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Glycosaminoglycan in Articular Cartilage: In Vivo Assessment with Delayed Gd(DTPA)$^{2-}$-enhanced MR Imaging[1]

PURPOSE: **To investigate the feasibility of applying magnetic resonance (MR) imaging with use of an anionic compound, Gd(DTPA)$^{2-}$ (gadolinium diethylenetriaminepentaacetic acid), for measuring glycosaminoglycan concentration in human cartilage in clinical studies.**

MATERIALS AND METHODS: **Penetration of Gd(DTPA)$^{2-}$ into cartilage was monitored through sequential T1-calculated images obtained after intraarticular (n = 2) or intravenous (n = 2) injection. T1-weighted and T1-calculated image series were then obtained in seven volunteers (nine knees) after penetration of Gd(DTPA)$^{2-}$ into cartilage. If T1 was heterogeneous on Gd(DTPA)$^{2-}$-enhanced images, images were also obtained after penetration of the cartilage with the nonionic contrast agent, gadoteridol.**

RESULTS: **Gd(DTPA)$^{2-}$ penetrated cartilage from the articular surface after intraarticular injection and from both the articular surface and the subchondral bone after intravenous injection. The latter resulted in shorter overall penetration time. T1 values on Gd(DTPA)$^{2-}$-enhanced images were homogeneous in four knees, but in five knees T1 differences of up to 30% were observed. These T1 differences were not seen in the presence of gadoteridol. These variations in T1 reflected about 50% variations in glycosaminoglycan.**

CONCLUSION: **The data suggest that Gd(DTPA)$^{2-}$-enhanced MR imaging has potential for monitoring glycosaminoglycan content of cartilage in vivo.**

OSTEOARTHRITIS, commonly referred to as degenerative joint disease, currently affects the lives of over 16 million people in the United States (1). This disease process tends to begin in midadult life, with autopsy studies demonstrating degenerative changes in the weight-bearing joints of 90% of people over age 40 years (2). Early osteoarthritis is characterized by a loosening of the cartilage extracellular collagen matrix and a substantial loss of glycosaminoglycan (3–6). Later degenerative changes manifest as gross anatomic abnormalities, including cartilage edema, fibrillation, fissuring, fragmentation, and denudation (7,8). Although magnetic resonance (MR) imaging can depict cartilage abnormalities earlier and more accurately than any other imaging modality (9), it has been an unreliable and insensitive means of detecting early cartilage degeneration. The general consensus among musculoskeletal radiologists, orthopedists, and rheumatologists is that substantial radiologic advances still are necessary (10,11).

With the aim of developing a more sensitive and specific MR imaging technique for evaluating cartilage abnormalities, during the past several years we have been developing MR techniques for monitoring the concentration of glycosaminoglycan in cartilage (12–14). We focus on glycosaminoglycan for several reasons: Glycosaminoglycans are lost early in the course of cartilage degeneration and would likely need to be replenished in the course of any effective therapy for cartilage disorders. Glycosaminoglycans also play a major role in the mechanical support function in normal cartilage and thereby provide a sensitive and specific measure of cartilage integrity (15–18). Effectively imaging the concentration of glycosaminoglycan would have a major influence on the ability to assess the natural progression of the disease, the timing of therapeutic interventions and the efficacy of these therapeutic measures, and the ability to provide an indication of the functional state of the tissue.

Our approach follows a paradigm pioneered by Maroudas and colleagues (19,20). It depends on the fact that glycosaminoglycan macromolecules contain numerous, highly negatively ionized side groups. We use the principle that a negatively charged ion is relatively excluded from normal cartilage containing a high concentration of (the highly negatively charged)

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Abbreviation: DTPA = diethylenetriaminepentaacetic acid.

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glycosaminoglycan. This relative exclusion would not occur when glycosaminoglycans are lost as part of the degenerative process, since the negative charge that they confer to cartilage also is lost (6,20). In particular, we looked at the distribution in tissue of the anionic compound $Gd(DTPA)^{2-}$ (gadolinium diethylenetriaminepentaacetic acid), obtained from the dissociation of the contrast agent gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ) in solution (21). A measurement of $Gd(DTPA)^{2-}$ concentration should serve as a surrogate for a measurement of glycosaminoglycan concentration as $Gd(DTPA)^{2-}$ is expected to distribute into degraded areas at a higher concentration than that in nondegraded areas (Fig 1). Since the concentration of gadolinium compounds can be determined from an MR measurement of T1, contrast on a T1-weighted image in the presence of $Gd(DTPA)^{2-}$, or on a T1-calculated image, should reflect variations in tissue glycosaminoglycan concentration. It is important to note that such a differential distribution pattern would not be expected to be seen with a nonionic compound such as gadoteridol (ProHance; Bracco Diagnostics, Princeton, NJ) (formerly Gd-HP-DO3A [gadolinium 2-tetraazacyclododecanetriacetate]).

This technique has already been validated in excised bovine and human samples (13,14). It has been applied to bovine cartilage cultured in interleukin-1β to demonstrate near-histologic level resolution of glycosaminoglycan loss (13) and to excised human cartilage samples to demonstrate that morphologically intact tissue may still have substantially lowered glycosaminoglycan concentration (22). To our knowledge, however, the technique has not yet been applied in vivo. The main goal of the current work was to determine the feasibility of applying this MR technique for evaluating cartilage glycosaminoglycan concentration in vivo in humans. Toward this end, the specific objectives of this work were to (*a*) calculate the theoretic sensitivity of the technique to expected variations in glycosaminoglycan concentration under clinical conditions; (*b*) compare delivery of $Gd(DTPA)^{2-}$ to articular cartilage in vivo by means of intraarticular and intravenous administration; (*c*) obtain T1-weighted and T1-calculated images after tissue penetration with an ionic contrast agent, $Gd(DTPA)^{2-}$; and (*d*) obtain T1-weighted and T1-calculated images after tissue penetration with the nonionic contrast agent, gadoteridol. Variations in T1 in the presence of $Gd(DTPA)^{2-}$ would be interpreted as variations in glycosaminoglycan concentration. This interpretation would be supported if the variations did not occur in the presence of gadoteridol, because the distribution of gadoteridol should not be affected by the charged glycosaminoglycan molecule.

