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Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) in Early Knee Osteoarthritis

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Delayed contrast-enhanced MRI of cartilage (dGEMRIC) is a noninvasive technique to study cartilage glycosaminoglycan (GAG) content in vivo. This study evaluates dGEMRIC in patients with preradiographic degenerative cartilage changes. Seventeen knees in 15 patients (age 35–70) with arthroscopically verified cartilage changes (softening and fibrillations) in the medial or lateral femoral compartment, knee pain, and normal weight-bearing radiography were included. MRI (1.5 T) was performed precontrast and at 1.5 and 3 hr after an intravenous injection of Gd-DTPA^{2-} at 0.3 mmol/kg body weight. T_1 measurements were made in regions of interest in medial and lateral femoral cartilage using sets of five turbo inversion recovery images. Precontrast, R_1 ($R_1 = 1/T_1$, 1/s) was slightly lower in diseased compared to reference compartment, indicating increased hydration ($P = 0.01$). Postcontrast, R_1 was higher in diseased than in reference compartment at 1.5 hr, 3.45 ± 0.90 and 2.64 ± 0.58 (mean ± SD), respectively ($P < 0.01$), as well as at 3 hr, 2.94 ± 0.60 and 2.50 ± 0.37, respectively ($P = 0.01$). The washout of the contrast medium was faster in diseased cartilage as shown by a higher R_1 at 1.5 than at 3 hr in the diseased but not in the reference compartment. In conclusion, dGEMRIC can identify GAG loss in early stage cartilage disease with a higher sensitivity at 1.5 than 3 hr. Magn Reson Med 49: 488–492, 2003. © 2003 Wiley-Liss, Inc.

Key words: dGEMRIC; glycosaminoglycan; osteoarthritis; knee

Symptomatic knee osteoarthritis (OA) affects approximately 10% of the elderly and is one of the leading causes of disability (1). In OA, cartilage is gradually lost due to an imbalance between biosynthesis and degradation of matrix constituents, such as type II collagen and glycosaminoglycans (GAG) (2,3). The diagnostic gold standard, joint space narrowing on weight-bearing radiography, underestimates the cartilage damage and the outcome varies with degree of knee flexion (4–6). In order to learn more about the initial stages of OA and to evaluate new therapeutic interventions, improved techniques to monitor early cartilage changes are needed.

Arthroscopy can be used to analyze preradiographic cartilage abnormalities, but as an invasive procedure it results in postoperative functional limitations and the technique is not free from complications (7,8). Furthermore, arthroscopy primarily examines the cartilage surface and not the deeper cartilage layers. MRI offers a safe way to assess all soft tissues within the joint noninvasively. Boegard et al. (9) monitored knee cartilage defects longitudinally using a standard 1 T MRI system. In that study, new cartilage defects were observed, whereas others disappeared during the 2-year interval. However, the vast majority also had joint space narrowing and/or osteophytes at radiography (9). In earlier stages of cartilage pathology, conventional MRI sequences have shown limitations in providing a detailed assessment of the matrix (10–12). Therefore, new MRI techniques are developed that focus on cartilage-specific macromolecules, especially GAG that are lost early in the OA disease (13). GAG have abundant negatively charged sidechains that provide a negative fixed charged density (FCD) to the cartilage. Shapiro et al. (14) recently showed that sodium MRI accurately measures FCD in vitro, but this technique has not yet been evaluated clinically.

Another method to study cartilage GAG content is delayed contrast-enhanced MRI of cartilage (dGEMRIC). This technique is based on the principle that the negatively charged contrast agent (Gd-DTPA^{2-}) distributes in the cartilage in an inverse relationship to the GAG content. In normal cartilage, Gd-DTPA^{2-} is repelled by the abundant negatively charged GAG, whereas in conditions of GAG loss, more Gd-DTPA^{2-} will be distributed within the cartilage matrix. The concentration of Gd-DTPA^{2-} can be calculated from pre- and postcontrast T_1 values.

dGEMRIC has been validated in several in vitro studies (15,16). Furthermore, in vivo, after an intravenous injection, the distribution of Gd-DTPA^{2-} in knee cartilage has shown to represent GAG concentration (17,18). In a previous study of dGEMRIC in healthy volunteers, we have shown a linear dose–response distribution of Gd-DTPA^{2-} in femoral weight-bearing cartilage with the highest concentration between 2 and 3 hr postcontrast (19).

