relaxation time is slightly shorter in patellar cartilage (17.7 ± 2.6 ms) than in the other parts of cartilage ($\sim 21 \pm 5$ ms). Averaging over the 4 locations in cartilage gives $T_1 = 20 \pm 1.7$ ms. Gels have an average $T_1 \sim 23 \pm 2.9$ ms which is close to the average in cartilage. Blood exhibits a $T_1 \sim 38.8 \pm 5.4$ ms, very similar to the liquid PBS, where it is $\sim 41.9 \pm 5.6$ ms, and for the muscle T_1 is intermediate $\sim 25.2 \pm 3.6$ ms.

Figure 4 shows a bar chart of the different T_1 values measured in all the ROIs, separately for male (N=4), female (N=4), and all volunteers (average for N=8). As a general trend for all the tissues, it is noticed that T_1 in female volunteers is slightly longer than for in male volunteers. The mean T_1 in cartilage was 22.5 ± 2 ms for female and 17.4 ± 1.4 ms for male.

Statistical analysis—From the Wilcoxon rank-sum test applied on all the T_1 values from all the pixels of all the maps, it was found that the difference in T_1 between male and female is statistically significant ($p \ll 10^{-5}$) for all cartilage regions, blood, and also for muscle. Similarly, the Wilcoxon test showed a significant difference in T_1 between all 4 regions in cartilage ($p \ll 10^{-5}$).

Transverse relaxation times

Table 2 shows the average T_{2short}^* and T_{2long}^* in the Agar gels, PBS, patellar, FT medial and lateral, F condyle cartilage, artery blood and muscle over all volunteers. We can see that PBS, which is liquid, exhibits a monoexponential T_2^* relaxation, as expected, with a decay time of approximately 20 ms. The relaxation times for the different regions of cartilage were as follows: patellar $T_{2short}^* = 0.5 \pm 0.1$ ms is shorter than the FT medial and F condyle $T_{2short}^* = 0.9 \pm 0.3$ ms and FT lateral $T_{2short}^* = 1.4 \pm 0.4$ ms. The long component of patellar cartilage ($T_{2long}^* = 11.4 \pm 1.8$ ms) is also shorter than for the three other parts ($T_{2long}^* = 13.1 - 14.8 \pm 1 - 1.8$ ms). Averaging the relaxation times over the 4 locations in cartilage gives $T_{2short}^* = 0.9 \pm 0.4$ ms and $T_{2long}^* = 13.3 \pm 1.4$ ms. Gels have a $T_{2short}^*/T_{2long}^* \sim 2/12$ ms which is close to the average cartilage relaxation times previously calculated, which allows these gels to be used as calibration phantoms for sodium quantification. The average percentage parts of the signal corresponding to T_{2short}^*/T_{2long}^* are 34%/66% in cartilage (mean value over all regions). In blood the transverse relaxation was also found biexponential with values of $\sim 2/15.8$ ms for T_{2short}^*/T_{2long}^* . The average percentage parts of the blood signal corresponding to T_{2short}^*/T_{2long}^* are $\sim 20\%/80\%$. In skeletal muscle, the biexponential transverse relaxation times were measured as $T_{2short}^* \sim 1.4$ ms ($\sim 50\%$ of signal) and $T_{2long}^* \sim 14.3$ ms ($\sim 50\%$).

Figure 5 shows a bar chart of the different long and short components of the T_2^* values measured in all the ROIs in male, female and all volunteers (average). The mean T_{2short}^*/T_{2long}^* in cartilage is $0.9 \pm 0.4 / 12.9 \pm 1.5$ ms for female and $0.9 \pm 0.4 / 13.6 \pm 1.5$ ms for male.

Figure 6 shows a bar chart of the different parts of the signal (in %) corresponding to the long and short components of the T_2^* measured in all the ROIs in male, female and all volunteers (average).

Statistical analysis—The Wilcoxon rank sum test over all the pixels of all the relaxation maps shows no significant difference in T_{2short}^* and T_{2long}^* between male and female volunteers ($p \gg 0.05$), but it shows significant difference between all the cartilage regions ($p \ll 10^{-5}$), except for the difference between F condyle and FT medial ($p \gg 0.05$).

