Delayed gadolinium-enhanced magnetic resonance imaging of hip joint cartilage: pearls and pitfalls

Bernd Bittersohl,1,2 Christoph Zilkens,2 Young-Jo Kim,3 Stefan Werlen,4 Klaus A. Siebenrock,1 Talal C. Mamisch,1,4 Harish S. Hosalkar,2
1Department of Orthopedic Surgery, Inselspital, Bern, Switzerland; 2Department of Orthopaedics, Heinrich-Heine University Medical School, Düsseldorf, Germany; 3Department of Orthopedic Surgery, Children’s Hospital, Boston, Massachusetts, USA; 4Department of Radiology, Sonnenhof Hospital, Bern, Switzerland; 5Department of Orthopedic Surgery, Rady Children’s Hospital, San Diego, CA, USA

Abstract
With the increasing advances in hip joint preservation surgery, accurate diagnosis and assessment of femoral head and acetabular cartilage status is becoming increasingly important. Magnetic resonance imaging (MRI) of the hip does present technical difficulties. The fairly thin cartilage lining necessitates high image resolution and high contrast-to-noise ratio (CNR). With MR arthrography (MRA) using intraarticular injected gadolinium, labral tears and cartilage clefts may be better identified through the contrast medium filling into the clefts. However, the ability of MRA to detect varying grades of cartilage damage is fairly limited.5,6 Additive MRI and MRA techniques that are sensitive to biochemical changes within cartilage may help to overcome this disadvantage.7,8 MRI technique of delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) is a well-documented, reliable and reproducible method that is sensitive to the charge density of cartilage contributed by glycosaminoglycans (GAGs).7,9,10 GAGs are important structural components of cartilage and relevant for maintaining the intrinsic mechanical properties that are lost early in the process of OA.11-15

Thus the dGEMRIC technique has a potential to detect early cartilage damage, which is turn is very helpful to clinicians for critical decision making regarding timely intervention for therapy. This review outlines the current status of dGEMRIC and technical considerations specific to dGEMRIC for assessment of hip joint cartilage. In addition, certain practical modifications of the standard dGEMRIC approach, which substantially help in its ability to improve hip joint imaging, have been outlined.

Theory of dGEMRIC
The dGEMRIC technique uses the negatively charged contrast agent gadolinium-diethylene triamine pentaacetic acid (Gd-DTPA2−) that is used as standard contrast medium for MRA in the routine clinical setup. After intraarticular injection and systemic circulation, Gd-DTPA2− distributes within cartilage inversely to the negatively charged GAG content (Figure 1). Gd-DTPA2− reduces the T1 relaxation time within the infiltrated tissue. Thereby, subsequent T1 measurement in cartilage described as dGEMRIC index or T1Gdu reflects the GAG content within a certain cartilage region where higher T1Gd values will be found in healthy cartilage whereas T1Gd values will be lower in degenerated cartilage based on the high amount of infiltrated Gd-DTPA2−. A time frame of 30 minutes to 60 minutes between Gd-DTPA2− injection and dGEMRIC is necessary for systemic circulation.11

There is an ongoing debate regarding the MRI parameters that have to be assessed using dGEMRIC to provide the most accurate status of cartilage degeneration in general. Key values of T1 relaxation that provide information are: T1u (i.e. T1 prior to contrast administration), T1nd (post-contrast T1) and ΔR1 that defines the difference in relaxation rate (ΔR1 = 1/T1u - 1/T1nd) between T1u and T1nd measurements (1/T1nd-1/T1u). According to some studies AR1 may be a more precise parameter to reflect the Gd-DTPA2− concentration within cartilage as post-contrast T1 variations can be factored in.13,15,16 Previous studies in the knee have elucidated that T1u values differ minimally in early cartilage degeneration and that there is nearly a linear relationship between the GAG content and T1nd making T1nd assessment in addition to T1nd unnecessary.2,17,22