MATERIALS AND METHODS

Theoretic Calculations

Normal human cartilage has a glycosaminoglycan concentration on the order of 60 mg/mL, whereas in osteoarthritis glycosaminoglycan concentration can decrease to nearly 0 mg/mL (5). As just described, the charge on the glycosaminoglycan will affect the tissue concentration of a charged contrast agent, in this case $Gd(DTPA)^{2-}$. The $Gd(DTPA)^{2-}$ concentration in turn determines the tissue T1. The goal of this section was to calculate the theoretic dependence of T1 on $Gd(DTPA)^{2-}$ concentration in the tissue, and hence tissue glycosaminoglycan concentration, to determine the sensitivity of the MR measurement to glycosaminoglycan variation expected in degenerating cartilage. The details of the calculations, which were performed according to previously validated relationships (13,14,23), are given in the Appendix and were performed for concentrations of $Gd(DTPA)^{2-}$ of 1 and 4 mmol/L, in the range of that expected clinically.

Similar relationships were calculated for the nonionic contrast agent, gadoteridol. In this case, the tissue gadoteridol concentration should not be affected by the tissue glycosaminoglycan concentration and was assumed to be equal to the concentration of gadoteridol outside the tissue. (This was validated in our laboratory [unpublished data]). The T1 was then calculated from the gadoteridol concentration, as given in the Appendix.

Intraarticular versus Intravenous Administration of Contrast Material

To characterize the effectiveness of intraarticular versus intravenous administration in achieving penetration of $Gd(DTPA)^{2-}$ into hyaline cartilage, T1-calculated images of articular cartilage were obtained at selected time points after intraarticular and intravenous administration of the contrast agent. Institutional review board approval was obtained for all studies described here, and informed consent was obtained from all participants after the nature of the procedure was fully explained.

General imaging methods.—All in vivo studies were performed at 1.5 T with a commercially available MR imager (Vision; Siemens, Iselin, NJ) and a dedicated knee coil or a small flex coil. To establish orientation, a sagittal scout image was obtained, from which multisection axial images were prescribed.

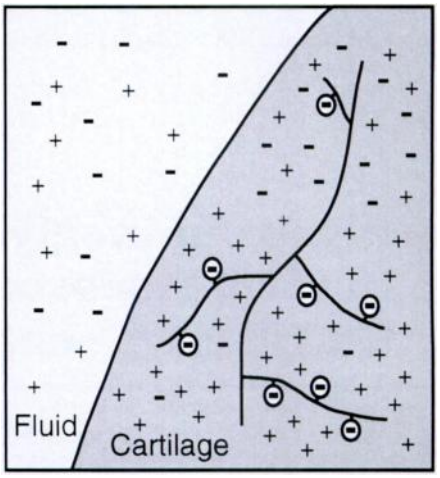


Figure 1. Schematic of synovial fluid and cartilage to demonstrate the distribution of charged ions in the tissue. The proteoglycan component of the tissue is represented by a black backbone with the glycosaminoglycan represented as charged negative side groups fixed to the matrix. Because of these negative ions "fixed" to the matrix, the concentration of free negative ions such as $Gd(DTPA)^{2-}$ will be in lower concentration in the normal cartilage (lower part of the Figure) than in synovial fluid. In cartilage that has lost much of the glycosaminoglycan (upper part of the Figure), the concentration of fixed negative charge is lower, and hence, the concentration of free negative ions will be higher than in the normal cartilage.

T1-weighted images were obtained with an inversion-recovery turbo spin-echo sequence with the following parameters: 350 × 400-μm in-plane resolution, 2- or 3-mm section thickness, 1,000/30/25–850 (repetition time msec/echo time msec/inversion time msec) for intraarticular studies or 1,800/14/25–1,680 for intravenous studies, four signals acquired (intraarticular) or one signal acquired (intravenous). The T1-weighted image series were transferred to a commercially available workstation (Indy; Silicon Graphics, Mountain View, Calif), and the T1 values from 10 to 20 voxels in a region of interest were calculated from selected areas in the images, as described in the next section.

Intraarticular administration.—In two subjects (one 35-year-old man and one 26-year-old woman), 40 mL of a 4 mmol/L $Gd(DTPA)^{2-}$ solution (diluted with normal saline) containing 0.3 mL of epinephrine (1:1,000) was injected intraarticularly with a sterile technique. Epinephrine was used since in two pilot studies without epinephrine, the $Gd(DTPA)^{2-}$ cleared from the joint space before full penetration of patellar cartilage was achieved; thus, epinephrine was used to slow resorption of the contrast medium, as has been previously described (24). In these subjects, each time point involved five T1-weighted images with the inversion delays varying between 25 and 850 msec, for a total imaging time of 16 minutes for the series, from which T1-calculated images were obtained.