Coefficient of determination

Table 3 shows the average adjusted R^2 from all the fits for all the pixels of all the relaxation maps. The average adjusted R^2 is 0.979 ± 0.008 for T_1 fitting and 0.977 ± 0.013 for biexponential T_2^* fitting. For monoexponential T_2^* fitting, R^2 was around 0.930.

Sodium B_0 maps

The magnetic field inhomogeneities were < 60 Hz (or equivalently < 0.7 ppm) in all pixels in cartilage.

Discussion

We wish to point out that measuring the ^{23}Na relaxation times (in particular biexponential ones) in vivo is challenging due to relatively low SNR (on the order of 40 for cartilage) and limited scan times (1 h 15 min in our case), resulting in low resolution images with significant partial volume artifact. Furthermore, due to RF hardware and specific absorption rate (SAR) limitations, TE cannot be made arbitrarily short and the excitation pulses are relatively long (0.5 ms). As a result, especially the short T_2 values and the fraction of the signal corresponding to short T_2 components are especially prone to errors, and caution has to be exercised in the interpretation of the in vivo results. In the procedure outlined below, a practical compromise was therefore struck in order to obtain in vivo values.

Relaxation time maps

The inhomogeneities in the FT cartilage and in the F condyle may be due to the presence of different quantities of synovial fluids within the pixels (due to low resolution images and large PSF). In order to minimize the partial volume effect of the synovial fluids on the relaxation times measured in cartilage, as fluids and cartilage have different T_1 , a future study will be to acquire the images for T_2^* measurements with fluid suppression by an inversion recovery preparation (22).

Longitudinal relaxation times

We can first notice that the longitudinal relaxation times measured in the present study are of the same order of the values given in (23) where $T_1 \sim 31$ ms for blood (ex vivo measurement) and $T_1 \sim 32$ ms for muscle (in vivo measurement) at 1.5T, and from (4) where $T_1 \sim 20$ ms for intact bovine cartilage at 4T.

Despite the small number of data ($N=8$) the difference in cartilage T_1 between male and female is statistically significant (Wilcoxon rank sum test, $p \ll 10^{-6}$), with T_1 shorter for men. This may come from physiological differences: in general, men are taller and heavier than women, with an average weight/height of 77.4 Kg/178 cm for men and of 59.1 Kg/163 cm for women (24). The average weight and height of our volunteers are of the same order: 75 Kg/178 cm for men and 48 Kg/161 cm for women. As a result, a possible explanation of this difference is that male cartilage is slightly more dense in collagen fibers (mainly in the deep zone where fibers are perpendicular to the surface of cartilage), which reduces the correlation time τ_c of the sodium ions in this zone and therefore also reduces the overall T_1 relaxation time (25, 26, 27). The difference seen between the patellar and the other cartilage locations may be interpreted in a similar way: the patella has more a shearing function than a

load-bearing function, therefore the collagen fibers might have a higher concentration of collagen fibers near the cartilage surface (and a bigger superficial zone where fibers are parallel to the surface), which therefore decreases slightly the correlation time of the $^{23}\text{Na}^+$ in this zone and leads to a slightly overall shorter T_1 .

Transverse relaxation times

The transverse relaxation times measured in the present study are of the same order of the values previously measured in (9) where $T_{2short}^*/T_{2long}^* \sim 1/12$ ms.

In cartilage, all the fractional parts of the signal differ from the usual 60%/40% part of signal for T_{2short}^*/T_{2long}^* seen when the relaxation is purely due to the quadrupolar interaction with slow motion, in the absence of B_0 inhomogeneities. In this study we measure the T_{2short}^* and T_{2long}^* , which are therefore affected by B_0 inhomogeneities which generate inhomogeneous line broadening. From the B_0 maps, the maximum inhomogeneities were around 60 Hz, which is relatively small compared to the inverse T_2^* values. The residual quadrupolar couplings (in the range 200–400 Hz) that occur in cartilage tissue, may further lead to complications in these measurements (28). These factors affect the fractional part of signal from T_{2short}^* and T_{2long}^* , and the ideal ratios of 60%/40% are not observed. Moreover, due to the low resolution of the images and the large FWHM of the PSF of the sequence, and despite the exclusion of the monoexponential T_2^* fits, a large presence of fluids is still expected around the cartilage (synovial fluid) and to be included in the signal from the voxels or ROIs, and therefore an increase of the part of the signal with a long T_2^* component is expected. Some other contributions such as chemical exchange can also have a non-negligible effect on the relaxation, mainly in biological tissues where one or both exchanging sites are not under conditions of extreme narrowing (29, 30). The differences between the short and long T_2^* components in the different parts of cartilage and their fractional parts of the signal can further arise from changes in the density of collagen fibers within the cartilage, their orientation distribution, the presence of different amounts of synovial fluid in the different ROIs, and are also influenced by the B_0 inhomogeneities. It can be noticed that the FT medial and lateral cartilage has more a load-bearing function while the F condyle and patellar cartilage has more a shearing function, they have therefore different fine structures leading to different quadrupolar interaction distributions and thus different extracted relaxation times with different weights in the signal.

