Intra-articular dGEMRIC in Patients Scheduled for MR Arthrography of the Hip Joint

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Abstract

Purpose: To assess the feasibility of performing intra-articular dGEMRIC in patients scheduled for MR arthrography of the hip joint, specifically to evaluate whether using fixed amount of contrast agent and applying additional medications to joint cavity influence the dGEMRIC index.

Materials and methods: Thirty-nine patients with hip pain, who had standard MR imaging of hip joint and longitudinal relaxation time (T1) mapping data following intra-articular administration of gadopentetate (Gd-DTPA2-) on either a 1.5T or 3.0T scanner, were reviewed. The T1s of articular cartilage and synovial fluid were analyzed with two-tailed t-test and regression analysis based on the presence or absence of morphological cartilage damage. A phantom study to mimic the synovial fluid changes during arthrography procedure was performed.

Results: T1 measured in damaged cartilage was significantly lower compared to global T1 value of cartilage in the same joint at both 1.5T (p<0.05) and 3.0T scanners (p<0.01). However, the T1 of articular cartilage and synovial fluid showed large inter-subject variation. Moderate correlations in T1 were observed between global cartilage and synovial fluid at both 1.5T (R=0.53, p<0.03) and 3T (R=0.45, p<0.05). The phantom study suggested an apparent direct influence of iohexol on T1 measurements.

Conclusion: ia-dGEMRIC may be useful to differentiate cartilage T1s within a joint based on health status. However, inter-subject comparison is limited because of the large variability in cartilage T1 between subjects. This limitation may be related to using of a fixed amount of contrast agent without normalization and applying additional medications to the joint cavity.

Keywords: ia-dGEMRIC; Hip; Arthrography; Cartilage; Iohexol

Introduction

Delayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC) is a method designed to image the distribution of fixed charge density in cartilage. It is based on the theory that if the negatively charged MRI contrast agent, such as Gd-DTPA2-, is allowed to penetrate into cartilage, it will distribute in inverse relation to the concentration of the endogenous negative fixed charge, which is predominantly determined by the concentration of the charged GAGs. The GAG distribution would then be inversely related to the Gd-DTPA2- concentration, or directly related to the longitudinal relaxation time (T1) values after penetration of the contrast agent into the cartilage, dGEMRIC index [1]. The first in vivo feasibility of dGEMRIC was illustrated using intra-articular (ia) administration of gadopentetate (Gd-DTPA2-) to obtain dGEMRIC index [1]. However, it was shown subsequently that intravenous (iv) dGEMRIC resulted in faster equilibration of contrast in the articular cartilage [3] and hence became the preferred method. Recently, the use of ia-dGEMRIC has re-emerged primarily in the clinical setting [4,5]. The dGEMRIC indices obtained by ia-dGEMRIC were reported to be similar to those obtained by iv-dGEMRIC [6,7]. Intra-articular administration of contrast agent may be helpful to better identify labral tears and cartilage clefts through the contrast medium filling into the tears and clefts [8]. The other inherent feature of ia-dGEMRIC is the reduced risk of developing nephrogenic systemic fibrosis [9,10] due to the smaller amount of Gd-DTPA2- used compared to iv-dGEMRIC. Considering these advantages, we conducted ia-dGEMRIC of hip joint clinically at our institution in patients scheduled for MR arthrography.

However, because of the inherent technical procedural differences between iv-dGEMRIC and ia-dGEMRIC performed in patients undergoing MR arthrography, we considered two technical factors that could influence contrast agent concentration in the joint cavity and T1 values of synovial fluid and hence the cartilage: (1) Unlike iv-dGEMRIC, ia-dGEMRIC uses a fixed amount of contrast agent with no normalization for different body sizes/weights/or joint size. This could cause a significant inter-subject variability in contrast agent concentration of joint cavity; (2) Since ia-dGEMRIC is performed following arthrography, some medications in addition to Gd-DTPA2- are often injected to the joint cavity during the procedure for e.g., needle positioning and anesthesia. These additional medications could dilute contrast agent in the joint cavity and may also directly impact T1 measurement. In this study, we retrospectively reviewed a group of patients who had ia-dGEMRIC of the hip joint performed following MR arthrography, specifically to evaluate whether using fixed amount of contrast agent and applying additional medications to joint cavity influence the dGEMRIC index. We also performed a phantom study to mimic the synovial fluid changes during arthrography procedure for better understanding and confirming the observations in patients.
Materials and Methods