Intravenous administration.—In two sub-

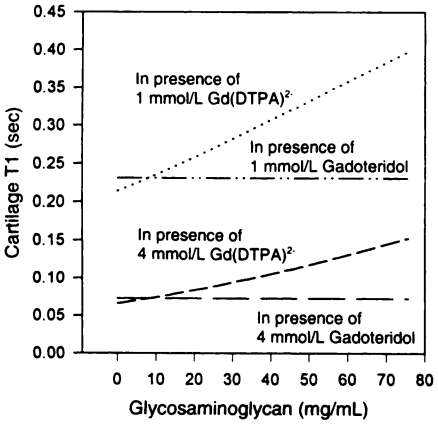


Figure 2. Calculated T1 of cartilage as a function of glycosaminoglycan concentration for tissue equilibrated in 4 mmol/L Gd-(DTPA)$^{2-}$, 4 mmol/L gadoteridol, 1 mmol/L Gd(DTPA)$^{2-}$, and 1 mmol/L gadoteridol. The concentration of Gd(DTPA)$^{2-}$ within cartilage is dependent on the concentration in the surrounding fluid (blood, synovial fluid) but varies with the tissue glycosaminoglycan concentration. The concentration of the nonionic contrast agent, gadoteridol, in tissue is the same as that in the surrounding fluid, independent of glycosaminoglycan concentration. Therefore, note the large variation in T1 values in the presence of Gd(DTPA)$^{2-}$ with differing glycosaminoglycan concentration, as compared with the constant T1 values in the presence of gadoteridol with differing glycosaminoglycan concentration. The crossover of the T1 values near 0 mg/mL glycosaminoglycan, where the concentration of Gd(DTPA)$^{2-}$ should equal that of gadoteridol, is due to the slightly higher relaxivity of Gd(DTPA)$^{2-}$ relative to that of gadoteridol (3.5 vs 3.2 L · mmol^{-1} · sec^{-1}).

jects (two men aged 29 and 34 years, respectively), 40 mL of a 0.5 mmol/L Gd-(DTPA)$^{2-}$ solution was administered over 3–5 minutes in a single bolus intravenously. Immediately after the bolus, volunteers exercised their lower extremity for 10 minutes (5 minutes of walking and 5 minutes of active knee flexion-extension while sitting on the edge of a table); the results of previous studies have suggested that this exercise increased the rate of delivery of Gd(DTPA)$^{2-}$ to the joint (25,26). A set of images were obtained in which each time point involved seven T1-weighted images with the inversion delays varying between 25 and 1,680 msec, for a total imaging time of 12 minutes. T1-calculated images were then computed for each time point.

T1 Imaging after Tissue Penetration with Gd(DTPA)$^{2-}$

MR imaging of the knee was performed in nine knees of seven volunteers (two women, five men; age range, 21–39; mean age, 31 years), which included three of the previously mentioned subjects. Unenhanced MR imaging employed conventional MR techniques currently used to image knee cartilage, that is, fast low-angle shot axial imaging with the following parameters: 480/15, 80° flip angle, 550 × 550-μm resolution, and 3-mm section thickness.

The volunteers each underwent T1-calculated imaging after penetration of the tissue with Gd(DTPA)$^{2-}$ (5–7 hours for intraarticular injection in two knees and 1½–3 hours for intravenous injection in seven knees). The T1-weighted images were obtained with the parameters described in the previous section.

T1 Imaging after Tissue Penetration with Gadoteridol

Gadoteridol-enhanced images were obtained in five knees that had previously demonstrated abnormalities on Gd-(DTPA)$^{2-}$–enhanced images. The gadoteridol-enhanced images were obtained under the same conditions and at approximately the same time point as the Gd(DTPA)$^{2-}$-enhanced images. Landmarks on the patella, femur, and tibia were used to ensure consistency in image selection for the T1-weighted series performed on different days (which were up to 3 months apart for different volunteers).

RESULTS

Theoretic Calculations

The predicted dependence of T1 on glycosaminoglycan (Fig 2) illustrates the large differences in T1 that would be expected between normal and osteoarthritic cartilage. If we assume the cartilage is in equilibrium with a 4-mmol/L Gd(DTPA)$^{2-}$ solution (similar to that of the intraarticular cases [see next section]), cartilage with a relatively normal glycosaminoglycan concentration of 60 mg/mL would have a T1 of 120 msec. Cartilage with a concentration of 0 mg/mL, as might be seen in severely arthritic tissue, would have a T1 of 60 msec. Therefore, the ratio of T1 in healthy cartilage to that in severely osteoarthritic cartilage would be expected to be up to about 2:1. Similarly, with 1 mmol/L Gd(DTPA)$^{2-}$ surrounding the cartilage (similar to that of the intravenous cases described in the next section), the normal cartilage would have a T1 of 375 msec and the osteoarthritic cartilage would have a T1 of 210 msec, still approximately a 2:1 ratio.

A nonionic contrast agent like gadoteridol would be expected to distribute in the tissue water at the same concentration as the surrounding fluid, independent of the glycosaminoglycan concentration. Therefore, for the same surrounding concentration, the intratissue concentration of gadoteridol will be higher than the concentration of the negatively charged Gd-(DTPA)$^{2-}$, and the resultant cartilage T1 values will be lower than those with Gd(DTPA)$^{2-}$ (given the almost equal relaxivities of the two compounds).

Intraarticular versus Intravenous Administration

Diffusion of Gd(DTPA)$^{2-}$ into cartilage in vivo was inferred from a decrease in T1 of the cartilage with time after administration of Gd(DTPA)$^{2-}$. We focused mainly on penetration of patellar cartilage, which (as one of the thickest cartilages in the human body) would take the longest to be penetrated.

After intraarticular administration, Gd(DTPA)$^{2-}$ diffused in from the articular surface. Penetration of the patellar cartilage (approximately 5 mm thick) occurred within approximately 7 hours after the intraarticular injection (Figs 3a–3c, 4a). Penetration of the cartilage on the femoral condyle (approximately 1 mm thick) occurred within 2½ hours (the earliest intraarticular image obtained in that plane).

Intravenous administration of the gadolinium compounds allowed the contrast agents to diffuse into patellar cartilage from both the articular surface and the subchondral bone. Penetration of the thick patellar cartilage after intravenous administration of Gd(DTPA)$^{2-}$ was achieved within 2½ hours (Figs 3d–3f, 4b). Penetration of the cartilage on the femoral condyle occurred within 45 minutes. The kinetics of gadoteridol penetration into cartilage was similar.