In the artery, the transverse relaxation was found biexponential with values of the same order of the values measured in Ref. (23) where $T_{2short}^*/T_{2long}^* \sim 3.2/18$ ms at 1.5T. This biexponential relaxation comes from the complex composition of the blood and the presence of erythrocytes where the sodium ions are in slow motion within the intracellular environment (31). Note that the fractions of the signal are $\sim 20\%/80\%$ for the short and long T_2^* components respectively. A probable interpretation would be that a part of the sodium ions are in a fluid environment (plasma, $\sim 55\%$ of blood volume (32)) where they have a monoexponential long relaxation time, and inside the cells ($\sim 45\%$ of the volume) where they exhibit a biexponential relaxation with the traditional fractions 60% for T_{2short}^* and 40% for T_{2long}^* due to the quadrupolar relaxation (31), leading to an average fraction of $\sim 27\%$ for the T_{2short}^* component over the whole blood volume.

In skeletal muscle, the biexponential transverse relaxation times measured are close to the values given in Ref. (27) where the sodium biexponential T_2 of skeletal muscle was measured at 2.35T, ex vivo in fresh rat muscle, where $T_{2short} \sim 1.6$ ms (60%) and $T_{2long} \sim 16$ ms (40%). Note these values are also in the same range of the relaxation times measured in

vivo at 1.5T given in (23) where they found $T_{2short}^* \sim 0.5$ ms and $T_{2long}^* \sim 12.3$ ms (however without information on the fractional parts of the signal). The difference in the fractions of signal may come from the presence of blood vessels in the ROI in the muscle where relaxation times were measured. We have seen such effects for blood, T_{2long}^* measured in the artery is quite similar to the one in the muscle but corresponds to 80% of the blood signal, so the presence of small blood vessels may slightly increase the T_{2long}^* in muscle in vivo.

Conclusion

This preliminary work was performed to show the feasibility of sodium T_1 and T_2^* measurements in different regions of the articular cartilage in the knee joint in vivo in a reasonable time ($\sim 35 - 40$ min for each relaxation time) and calculating localized sodium relaxation maps. These maps could prove to be useful as a complement to the sodium concentration maps for assessing early OA in patients. It was already shown that not only does sodium concentration change with the degradation of cartilage using trypsin but so do the T_1 and biexponential T_2^* (8). In this work we report significant differences in longitudinal and transverse relaxation between different cartilage regions (patellar, FT medial and lateral, F condyle) and in T_1 relaxation in cartilage between males and females, but the number of volunteers ($N=8$) is at present too small to draw any conclusion. Despite the current practical limitations due to low SNR and limited scan time for patients, we hope that our work can serve as a guide for estimating in vivo values of sodium T_1 and T_2^* relaxation parameters. Future studies include scanning more healthy volunteers and OA patients of different sex and age at both 3T and 7T, and will include fluid suppression for reducing partial volume effects on the T_2^* measurements and their respective fractional parts of the signal.

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Abbreviations

OA	Osteoarthritis
PG	Proteoglycans
F	Femoral
FT	Femoro-Tibial
UTE	Ultrashort TE
NUFFT	Non-Uniform Fast Fourier Transform
PBS	Phosphate Buffered Saline

References

1. Woolf A, Pfleger B. Burden of major musculoskeletal conditions. Bulletin of the World Health Organization. 2003; 81(9):646–656. [PubMed: 14710506]
2. Borthakur A, Mellon E, Niyogi S, Witschey W, Kneeland J, Reddy R. Sodium and T1ρ MRI for molecular and diagnostic imaging of articular cartilage. NMR in Biomedicine. 2006; 19(7):781–821. [PubMed: 17075961]
3. Reddy R, Insko E, Noyszewski E, Dandora R, Kneeland J, Leigh J. Sodium MRI of human articular cartilage in vivo. Magnetic Resonance in Medicine. 1998; 39(5):697–701. [PubMed: 9581599]