The purpose of the present study was to evaluate dGEMRIC as a diagnostic tool in preradiographic OA. Here, we examine, at 1.5 and 3 hr, Gd-DTPA^{2-} distribution in femoral cartilage with arthroscopically verified degenerative cartilage changes (softening and fibrillations) and compare the distribution between arthroscopically diseased and normal compartments in the same knee.

METHODS

Patients

Seventeen knees in 11 males and four females (age 35–70, mean 50 years) were included in the study. Patients were identified by reviewing surgery reports and clinical journals. Inclusion criteria were: arthroscopically verified degenerative cartilage changes in the medial or the lateral femoral compartment, normal weight-bearing radiography, and knee pain. The cartilage changes ranged from superficial fibrillation to fissuring and softening. No patient had palpable or visual subchondral bone. The cartilage changes were located medially in 14 knees and later-

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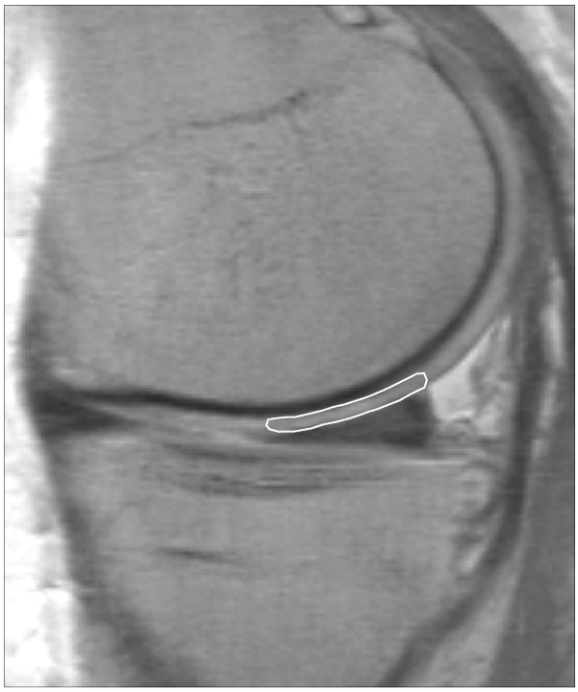

FIG. 1. Illustration of a ROI in the medial femoral weight-bearing cartilage 1.5 hr after contrast injection in a patient with medial degenerative cartilage changes.

ally in three. One male and one female had medial cartilage changes in both knees. In all knees the contralateral compartment was arthroscopically normal and served as a reference. The study was approved by the institutional review board.

MRI

A standard 1.5 T MRI-system (Magnetom Vision; Siemens Medical Systems, Erlangen, Germany) with a dedicated knee coil was used for the investigations.

Precontrast

MRI was performed according to our previous protocol (19). Central parts of the medial and lateral femoral condyles were identified using a routine diagnostic series. In the selected central parts of the cartilage, quantitative relaxation time measurements were made in sagittal slices (5 mm), using sets of five turbo inversion recovery images with different inversion times (TR = 2000 ms, TE = 15 ms, turbofactor 11, FOV 120 × 120 mm^2, matrix = 256 × 256, TI = 100, 200, 400, 800, and 1600 ms). In each set of five images, a full thickness region of interest (ROI) was drawn in the medial and lateral femoral weight-bearing cartilage between the center of the tibial plateau and the rear insertion of the meniscus (Fig. 1). T_1 and R_1 ($1/T_1$) were calculated using the mean signal intensity from each ROI as input to a three-parameter fit (20).

Postcontrast

The contrast medium Gd-DTPA^{2-} (Magnevist®, Schering Ag, Berlin, Germany) was used at 0.3 mmol/kg body weight (triple dose). Gd-DTPA^{2-} is eliminated by glomerular filtration with a plasma half-life of about 90 min (21). To avoid thrombophlebitis at the injection site, the contrast medium was injected over 2–3 min in an antecubital vein with the patient in the supine position. In order to optimize the distribution of Gd-DTPA^{2-} into the cartilage, the patients exercised by walking on stairs for ~7 min, starting 5 min after injection. Postcontrast imaging was performed 1.5 and 3 hr after injection, using an identical MRI protocol as precontrast. The Gd-DTPA^{2-} concentration in the cartilage is represented by delta R_1 (ΔR_1), that is, the difference between R_1 before ($R_{1\text{-pre}}$) and after contrast administration.