T1 Imaging after Tissue Penetration with Gd(DTPA)$^{2-}$

Although not explicitly validated in vivo, there is extensive evidence (see Discussion) to support the interpretation that these T1 values, Gd(DTPA)$^{2-}$ concentrations, are directly related to tissue glycosaminoglycan concentration. Therefore, for the purpose of presentation, we will directly refer to T1 variations in the presence of Gd-(DTPA)$^{2-}$ as glycosaminoglycan variations.

In four of nine knees imaged, there was no visualized variation in signal intensity on the delayed Gd(DTPA)$^{2-}$-enhanced images. Two of these volunteers also underwent unenhanced MR imaging of the knee, which did not show any cartilage abnormalities. These data suggest that their cartilage had a uniform glycosaminoglycan content and was also morphologically intact. In one knee (knee 1, Table), the T1 was much lower than that of the

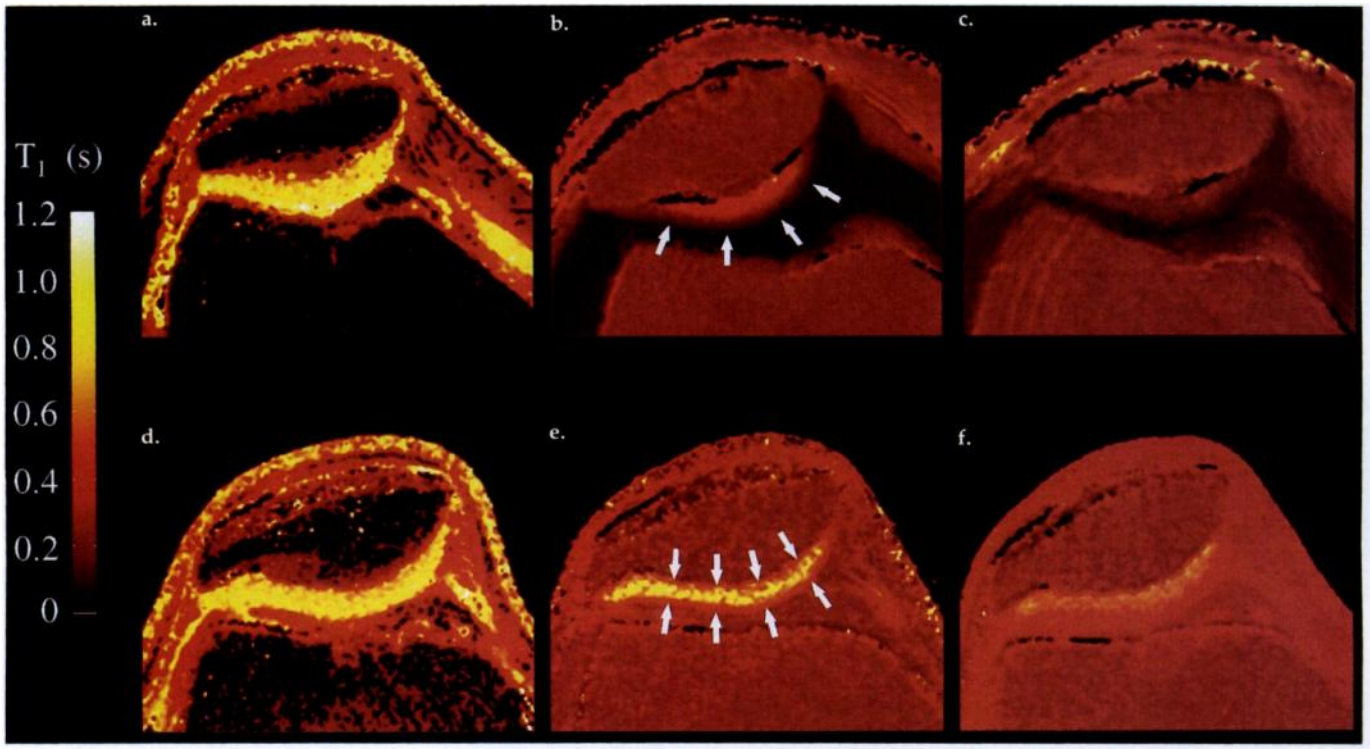


Figure 3. T1-calculated images obtained **(a)** before administration of contrast material and **(b)** 2½ hours and **(c)** 7 hours after intraarticular injection of $Gd(DTPA)^{2-}$. With intraarticular administration, diffusion of contrast material occurs from the articular surface only, as evidenced by the lower T1 values along the joint surface of the cartilage (arrows in **b**) as contrast agent penetrates over time. T1-calculated images obtained **(d)** before administration of contrast material and **(e)** 50 minutes and **(f)** 150 minutes after intravenous injection. With intravenous administration, $Gd(DTPA)^{2-}$ penetrates from both the articular surface and from the bone (arrows in **e**). Note the lower values for T1 with the intraarticular injection due to the higher concentration of $Gd(DTPA)^{2-}$ in this case. While the rate of penetration is the same for both, the overall penetration of the $Gd(DTPA)^{2-}$ takes less time with the intravenous injection, since $Gd(DTPA)^{2-}$ is penetrating the cartilage from both sides.

others. This patellar cartilage was particularly thin, on the order of 2 mm. It is possible that the glycosaminoglycan content was also low, although it was homogeneous across the patella. This example illustrates a situation in which absolute quantitation of glycosaminoglycan concentration would be particularly useful.