4. Shapiro E, Borthakur A, Dandora R, Kriss A, Leigh J, Reddy R. Sodium visibility and quantitation in intact bovine articular cartilage using high field ^{23}Na MRI and MRS. *Journal of Magnetic Resonance*. 2000; 142(1):24–31. [PubMed: 10617432]
5. Shapiro E, Borthakur A, Gougoutas A, Reddy R. ^{23}Na MRI accurately measures fixed charge density in articular cartilage. *Magnetic Resonance in Medicine*. 2002; 47(2):284–291. [PubMed: 11810671]
6. Wang L, Wu Y, Chang G, Oesingmann N, Schweitzer M, Jerschow A, Regatte R. Rapid isotropic 3D-sodium MRI of the knee joint in vivo at 7T. *Journal of Magnetic Resonance Imaging*. 2009; 30(3):606–614. [PubMed: 19711406]
7. Wheaton A, Borthakur A, Shapiro E, Regatte R, Akella S, Kneeland J, Reddy R. Proteoglycan Loss in Human Knee Cartilage: Quantitation with Sodium MR Imaging Feasibility Study. *Radiology*. 2004; 231(3):900–905. [PubMed: 15163825]
8. Insko E, Kaufman J, Leigh J, Reddy R. Sodium NMR evaluation of articular cartilage degradation. *Magnetic Resonance in Medicine*. 1999; 41(1):30–34. [PubMed: 10025608]
9. Reddy R, Li S, Noyszewski E, Kneeland J, Leigh J. In vivo sodium multiple quantum spectroscopy of human articular cartilage. *Magnetic Resonance in Medicine*. 1997; 38(2):207–214. [PubMed: 9256099]
10. Staroswiecki E, Bangerter N, Gurney P, Grafendorfer T, Gold G, Hargreaves B. In vivo sodium imaging of human patellar cartilage with a 3D cones sequence at 3 T and 7 T. *Journal of Magnetic Resonance Imaging*. 2010; 32(2):446–451. [PubMed: 20677276]
11. Nielles-Vallespin S, Weber M, Bock M, Bongers A, Speier P, Combs S, Wohrle J, Lehmann-Horn F, Essig M, Schad L. 3D radial projection technique with ultrashort echo times for sodium MRI: clinical applications in human brain and skeletal muscle. *Magnetic Resonance in Medicine*. 2006; 57(1):74–81. [PubMed: 17191248]
12. Magland, J.; Wehrli, F. Pulse sequence programming in a dynamic visual environment. *Proceedings of the 14th Annual Meeting of ISMRM*; Seattle, WA, USA. 2006. p. 3032
13. Inati, S.; Lee, JY.; Fleysher, L.; Fleysher, R.; Greengard, L. Fast optimal weighting for image reconstruction from arbitrary k-space trajectories. *Proceedings of the 13th Annual Meeting of ISMRM*; Miami Beach, FL, USA. 2005. p. 2297
14. Inati, S.; Greengard, L. Fast iterative approximate pseudo-inverse image reconstruction from data acquired on arbitrary k-space trajectories. *Proceedings of the 14th Annual Meeting of ISMRM*; Seattle, WA, USA. 2006. p. 2953
15. Greengard L, Lee J, Inati S. The fast sinc transform and image reconstruction from nonuniform samples in k-space. *Commun Appl Math Comput Sci*. 2006; 1:121–131.
16. Greengard L, Lee J. Accelerating the nonuniform fast Fourier transform. *SIAM review*. 2004; 46(3):443–454.
17. Rahmer J, Bornert P, Groen J, Bos C. Three-dimensional radial ultrashort echo-time imaging with T2 adapted sampling. *Magnetic Resonance in Medicine*. 2006; 55(5):1075–1082. [PubMed: 16538604]
18. Draper, N.; Smith, H.; Pownell, E. Vol. volume 706. New York: Wiley; 1998. Applied regression analysis.
19. Irrazabal P, Meyer C, Nishimura D, Macovski A. Inhomogeneity correction using an estimated linear field map. *Magnetic Resonance in Medicine*. 1996; 35(2):278–282. [PubMed: 8622593]
20. Wilcoxon F. Individual comparisons by ranking methods. *Biometrics Bulletin*. 1945; 1(6):80–83.
21. Mann H, Whitney D. On a test of whether one of two random variables is stochastically larger than the other. *The Annals of Mathematical Statistics*. 1947; 18(1):50–60.
22. Madelin G, Lee J, Inati S, Jerschow A, Regatte R. Sodium Inversion Recovery MRI of the Knee Joint In Vivo at 7T. *Journal of Magnetic Resonance*. 2010; 207:42–52. [PubMed: 20813569]
23. Constantinides C, Gillen J, Boada F, Pomper M, Bottomley P. Human Skeletal Muscle: Sodium MR Imaging and Quantification Potential Applications in Exercise and Disease. *Radiology*. 2000; 216(2):559–568. [PubMed: 10924586]
24. Ellis K. Reference man and woman more fully characterized. *Biological Trace Element Research*. 1990; 26(1):385–400. [PubMed: 1704742]