In order to relate the contrast distribution to cartilage thickness, the height of each ROI was determined by measurements in the images. Furthermore, the relationship between R_1 and age was studied. *T*-test and regression analyses were used for the statistical evaluation.

RESULTS

Precontrast ($R_{1\text{-pre}}$)

There was a small difference in $R_{1\text{-pre}}$ between the diseased and reference compartments: R_1 = (1/s, mean ± SD) = 0.95 ± 0.11 and 1.00 ± 0.10, respectively ($P = 0.01$) (Table 1, Fig. 2).

Postcontrast R_1

The postcontrast analyses were made at 84 ± 12 and 177 ± 9 min, respectively. All postcontrast R_1 values were higher than precontrast in the diseased as well as in the reference compartments as a result of the contrast medium distribu-

Table 1
R_1 and Delta R_1 (ΔR_1) Values in Reference and Diseased Compartments, Respectively

Time (min ± SD)	Precontrast		84 ± 12 min		177 ± 9 min	
Compartment	Reference	Diseased	Reference	Diseased	Reference	Diseased
R_1 (1/s ± SD)	1.00 ± 0.10	0.95 ± 0.11 *	2.64 ± 0.58	3.45 ± 0.90 **	2.50 ± 0.37	2.94 ± 0.60 *
Δ R_1 (1/s ± SD)	—	—	1.63 ± 0.56	2.50 ± 0.93 **	1.49 ± 0.36	1.98 ± 0.62 **

ΔR_1 is proportional to the concentration of Gd-DTPA^{2-} in the cartilage.
Statistical significance between reference and diseased compartments:
*$P < 0.05$,
**$P < 0.01$.

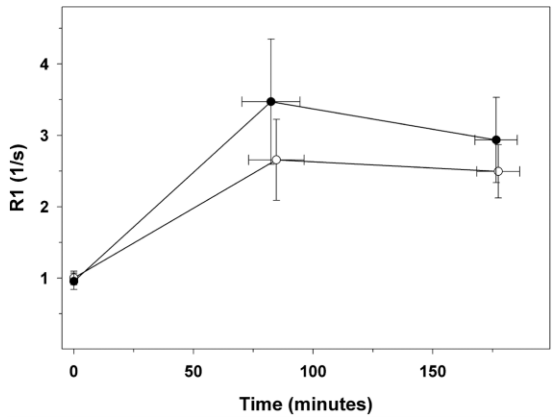

FIG. 2. R_1 (1/s, mean ± SD) precontrast and at 1.5 and 3 hr (mean ± SD) postcontrast in reference (○) and diseased (●) compartments, n = 17. R_1 was higher in diseased compared with reference compartment at 1.5 hr and at 3 hr, $P = 0.004$ and $P = 0.01$, respectively.

tion in the cartilage ($P < 10^{-8}$)(Table 1, Fig. 2). The temporal analysis showed that in the diseased compartment, R_1 was higher at 1.5 than at 2 hr, 3.45 ± 0.90 and 2.94 ± 0.60, respectively ($P = 0.002$) (Table 1, Fig. 2). R_1 in the reference compartment was similar at 1.5 and 3 hr, 2.64 ± 0.58 and 2.50 ± 0.37, respectively ($P = 0.07$) (Table 1, Fig. 2).

Postcontrast ΔR_1

As shown in Table 1, ΔR_1 and R_1 provide similar information due to the small difference in $R_{1\text{-pre}}$ between diseased and reference compartments compared to the large increase in R_1 postcontrast at both imagings (1.5 and 3 hr).

Postcontrast Comparison Between Diseased and Reference Compartments

R_1 was higher in the diseased than in the reference compartment at 1.5 as well as at 3 hr, $P = 0.004$ and 0.01, respectively (Fig. 2). The three patients with lateral disease had a higher R_1 in the lateral compared to medial reference compartment. In comparison, two of the 14 knees with medial disease had a higher R_1 in the lateral reference compartment. However, in both these patients the R_1 values were above the mean in the reference *as well as* in the diseased compartment. Individual ratio analysis between R_1 in diseased and reference compartment gave a median of 1.26 (1.11 and 1.40, 25th and 75th percentile) at 1.5 hr and 1.15 (1.03 and 1.24, 25th and 75th percentile) at 3 hr.