The $Gd(DTPA)^{2-}$-enhanced images in the other five knees showed visualizable T1 variations in the presence of $Gd(DTPA)^{2-}$. On all images, regions of interest were chosen from which to calculate T1 values for cartilage after penetration with $Gd(DTPA)^{2-}$ (Table). One region of interest was chosen in the "high T1" area and one in the "low T1" area. At least 10 voxels were in each region of interest. The T1 values of these two regions were compared by means of the Student *t* test. In all cases, the *P* values were less than .05, indicating significantly different values of T1 in these areas and, hence, different concentrations of $Gd(DTPA)^{2-}$. One knee (knee 6) was studied with both intraarticular and intravenous administration. Although the absolute values of T1 differed owing to the different concentrations surrounding the cartilage with intraarticular versus intravenous administration, the ratio of the T1 values in the different regions of interest (A and B) were 24% and 25% for intraarticular and intravenous administration, respectively. These data confirm the prediction of Figure 2 that the contrast, and differences in T1, are not heavily dependent on the background level of $GD(DTPA)^{2-}$ (or absolute T1). While this study is too small to draw clinical conclusions, it is interesting to note that some volunteers (knees 1 and 6–9, Table) reported history of knee injury.

One volunteer (knee 5, Table; Fig 5) showed a focal lesion on the $Gd(DTPA)^{2-}$-enhanced images evidenced

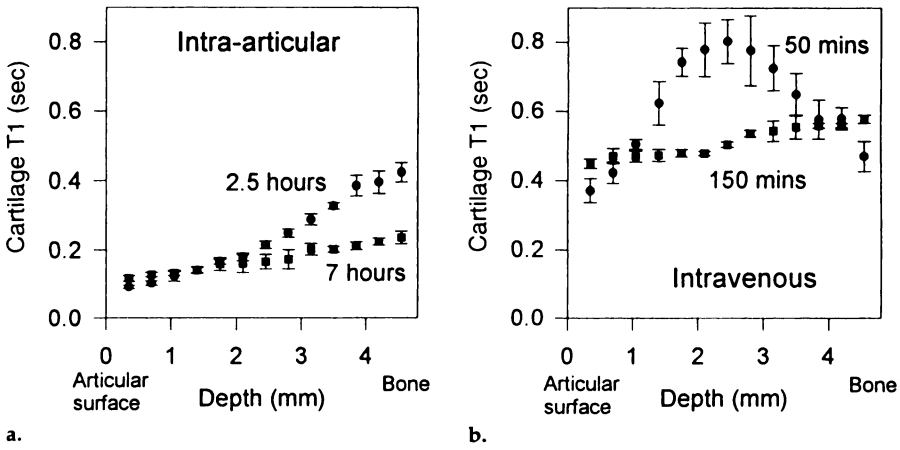


Figure 4. Plot of quantitative T1 values versus depth after **(a)** intraarticular and **(b)** intravenous administration of $Gd(DTPA)^{2-}$ from a study similar to that shown in Figure 3. The error bars represent the standard deviation of the T1 values of the voxels in the region of interest. The absolute values of T1 differ due to the different concentration of $Gd(DTPA)^{2-}$ in the body fluids in the intraarticular and intravenous cases. Note that with intraarticular injection, contrast material penetrates from the articular side only. With intravenous injection, contrast material penetrates from both the superficial and deep margins of the cartilage.

T1 Values Obtained from Regions of Interest in the Patellar Cartilage of Seven Volunteers (Nine Knees)

Knee No.	Delivery*	T1 Values (msec) with $Gd(DTPA)^{2-}$		T1 Values (msec) with Gadoteridol	
		ROI A	ROI B	ROI A	ROI B
1	IV	237 ± 27	NP	NP	NP
2	IV	416 ± 76	NP	NP	NP
3	IV	469 ± 28	NP	NP	NP
4	IV	464 ± 19	NP	NP	NP
5	IA	280 ± 38	185 ± 39†	157 ± 22	159 ± 24
6	IA	168 ± 61	128 ± 16†	NP	NP
	IV	362 ± 59	269 ± 53†	243 ± 31	247 ± 39
7	IV	376 ± 60	273 ± 19†	310 ± 60	306 ± 60
8	IV	471 ± 9	313 ± 49†	248 ± 37	235 ± 18
9	IV	478 ± 96	374 ± 48†	319 ± 32	334 ± 42

Note.—NP = not performed, ROI = region of interest.
* IA = intraarticular, IV = intravenous.
† T1 values from ROI A and B were significantly different ($P < .05$).