25. Berendsen H, Edzes H. The observation and general interpretation of sodium magnetic resonance in biological material. *Annals of the New York Academy of Sciences*. 1973; 204:459–485. (Physicochemical State of Ions and Water in Living Tissues and Model Systems). [PubMed: 4513164]
26. Hubbard P. Nonexponential nuclear magnetic relaxation by quadrupole interactions. *The Journal of Chemical Physics*. 1970; 53:985–987.
27. Chang D, Woessner D. Spin-echo study of ^{23}Na relaxation in skeletal muscle. Evidence of sodium ion binding inside a biological cell. *Journal of Magnetic Resonance*. 1978; 30:185–191.
28. Ling W, Regatte R, Schweitzer M, Jerschow A. Behavior of ordered sodium in enzymatically depleted cartilage tissue. *Magnetic Resonance in Medicine*. 2006; 56(5):1151–1155. [PubMed: 17029232]
29. Bull T. Nuclear magnetic relaxation of spin-3/2 nuclei involved in chemical exchange. *Journal of Magnetic Resonance* (1969). 1972; 8(4):344–353.
30. Eliav U, Navon G. Criteria for multiexponential relaxation of exchanging nuclei. *Journal of Magnetic Resonance* (1969). 1990; 88(2):223–240.
31. Shinar H, Navon G. Sodium-23 NMR relaxation times in nucleated red blood cells and suspensions of nuclei. *Biophysical Journal*. 1991; 59:203–208. [PubMed: 2015384]
32. Dill D, Costill D. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *Journal of Applied Physiology*. 1974; 37(2):247. [PubMed: 4850854]

Figure 1.

Representative examples of fitting from one pixel in FT lateral cartilage from one volunteer.

(A) Monoexponential T_1 with $T_1 = 14$ ms. (B) Biexponential

T_2^* with $T_{2short}^* = 0.7$ ms and $T_{2long}^* = 16$ ms.

Figure 2. Sodium T_1 maps in: (A) the patellar, (B) FT medial and FT lateral, (C) F condyle cartilage. Times are given in milliseconds. Position of the ROIs drawn in the cartilage for the relaxation time measurements and mapping are also indicated. Background image was acquired with TE = 0.15 ms, FA = 90° and TR 250 ms (last image acquired for T_1 measurement).

Figure 3.

Sodium T_{2short}^* and T_{2long}^* maps in: (A) the patellar, (B) FT medial and FT lateral, (C) F condyle cartilage. Times are given in milliseconds. Background image was acquired with TE = 0.15 ms, FA = 70° and TR 70 ms (first image for T_2^* measurement).

Figure 4.

Comparison of the average T_1 in male (N=4), female (N=4) and all volunteers (N=8) in the patellar, FT medial, FT lateral, F condyle cartilage, in the muscle and in the blood. The positions of the ROIs drawn in the cartilage for the relaxation time measurements and mapping are shown in Fig. 4. Note the significant difference in T_1 between male and female in all regions.

Figure 5.

Comparison of the average T_{2short}^* (A) and T_{2long}^* (B) in male (N=4), female (N=4) and all volunteers (N=8) in the patellar, FT medial, FT lateral, F condyle cartilage, in the muscle and in the blood. The positions of the ROIs drawn in the cartilage for the relaxation time measurements and mapping are shown in Fig. 4.