The washout of the contrast medium was faster in diseased cartilage, as shown by a higher R_1 at 1.5 than at 3 hr in the diseased but not in the reference compartment (Fig. 2).

Contrast Distribution in Relationship to Cartilage Thickness and Age

The ROI height, reflecting cartilage thickness, was 2.1 ± 0.5 mm in the reference compartment and 1.9 ± 0.6 mm in the diseased compartment ($P = 0.12$). No correlation was found between R_1 and cartilage thickness in the diseased or in the reference compartment (data not shown). Figure 3 shows the relationship between R_1 and age in both compartments. No statistically significant correlation was present in this number of observations at 1.5 or 3 hr. At 1.5 hr the correlation coefficient was r = 0.22, $P = 0.43$ in the reference, and r = 0.47, $P = 0.08$ in the diseased compartment.

DISCUSSION

In this first clinical study of dGEMRIC in patients with preradiographic cartilage changes, we find increased R_1 values, median 26% at 1.5 hr, in diseased compared with reference femoral cartilage. In comparison, in homogeneously GAG-depleted cartilage in vitro R_1 values were twice as high as in normal cartilage (17). We used a similar design as in the previous study of healthy volunteers in order to develop a standardized technique with comparable results (19). The central weight-bearing femoral cartilage in the semiflexed position was chosen because this region is most frequently involved in early cartilage disease (22). The relatively large, full thickness, ROI (150–250 pixels) provide a representative R_1 for each compartment but also decreases the sensitivity to focal or isolated superficial areas of low GAG concentration. This can be overcome by adding T_1-maps to the protocol (17). In the clinical situation, superficial cartilage degenerative changes are difficult to evaluate, but when associated with pain such changes are often considered early OA. However, the low R_1 values in some patients in the present study may indicate that, despite superficial fibrillation, no significant GAG loss is present in the deeper cartilage layers. We believe that the range of R_1 values in the present study illustrates the heterogeneity of the OA disease. Future studies have to evaluate whether a high R_1 is associated with an increased risk of OA development.

In vitro at high field strength (8 T), dGEMRIC has proved to be sensitive as well as specific to GAG concentration (15,17). However, it has been shown that the relaxivity of $Gd\text{-}DTPA^{2-}$ varies with the macromolecular content at

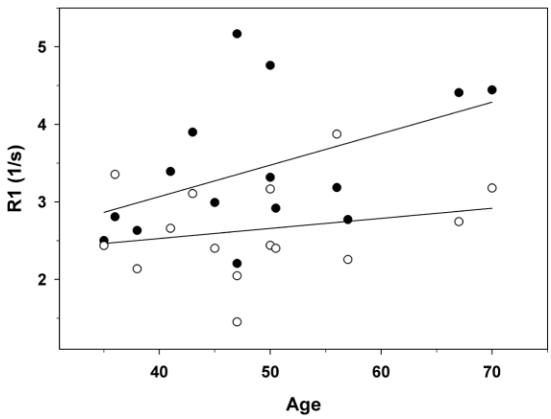

FIG. 3. Correlation between individual (n = 15) R_1-values (1/s) and age in reference (○) and diseased (●) compartments, respectively. The solid lines represent the regression lines in the reference (r = 0.22, $P = 0.43$.) and in the diseased (r = 0.47, $P = 0.08$) compartments, respectively.

clinical field strengths (~1.5 T) so that in tissues with low macromolecular content, GAG is underestimated (23). Consequently, the GAG difference between diseased and reference compartment in our study may be larger than what is shown from the R_1 values. However, in the clinical situation it may be equally important to establish the *relative* GAG content, between compartments, as in this case, or between different time-points in longitudinal studies, as to determine *absolute* GAG concentration.