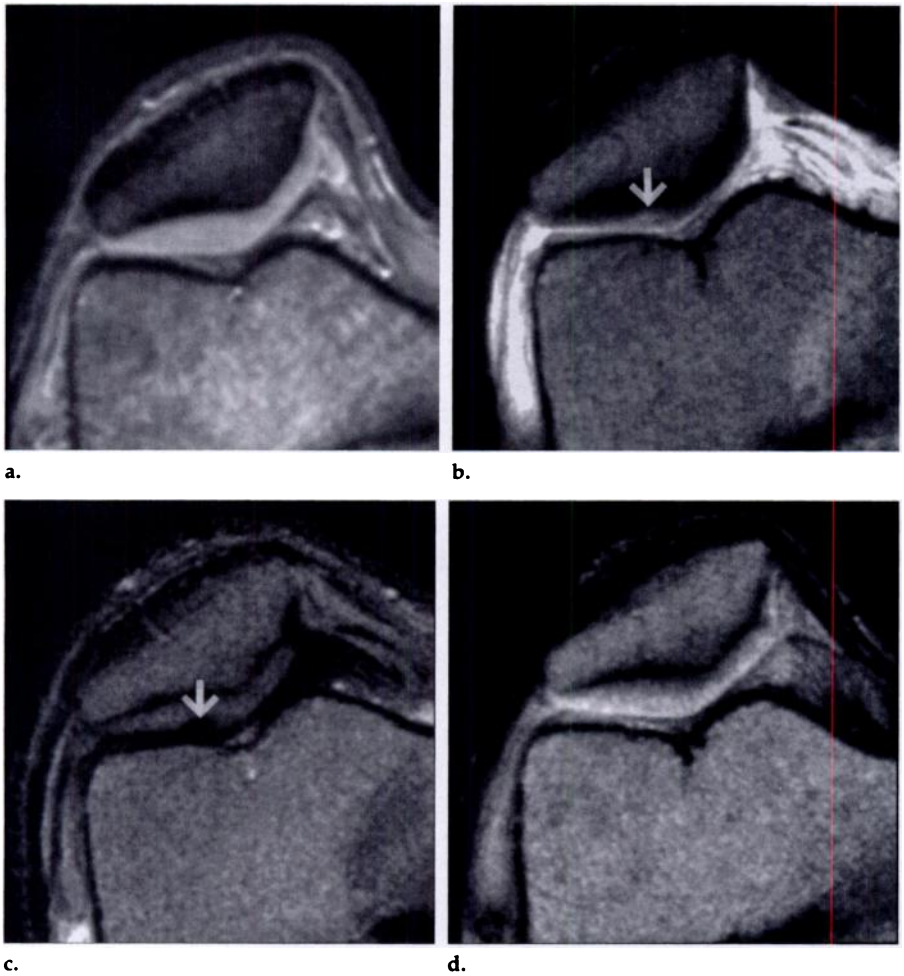


Figure 5. **(a)** Unenhanced (fast low-angle shot) axial MR image shows a patella with no obvious abnormality. **(b)** $Gd(DTPA)^{2-}$-enhanced T1-weighted image (inversion time = 250 msec) from the T1-calculated series obtained 6 hours after intraarticular administration of contrast agent. A focal region of increased enhancement (arrow) can easily be seen. The T1 of the "lesion" is 185 msec ± 39 compared with a T1 of 280 msec ± 38 in a another region at the same depth from the articular surface. These values demonstrate a 34% difference in T1 in the lesion versus that in the surrounding tissue. **(c)** Image from the same T1-weighted series shown in **b** but with an inversion delay of 100 msec. The lesion here is seen with a lower signal intensity (arrow) than that of the surrounding tissue, illustrating the strong effect of the image parameters on the appearance of the image. **(d)** Gadoteridol-enhanced T1-weighted MR image (inversion time = 250 msec) obtained 7 hours after intraarticular administration of contrast agent. The T1 is relatively homogeneous with values of 159 msec ± 24 in the area of the "lesion" shown in **b** and **c** and 157 msec ± 22 in the surrounding tissue.

by regions of lower T1, or high $Gd(DTPA)^{2-}$, suggesting a lower glycosaminoglycan content than that of the surrounding regions. The unenhanced images did not show any evidence of an anatomic defect or substantial signal variation. These data suggest that this subject had an area of morphologically intact cartilage with low glycosaminoglycan concentration, an area not seen with the conventional MR imaging method. Another volunteer (knee 6, Table) showed heterogeneous T1 across the patella, while the other volunteers demonstrated substantial medial to lateral differences in T1 in the presence of $Gd(DTPA)^{2-}$ (Fig 6).

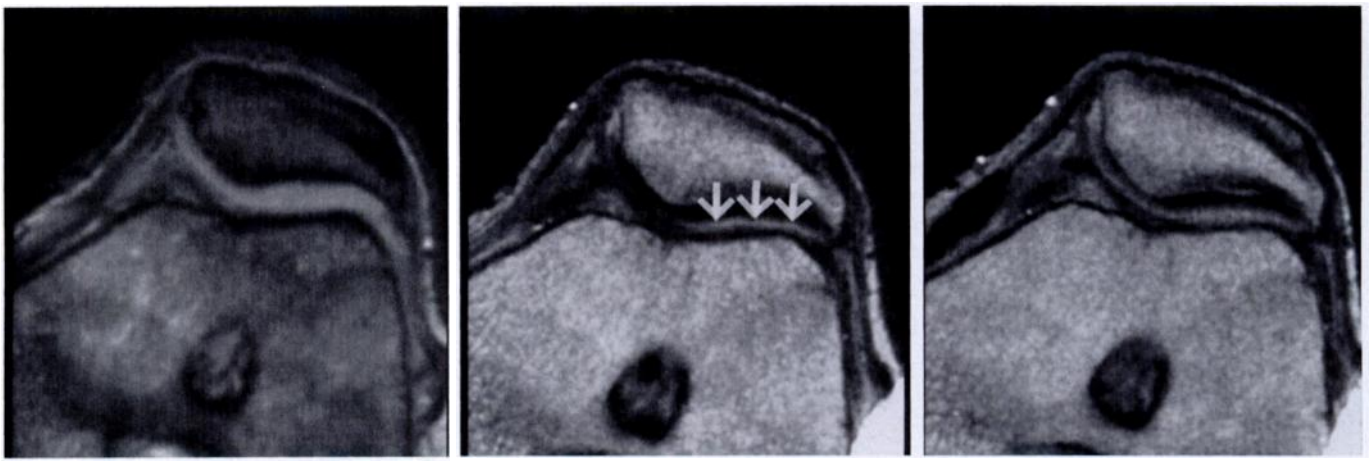
On several images of knees penetrated with $Gd(DTPA)^{2-}$ (with both intraarticular and intravenous administration), the T1 of the articular surface was slightly (2%–10%) lower than that near the bone, suggesting a lower glycosaminoglycan content near the articular surface. This glycosaminoglycan profile with depth is consistent with previous literature reports of lower glycosaminoglycan at the articular surface (6). However, particularly for intraarticular administration, this T1 profile may also possibly be due to incomplete penetration by $Gd(DTPA)^{2-}$.