Subjects and MR scanners

The study was approved by institutional review board, and the requirement to obtain informed consent was waived. Forty-four continuous patients with hip pain, who had T1 mapping data and standard hip joint MR imaging following Gd-DTPA\(^2\) arthrography between September of 2010 and March of 2011, were reviewed. Thirty-nine patients were included in the study and the other 5 patients were excluded because of motion artifacts. MR imaging was performed on either a 1.5T scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) or a 3.0T (Magnetom Verio, Siemens Medical Solutions, Erlangen, Germany) based on scanner availability. Seventeen subjects [male=7, female=10, mean age=35.7 ± 14.3 years (18 to 59), mean body weight=76 ± 21 kg (51 to 123), body mass index (BMI)=24.8 ± 5.0 (20.0 to 39.9)] were scanned on the 1.5T scanner, and twenty-two subjects [male=6, female=16, mean age=39.3 ± 12.5 years (18 to 62), mean body weight=68 ± 17 kg (50 to 102), mean BMI=23.6 ± 3.7 (19.3 to 29.8)] were scanned on the 3.0T scanner.

Arthrography procedure

The technical records of arthrography of the 39 subjects were reviewed. Patients were prepped and draped using standard sterile technique. Subsequently, 1% Lidocaine HCI (10 mg/mL, Hospira, Inc, Lake Forest, IL 60045, USA) was injected into superficial and deep soft tissues surrounding the hip joint. A spinal needle of 20-gauge was advanced into the hip joint under fluoroscopic guidance. Proper position was confirmed by injecting iohexol with concentration of 300 mg/mL (Omnipaque\(^{16}\), GE Healthcare, Princeton, NJ 08540, USA) to hip joint space. Ten mL of diluted Gd-DTPA\(^2\) (Magnevist, Bayer HealthCare, Pharmaceuticals Inc, Wayne, NJ 07470) with concentration of 2.5 mM (1 mL Gd-DTPA\(^2\) diluted to 200 mL with normal saline) was injected intra-articularly. In all but one case, in which Bupivacaine was used, Ropivacaine HCL (Naropin\(^{16}\), 10 mg/mL, APP Pharmaceuticals, LLC; Schaumburg, IL 60173, USA) was injected for local anesthesia. In five subjects, SoluMedrol was also injected into hip joint space as an anti-inflammatory. Table 1 summarizes the medications injected to hip joint space and their amounts in addition to Gd-DTPA\(^2\). The average amount of total additional medications injected into joint space was 4.7 mL (range 2-8 mL), in which Iohexol (range 1-5 mL).

MR imaging

After the arthrography completed, patients walked to MRI scan room immediately without additional exercise. Flexible Body Matrix coil and relevant elements of Spine Matrix coil were used in patient imaging. The flexible body matrix coil was placed anteriorly and asymmetrically (to the target hip joint) and then bent to the side of the target hip joint. Standard morphological imaging included T1 weighted asymmetrically (to the target hip joint) and then bent to the side of the joint plane. The sequence used for T1 mapping was a variable flip-angle based Three-Dimensional (3D) sequence with parallel imaging [Generalized Auto-Calibrating Partially Parallel Acquisition (GRAPPA)]. The acquisition was started at an average time of 38.8 ± 13.8 min (21 to 69) after Gd-DTPA\(^2\) injection, which was close to the suggested 15-45 minutes by a previous report [5]. An axial slab with 96 slices was applied. Other parameters of the sequence on the 1.5T scanner were TR/TE=25/1.64 ms, dual flip-angle=7° and 38° (estimate T1=600 ms), field-of-view=200 mm, voxel size=0.8x0.8x0.8 mm, acceleration factor=2, acquisition time=8 minutes and 45 seconds. The parameters used on the 3.0T scanner were identical with 1.5T scanner except for a longer TE (1.83 ms). B1-correction scan was performed immediately before acquiring T1 mapping data [11].

Data analysis

Clinical MR-arthrography reports of all patients were reviewed. In order to compare the dGEMRIC indices between damaged cartilage and undamaged cartilage, the subjects were divided into two groups based on morphological status of articular cartilage using a 5 grade classification method: those with cartilage damage (group 1, grade=1-4) and those without (group 2, grade=0).

3D T1 maps on a pixel-by-pixel basis with B1-correction were calculated inline on the scanner platform. Global T1 values of cartilage and synovial fluid were measured for both groups. To measure global T1 values of cartilage, each 3D data set was reformatted to six radial cuts perpendicular to axial plane with 0.8 mm slice thickness and 30° apart (sagittal and sagittal ± 30°, coronal and coronal ± 30°), which covered superior-anterior-lateral portion of the hip joint (Figure 1, top row). The Regions of Interest (ROIs) were placed peripherally (Figure 1, mid row) in the six reformatted cuts, which included both acetabular cartilage and femoral head cartilage. The average of the six T1 values