Figure 6.

Comparison of the average parts of the signal with T_{2short}^* (A) and T_{2long}^* (B) in male (N=4), female (N=4) and all volunteers (N=8) in the patellar, FT medial, FT lateral, F condyle cartilage, in the muscle and in the blood. The positions of the ROIs drawn in the cartilage for the relaxation time measurements and mapping are shown in Fig. 4.

Table 1

Average T_1 in 4% Agar gel, PBS, patellar cartilage (PAT), FT medial (MED) and lateral (LAT) cartilage, F condyle (CON) cartilage, muscle and blood, in ms (F is for femoral, T is for tibial). Std (ms) stands for the statistical standard deviation of the T_1 over all the volunteers and Std_{Map} (ms) is the mean value of all the standard deviations from each individual relaxation map.

	T_1 (ms)	Std (ms)	Std _{Map} (ms)	Min (ms)	Max (ms)
Gels 4%	23.0	2.9	3.9	17.9	29.5
PBS	41.9	5.6	5.4	33.5	48.3
Cart PAT	17.7	2.6	2.9	14.0	21.4
Cart MED	19.8	3.8	5.1	14.8	25.7
Cart LAT	21.4	4.4	6.2	14.0	28.5
Cart CON	21.0	5.4	4.6	10.3	21.0
Muscle	25.2	3.6	6.6	17.1	28.2
Blood	38.4	5.4	4.6	31.0	45.2

Table 2

Average T_{2short}^* and T_{2long}^* in 4% Agar gel, PBS, patellar cartilage (PAT), FT medial (MED) and lateral (LAT) cartilage, F condyle (CON) cartilage, muscle and blood, in ms (F is for femoral, T is for tibial). Std (ms) stands for the statistical standard deviation of the T_2^* over all the volunteers and StdMap (ms) is the mean value of all the standard deviations from each individual relaxation map. Part (%) is the average percentage of signal with the respective T_2^* . Std (%) is its statistical standard deviation over all volunteers and StdMap (%) is the mean value of all the standard deviations from each individual relaxation map.

	T_{2short}^* (ms)	Std (ms)	StdMap (ms)	Part (%)	Std (%)	StdMap (%)	Min (ms)	Max (ms)
Gels 4%	1.9	0.6	0.7	44	7	12	0.8	3.4
PBS	-	-	-	-	-	-	-	-
Cart PAT	0.5	0.1	0.3	39	4	14	0.3	0.7
Cart MED	0.9	0.3	0.9	32	7	20	0.4	1.3
Cart LAT	1.4	0.4	1.1	28	6	16	0.9	1.8
Cart CON	0.8	0.2	0.7	38	6	16	0.5	1.1
Muscle	1.4	0.1	1.1	47	5	19	1.2	1.6
Blood	2.0	0.7	1.7	22	5	14	1.1	3.0

(a) Average T_{2short}^* in ms.

	T_{2long}^* (ms)	Std (ms)	StdMap (ms)	Part (%)	Std (%)	StdMap (%)	Min (ms)	Max (ms)
Gels 4%	11.9	2.0	2.9	56	7	12	7.6	15.7
PBS	19.8	4.6	3.7	100	0	0	11.6	24.9
Cart PAT	11.4	1.8	1.6	61	4	14	10.4	12.4
Cart MED	13.1	1.8	3.0	68	7	20	11.0	17.0
Cart LAT	13.9	1.0	4.6	72	6	16	12.9	15.6
Cart CON	14.8	1.5	3.2	62	6	16	12.9	17.6
Muscle	14.3	1.2	7.1	53	5	19	12.1	15.8
Blood	15.8	1.8	4.8	78	5	14	13.8	19.2

(b) Average T_{2long}^* in ms.

Table 3

Average adjusted coefficient of determination (adjusted R^2) from the monoexponential T_1 fitting and biexponential T_2^* fitting of all the pixels used for calculating the relaxation maps.

R_{adj}^2	T_1	T_2^*
Gels 4%	0.984	0.990
PBS	0.988	0.974
Cart PAT	0.985	0.983
Cart MED	0.975	0.975
Cart LAT	0.975	0.979
Cart CON	0.982	0.978
Muscle	0.960	0.948
Blood	0.983	0.987