T1 Imaging after Tissue Penetration with Gadoteridol

In the five cases that were reimaged after administration of gadoteridol (Figs 5d, 6c) (Table), the heterogeneity observed with the negatively charged $Gd(DTPA)^{2-}$ was not observed with the nonionic contrast agent, gadoteridol. T1 values were calculated on the gadoteridol-enhanced images from approximately the same regions as those on the $Gd(DTPA)^{2-}$-enhanced images. No statistically significant difference was found in the T1 values on the gadoteridol-enhanced images.

DISCUSSION

The main goal of this work was to investigate the feasibility of an MR imaging technique for in vivo imaging of the glycosaminoglycan concentration of cartilage. One of the strengths of this approach is the large T1 difference expected between normal and diseased tissue in the presence of $Gd(DTPA)^{2-}$. As illustrated by means of both the theoretic analysis and in vivo observations, T1 in the presence of $Gd(DTPA)^{2-}$ can differ by more than twofold when comparing regions of "normal" and "low" glycosaminoglycan concentration. Note that this study used T1-calculated images



a. b. c.

Figure 6. **(a)** Unenhanced (fast low-angle shot) axial MR image shows a patella with no obvious abnormality. **(b)** T1-weighted image (inversion time = 250 msec) obtained 1½ hours after intravenous injection of $Gd(DTPA)^{2-}$. The T1 on the lateral aspect of the knee in the presence of $Gd(DTPA)^{2-}$ is 374 msec ± 48 (arrows), while it is 478 msec ± 96 on the medial aspect (22% difference). **(c)** Inversion-recovery turbo spin-echo image (inversion time = 350 msec) obtained 2 hours after intravenous injection of gadoteridol. The values of T1 are relatively homogeneous with a value of 334 msec ± 37 (lateral) and 319 msec ± 42 (medial). The actual signal intensity is hypointense in the deep zone of the cartilage due to the combined T1 and T2 weighting with this sequence.

(where the T1 values can be quantified and compared directly) as well as inversion-recovery T1-weighted images. The inversion-recovery images provided very high contrast between regions of differing T1 when the inversion time was set close to the null of the T1 of one part of the tissue (Figs 5b, 5c, 6b). Suboptimal image settings may be the reason that previous studies employing $Gd(DTPA)^{2-}$ penetration into cartilage did not observe contrast between regions of high and low glycosaminoglycan concentration (27,28).

Another strength of this technique is the specific interpretation of the resultant image T1, which is dominated by the $Gd(DTPA)^{2-}$ concentration, for cartilage glycosaminoglycan concentration. The basis for this interpretation is the extensive theoretic and experimental evidence showing that the charged glycosaminoglycans strongly influence the concentration of charged solutes (12,20,29). This interpretation that the charged glycosaminoglycan is the primary determinant of $Gd(DTPA)^{2-}$ distribution is further supported by our data showing that a similarly sized, uncharged agent (gadoteridol) has a uniform distribution within cartilage matrix. This finding strongly suggests it is the charge of the ionic contrast agent that enables it to distribute in accordance with tissue glycosaminoglycan concentration (as has been demonstrated previously through in vitro studies). Indeed, the measured T1s (Table) indicated that the concentration of the nonionic agent is higher than that of the ionic agent, a finding that is consistent with the notion that the ionic agent will be relatively excluded (ie, at a lower concentration) compared with a nonionic agent.

There are, however, disadvantages of this approach. First, it involves the administration of a contrast agent, thereby increasing the risk and expense of any study. Second, though the MR study itself can take less than 10 minutes, it is necessary to wait over 1 hour before initiating the MR study to allow the $Gd(DTPA)^{2-}$ to penetrate the tissue.

Contrast agent was found to penetrate the cartilage with both intraarticular and intravenous administration. With intraarticular delivery, $Gd(DTPA)^{2-}$ penetration appeared to proceed from the articular surface inward. Intraarticular administration of $Gd(DTPA)^{2-}$ has the advantage of providing a lower systemic dose of contrast agent, but has the disadvantages of both the discomfort associated with an intraarticular injection and the long time between intraarticular administration and the MR study. Intravenous delivery of $Gd(DTPA)^{2-}$ was notably quicker, as $Gd(DTPA)^{2-}$ was able to penetrate the cartilage from both the bone-cartilage and synovial fluid–cartilage interfaces. This would be expected to reduce penetration time by about a factor of 4, an expectation that was consistent with our observation of penetration of patellar cartilage within 2½ hours. (Penetration of the 1-mm-thick condylar cartilage occurred in less than 45 minutes.) Thus, intravenous administration of $Gd(DTPA)^{2-}$ has the advantage of achieving more rapid penetration of the cartilage and is a more comfortable route of administration, but it involves a higher systemic dose and is more costly.

The information on glycosaminoglycan content can be derived from the eventual distribution of contrast material within the cartilage. After allowing sufficient time for penetration of $Gd(DTPA)^{2-}$ into cartilage, in four of nine knees we saw homogeneous enhancement (and correspondingly normal unenhanced images), whereas in five knees we were able to observe variations in signal intensity that were not observable with standard unenhanced MR imaging or contrast material–enhanced MR imaging with a nonionic contrast agent. As noted above, we interpreted these variations as reflecting variations in tissue glycosaminoglycan concentration for two main reasons: (*a*) Extensive in vitro data with use of bovine and human cartilage have demonstrated a quantitative relationship between tissue glycosaminoglycan concentration and T1 in the presence of $Gd(DTPA)^{2-}$ (13,14,23), and (*b*) signal intensity in cartilage in the presence of the nonionic contrast agent, gadoteridol, was consistently homogeneous. At these late time points after injection, we believe it is unlikely that $Gd(DTPA)^{2-}$ transport could alone account for the signal intensity variations that we are referring to as "lesions." These variations are evident when comparing cartilage of the same depth, and they do not show up on images obtained with use of a

nonionic contrast agent, which penetrated the tissue in the same time course as that of the ionic contrast agent.