<table>
<thead>
<tr>
<th>Name</th>
<th>Major function</th>
<th>Cases</th>
<th>Amount (range)</th>
<th>Amount (average)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iohexol 300</td>
<td>Position confirmation</td>
<td>39/39</td>
<td>1-5 mL</td>
<td>3.0 mL</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>Anesthesia</td>
<td>38/39</td>
<td>1-4 mL</td>
<td>1.5 mL</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Anesthesia</td>
<td>1/39</td>
<td>1 mL</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>SoluMedrol</td>
<td>Anti-inflammation</td>
<td>5/39</td>
<td>1 mL</td>
<td>1.0 mL</td>
</tr>
<tr>
<td>Total</td>
<td>–</td>
<td>39/39</td>
<td>2-8 mL</td>
<td>4.7 mL</td>
</tr>
</tbody>
</table>

Table 1: Additional drugs injected to articular cavity in hip arthrography.
Moderate correlations in T1 values between global cartilage and synovial fluid were observed on both 1.5T and 3.0T scanners with the same T1 mapping sequence as for patients. The absolute T1 values of each tube were measured.

**Results**

**Patient study**

MR morphological findings suggested 21 cases with cartilage damages (group 1), including 9 at 1.5T (male=5, female=4) and 12 at 3.0T (male=4, female=8); and 18 cases without (group 2), including 8 at 1.5T (male=2, female=6), 10 at 3.0T (male=2, female=8).

Regional and global T1 values of cartilage and average T1 values of hip-synovial fluid are shown in Table 3. The p-values of comparisons in cartilage T1 measurements are shown in Table 4. In group 1 (the group with cartilage damage), significantly lower regional T1 (measured in the damaged area) were observed compared to corresponding global T1 (the average of the six reformed cuts of the same case) at both 1.5T (p<0.05) and 3.0T scanners (p<0.01). However, large standard deviations were observed in both cartilage and synovial fluid T1 values across patients. No significant difference was observed in global T1 of cartilage between the group with cartilage damage and the group without. The differences between 1.5T and 3.0T scanners in either cartilage (with all comparison pairs) or synovial fluid were measured. For each case, ROIs were placed on the T1 maps from the matching position of the damaged area, in addition to the global T1 values.

**Phantom study**

A phantom was scanned on both 1.5T and 3.0T scanners with the same T1 mapping sequence as for patients. The absolute T1 values of each tube were measured.

**Phantom study**

For group 1, regional T1 values of cartilage were also measured at morphologically damaged area, in addition to the global T1 values. The ROIs were placed on the T1 maps from the matching position of the specific images indicated in the clinical MR-arthrography reports (Figure 2).

The average ROI sizes for cartilage and synovial fluid were 904 ± 299 pixels and 455 ± 289 pixels, respectively. Two-tailed t-test and Regression analysis (programs of Microsoft Excel 2010) were performed for data analyses.

**Table 2:** Phantom mixtures simulating synovial fluid during arthrography. As measured in six cuts was considered as the global cartilage T1 value of the joint. ROIs for synovial fluid were placed in two (best showing synovial fluid) of the six reformed cuts (Figure 1, bottom row), and the average T1 of the two was considered as the synovial fluid T1 value of the case.

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**Table 2:** Phantom mixtures simulating synovial fluid during arthrography.

<table>
<thead>
<tr>
<th>No. of tubes</th>
<th>Mixture contents (per 10 mL solution)</th>
<th>T1 (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G (mL)</td>
<td>S (mL)</td>
<td>I (mL)</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>-</td>
</tr>
</tbody>
</table>

G=2.5 mM Gd-DTPA2-, S=0.9% Saline; I=Iohexol; R=Ropivacaine; Gd. Con=Gd-DTPA2- concentration

**Figure 2:** An example case with cartilage damage: (a) A sagittal T1 weighted image (TR/TE = 700 ms/9 ms) with FATSAT. The anterior half of the acetabular cartilage is thinned and irregular (small arrows). Abnormal morphology of the anterior-superior labrum can be seen (large arrow). (b) The corresponding T1 map with an ROI in the cartilage.

**Figure 3:** Moderate correlations in T1 values between global cartilage and synovial fluid were observed on both 1.5T (R=0.53, p<0.03) and 3T (R=0.45, p<0.05) scanners.
not statistically significant. The global T1 of articular cartilage were moderately but significantly correlated with the T1 of synovial fluid at both 1.5T (R=0.33, p<0.03) and 3T (R=0.45, p<0.05) scanners (Figure 3). No significant correlation was observed between dGEMRIC indices and different amount of drugs added.

**Phantom study**

As shown in Table 2, T1 value of tube 2 (2.0 mM Gd-DTPA²⁻ diluted with normal saline) was ~31% higher comparing to T1 value of tube 1 (2.5 mM Gd-DTPA²⁻) on both 1.5T and 3.0T scanners. When the concentration of Gd-DTPA²⁻ was kept at 2.0 mM (tubes 2-4), the mixtures with iohexol showed more than 27% lower T1 (tube 3) compared to tube 2; the mixtures with Ropivacaine also showed lower T1 (tube 4) than tube 2, but the magnitude of change was much smaller compared to iohexol.