We have previously shown that the saturation of Gd-DTPA^{2-} in femoral weight-bearing cartilage in healthy volunteers occurs 2–3 hr postcontrast (19). Accordingly, R_1 in the reference compartment was similar at 1.5 and 3 hr. In contrast, in the diseased compartment R_1 was higher at 1.5 than at 3 hr ($P < 0.002$), due to a faster washout of the contrast medium. The facilitated diffusion in diseased cartilage is related to decreased GAG content as well as to increased hydration (24–27). Gu et al. (27) have shown that cartilage permeability increases linearly with increased hydration, but almost quadratically with decreasing GAG content. The diffusion rate has to be considered when deciding the optimal time for postcontrast imaging in dGEMRIC. So far, studies do not support postcontrast analysis beyond 2 hr in dGEMRIC of weight-bearing femoral cartilage.

In the present study, an increased hydration in the diseased compartment was further supported by a lower $R_{1\text{-pre}}$ (Table 1), since a low $R_{1\text{-pre}}$ is consistent with a decreased protein/water ratio (28). In healthy volunteers, $R_{1\text{-pre}}$ in the same area of weight-bearing femoral cartilage was 1.05 ± 0.07 (1/s) (19). This is higher than in the diseased ($P < 0.001$), but not in the reference ($P = 0.09$) compartment in the present study. Because $R_{1\text{-pre}}$ is included in ΔR_1 calculations ($\Delta R_1 = R_1 - R_{1\text{-pre}}$), such differences in $R_{1\text{-pre}}$ will result in different ΔR_1, despite identical postcontrast R_1. However, since postcontrast R_1 in the present study were more than 50 times higher than the difference in $R_{1\text{-pre}}$, postcontrast R_1 and ΔR_1 provided similar results (Table 1). Consequently, it can be speculated whether $R_{1\text{-pre}}$ is necessary in dGEMRIC. An exclusion of $R_{1\text{-pre}}$ would facilitate the clinical use of the method. The contrast injection may then be administered at an orthopedic outpatient clinic 1.5–2 hr before imaging at the department of radiology.

The contrast distribution in arthrosopically *normal* reference cartilage was higher than what we previously found in healthy volunteers (mean age: 24) (19). At 3 hr postcontrast, using the same protocol, R_1 was approximately 10% higher in the lateral reference compartment in patients than in the lateral compartment in healthy volunteers ($P = 0.004$) (Fig. 4). This difference may be due to an early degenerative process with GAG loss also in the reference compartment, suggesting that dGEMRIC may be sensitive to subclinical stages of cartilage disease. The lower GAG may also be related to normal aging, as suggested by Mosher et al. (29). However, in this limited material we could not confirm a correlation between increasing age and R_1 in the reference compartment. In the diseased compartment the correlation with age was close to significant ($P = 0.08$), but this likely represents a later-stage disease with age.

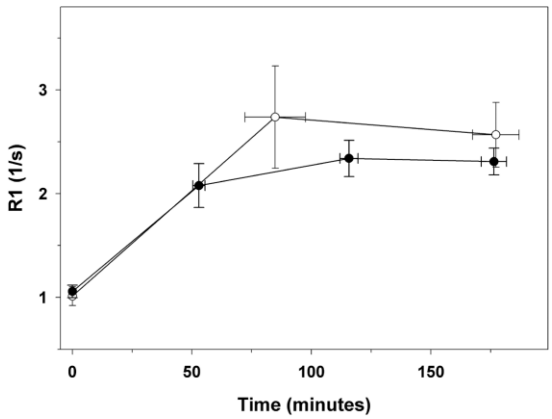

FIG. 4. Comparison between R_1 (1/s, mean ± SD) in the arthroscopically normal lateral compartment (○) in the present study (n = 14) and the lateral compartment in healthy volunteers (●) previously investigated at different time points (mean ± SD) using the same protocol (n = 19) (19). R_1 was higher in the patients than in the healthy volunteers, 2.57 ± 0.31 and 2.32 ± 0.13 at 3 hr, respectively ($P = 0.004$).

In conclusion, this study shows that dGEMRIC can identify early stage cartilage disease consistent with early OA with higher sensitivity at 1.5 than 3 hr postcontrast. A low GAG content in the diseased cartilage was supported by a high-contrast distribution and a facilitated diffusion. Ongoing studies will evaluate dGEMRIC as a means to monitor medical and surgical treatments in cartilage disease.

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