The ability to image cartilage glycosaminoglycan concentration in vivo and to observe contrast indicating differences in glycosaminoglycan content in anatomically intact cartilage is exciting. Several caveats, however, are important to note. The prevalence and physiologic relevance of these "lesions" in the general population is unknown and would require more widespread studies. In addition, although we have extensive in vitro validation, including correlations between MR measures and histologic and biochemical analyses, we have no such direct validation for the in vivo studies to prove that the areas we are referring to as "lesions" are relatively low in glycosaminoglycan concentration. These studies, involving in vivo imaging and in vitro validation after total joint replacement surgery, are currently underway. Finally, we do not yet have enough information to quantify glycosaminoglycan concentration from these in vivo measurements. Such quantification requires that we measure (or know) the concentration of $Gd(DTPA)^{2-}$ in the blood and synovial fluid. We have not accounted for the fact that blood and synovial concentrations of $Gd(DTPA)^{2-}$ are not constant over time. The T1-calculated images should provide a relatively quantitative assessment of relative glycosaminoglycan concentration (eg, when comparing one region with another). Particularly in circumstances in which one wishes to compare data from one time with another (eg, annual examinations), quantification of glycosaminoglycan concentration may be more important.

In conclusion, these studies demonstrated that $Gd(DTPA)^{2-}$ will penetrate articular cartilage after intraarticular and intravenous injection. Variations in cartilage T1 in the presence of the ionic contrast agent $Gd(DTPA)^{2-}$ were interpreted as reflecting approximately 50% variations in the charged glycosaminoglycan constituent of cartilage. This interpretation is supported by the finding that T1 variations were not observed in the presence of the nonionic contrast agent gadoteridol and by previous in vitro work (13,14,23). Various aspects of the method must be more thoroughly investigated, in particular those pertaining to the pharmacokinetics of $Gd(DTPA)^{2-}$ delivery within cartilage and direct in vitro validation of the in vivo findings. To our knowledge, this is the first clinical study suggesting the ability to noninvasively monitor the concentration of glycosaminoglycan and, hence, early osteoarthritic changes, in humans.

APPENDIX

As described in the text, the goal of this section was to calculate the theoretic dependence of tissue T1 on glycosaminoglycan concentration in the presence of either an ionic contrast agent, $Gd(DTPA)^{2-}$, or a nonionic contrast agent, gadoteridol.

In the case of $Gd(DTPA)^{2-}$, the tissue T1, $T1_t$, is related to the tissue $Gd(DTPA)^{2-}$ concentration, $[Gd(DTPA)^{2-}]_t$, through the following relation:

$$T1_t = T1_{unenhanced} \div [T1_{unenhanced} \cdot R \cdot [Gd(DTPA)^{2-}]_t + 1],$$

where $T1_{unenhanced}$ = T1 of cartilage in the absence of contrast agent and R = relaxivity of the $Gd(DTPA)^{2-}$ in tissue, measured to be 3.5 $L \cdot mmol^{-1} \cdot sec^{-1}$ at 1.5 T and body temperature. R and $T1_{unenhanced}$ were assumed to be relatively constant and unaffected by tissue degradation (30). The small change in T1 with the hydration changes in the tissue would affect these calculations by 5% or less.

The tissue $Gd(DTPA)^{2-}$ concentration is then related to the tissue fixed charge density (FCD, the concentration of charge on the extracellular matrix). This is done through the empirically derived modification of a single-compartment ideal Donnan model of the tissue (13):

$$[Gd(DTPA)^{2-}]_t = \left\{ \frac{FCD\sqrt{[Gd(DTPA)^{2-}]_o}}{4[Na^+]_o} + \sqrt{\frac{FCD^2[Gd(DTPA)^{2-}]_o}{16[Na^+]_o^2} + [Gd(DTPA)^{2-}]_o} \right\}^2,$$

where $[Na^+]_o$ and $[Gd(DTPA)^{2-}]_o$ refer to the concentration outside the tissue (eg, in the synovial fluid and surrounding tissue). $[Na^+]_o$ was assumed to be 0.15 mol/L, and $[Gd(DTPA)^{2-}]_t$ = 1 or 4 mmol/L as indicated in Figure 2.

Finally, we assume that glycosaminoglycans are the only macromolecules in cartilage that contribute to the net tissue fixed charge density. Collagen, the other predominant constituent of cartilage matrix, is net neutral (31). Tissue fixed charge density is then quantitatively related to glycosaminoglycan concentration assuming glycosaminoglycans have two negative charges per disaccharide (glycosaminoglycans are repeating disaccharides) and the predominant disaccharide (chondroitin sulfate) has a molecular weight of 502.5 g/mol. FCD = $-2[GAG]/502.5$, where FCD = fixed charge density and [GAG] = glycosaminoglycan concentration. The previous three equations were solved to relate cartilage T1 in the presence of $Gd(DTPA)^{2-}$ to tissue glycosaminoglycan concentration.

In the case of gadoteridol, the tissue T1, $T1_t$, is similarly related to the gadoteridol concentration, [gadoteridol], through the following equation:

$$T1_t = T1_{unenhanced} \div [T1_{unenhanced} \cdot R \cdot [gadoteridol]_t + 1],$$

where R was measured to be 3.2 $L \cdot mmol^{-1} \cdot sec^{-1}$ at 1.5 T and body temperature. Tissue gadoteridol concentration was assumed to be equal to the concentration of gadoteridol outside the tissue, independent of tissue glycosaminoglycan concentration:

$$[gadoteridol]_t = [gadoteridol]_o.$$

The previous two equations were solved to provide the value for cartilage T1 in the presence of gadoteridol. ■

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