**Discussion**

It is now well accepted that Glycosaminoglycan (GAG) content in articular cartilage decreases at the early stages of Osteoarthritis (OA) [12]. Intra-venous dGEMRIC technique has been used for more than a decade to obtain dGEMRIC index (T1 value post GD-DTPA²⁻ injection) as a means to assess GAG content in articular cartilage in vivo [15]. But the use of iv-dGEMRIC has been limited recently, at least in part due to the concern of nephrogenic systemic fibrosis. Using ia-dGEMRIC in this study, we did observe significantly lower regional T1 values (in the area of cartilage damaged) compared to the global T1 values (Tables 3 and 4). This suggests that ia-dGEMRIC as performed here could be useful to evaluate relative changes within a joint. However, the cartilage T1 values at both 1.5T and 3.0T were associated with very large inter-subject standard deviations, which could impact the interpretation of cartilage status. Such variability will also impact the ability to generalize the findings and determine any threshold values for differentiating healthy from diseased cartilage.

Such inter-subject variability with our data is consistent with our hypothesis that a fixed amount of contrast administered without normalization may contribute the T1 inter-subject variability of the synovial fluid and articular cartilage. In this study, we used a standard amount of contrast for our patients who had a large range of body weight (51.8-122.7 kg) without any normalization (e.g. to body weight, or joint size, or synovial volume). It was quite possible that the amount of contrast was not enough to fully fill the joint cavity with patients with large hip joint. We also found a moderate but statistically significant correlation in T1 values between the cartilage and the synovial fluid. While this is itself is not surprising, given that the source of contrast medium is the synovial fluid, the interesting aspect is the level of variation observed in the synovial fluid T1 values [267 ± 108 ms (range 102-444) at 1.5T, 238 ± 154 ms (range 24-554) at 3.0T]. As expected, our phantom data showed a large difference of T1 value when Gd-DTPA²⁻ concentration changed from 2.5 mM to 2.0 mM (diluted with normal saline). Our observations are consistent with a recent report that suggested the importance of contrast agent concentration in the synovial fluid in ia-dGEMRIC [14].

Moreover, our study also suggests an impact of additional medications used during arthrography procedure. Our phantom data demonstrated the apparent influence of iohexol on T1 measurements. This observation is consistent with a previous study by Ugas et al. which indicated the impact of additional medications on gadolinium enhanced signal intensity in MR arthrography phantom [15]. In our patient, the average amount of total additional medications injected into joint space was as much as 4.7 mL, in which 3.0 mL was iohexol, and the volumes of these medications were not constant across subjects (2-8 mL). Although we did not observe significant correlation between dGEMRIC indices and different amount of drugs added, we believe this is at least partially because dGEMRIC indices were affected by multiple factors which caused a large inter-subject variability, the amount of drugs added is only one of the factors. These additional medications usually necessary for needle position confirmation and anesthesia and so are often hard to be avoided; the injection amounts are usually based on each individual and so are often hard to be standardized. These medications not only could lead to further dilution of the contrast agent, but also may have direct influence on measured T1. Therefore, the impact of additional medications on T1 measurement has to be taken into account when performing ia-dGEMRIC.

Our study had limitations. A major limitation was that no healthy subjects were included as a control group, which was purely because of ethical issues. The study also lacked other clinical correlates for the MRI morphologically determined cartilage damage. The molecular makeup of the articular cartilage in the patients could be different from healthy cartilage even in the absence of morphological changes. Based on the spatial resolution of our acquisitions, the ROIs for articular cartilage included both acetabular and femoral cartilages, as well as the synovial fluid between the two cartilaginous layers. The inclusion of synovial fluid surely would influence the measured T1 values. The spatial resolution of our 3D acquisition was 0.8 mm isotropic which is relatively high resolution. However, given the cartilage in the hip joint is relatively thin, this may not be sufficient to minimize partial volume effects near bone and articular surface. While our data suggest potential contributions from variations in dose of Gd-DTPA²⁻ and application of other medications, it is hard to differentiate between the two sources. Future studies could include groups with different amount of drugs added to specifically evaluate their contribution to the dGEMRIC index.

In summary, our results indicated that while ia-dGEMRIC may be useful in comparison of cartilage T1 values in the same joint between regions with and without morphological changes, inter-subject comparisons are limited because of the large variability in cartilage T1 between subjects. This limitation may be related to the use a fixed amount of contrast agent without normalization, and the administration of additional medications to the joint cavity during arthrography procedure, both of which could influence the measured T1 values.

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**References**