Williams et al. performed measurements of T1u and T1nd in the knee of 20 volunteers at 1.5T and 3T to analyze the correlation between T1nd and AR1. A high correlation between the two metrics at both field strengths was noted with high correlation coefficients ranging from r = 0.87 to r = 0.96 at 1.5T and r = 0.90 to r = 0.94 at 3T (P < 0.0001 in all cases). We evaluated T1u and AR1 in two different radiographic grades of hip osteoarthritis (Tonnis grade 0 and Tonnis grade 1) in symptomatic femoroacetabular impingement (FAI) patients.23 Asymptomatic young-adult volun-
teers served as control. In this study, we observed a very high correlation between $T_{1\beta}$ and $\Delta R1\text{ln}$ in all study groups. In the study cohort with no radiographic signs of OA (Tonnis grade 0), the correlation was $r=0.95$. In the patient group that revealed early signs of OA in plain radiographs (Tonnis grade 1) a correlation of $r=0.89$ was noted. In the control cohort of asymptomatic young adult volunteers, the correlation between $T_{1\beta}$ and $\Delta R1$ was $r=0.88$. Correlation was statistically significant ($P<0.001$) for all study groups. Based on these results, we conclude that $T_{1\beta}$ assessment is sufficient for assessing the status of hip joint cartilage and a further time-consuming and expensive pre-contrast imaging may not be essential. However, there are circumstances that sometimes require the calculation of $\Delta R1$ for accurate GAG evaluation. These include cartilage fibrillation, follow-up of cartilage repair therapy (example cartilage transplantation) where $T_{1\beta}$ values may differ to a great extent from those in normal hyaline cartilage especially in the early post-surgical period.3,12,24

**2D dGEMRIC**

Kim et al. reported the diagnostic potential of dGEMRIC for assessment of early OA in patients with hip dysplasia (mean age 30 years, range 11 to 47 years).5 $T_{1\beta}$ values decreased depending on the grade of dysplasia ranging from approximately 550 ms (in mild changes) to 500 ms (for moderate changes) and 420 ms (in cases of severe changes). For comparison, $T_{1\beta}$ values in eight asymptomatic and morphologically normal appearing hips on the opposite side (mean age 37 years, range 20 to 48 years) were assessed. In this group, mean values and standard deviation were 570±90 ms. For MR imaging the authors used a 1.5 T system and a fast-spin echo technique with inversion recovery to obtain four coronal MR slices in the weight-bearing zone.

Tiderius et al. evaluated the time course of $T1$ values after Gd-DTPA2 injection in eight asymptomatic volunteers (mean age 28 years, range 20 to 47 years) and ten patients (mean age 39 years, range 25 to 58 years) with hip dysplasia having radiographic signs of early OA.22 Coronal $T1$ mapping was obtained utilizing a fast-spin echo sequence with inversion recovery. At 90 minutes after Gd-DTPA injection $T1 gd$ values were approximately 540 ms in healthy volunteers and approximately 420 ms in the symptomatic patient group. In a further study of 47 patients undergoing a Bernese periacetabular osteotomy for the treatment of hip dysplasia, preoperative dGEMRIC values and radiographic parameters were assessed and correlated with the treatment outcome.22 Hips in which the osteotomy did fail had significantly more arthritis on preoperative radiographs ($P=0.01$), more subluxation ($P=0.02$), and a lower dGEMRIC index ($P<0.001$) than hips in which the osteotomy did not fail. Interestingly, multivariate analysis identified the dGEMRIC index as the most important predictor of failure of the osteotomy.

As performed by the same study group in 2003,4 a multi-slice fast-spin-echo sequence was used to obtain four coronal slices (inversion recovery technique). A similar study was reported in 2000 by Jessel et al. who retrospectively analyzed 37 hips with symptomatic FAI.25 Surgical intervention is often necessary in symptomatic FAI and the outcome largely depends on the degree of pre-existing OA with reported poor results in patients with advanced cartilage damage.21,22 Clinical symptoms, radiographic parameters such as Tonnis grade (of osteoarthritis) and dGEMRIC values were assessed. Furthermore, on MRI, the head-neck offset was graded using the alpha angle. This study noted significant correlation between dGEMRIC index, pain ($P<0.05$), and increased alpha angle ($P<0.05$). The amount of radiographic arthritis was mild for the majority of the hips (26 of 37) having Tonnis grade 0 or 1. However, despite the mild radiographic arthritis, a significant drop of $T_{1\beta}$ ($T_{1\beta}=464±64$ ms) was noted. In these mildly arthritic hips, neither Tonnis gradenor joint space width correlated with patient symptoms. Lattanzi et al. have recently reported on a new high resolution two-dimensional (2D) $T1$ mapping of asymptomatic hip joint cartilage.33 The acquisition time for 3D dGEMRIC was below nine minutes in this study.

In a preliminary study on 26 symptomatic FAI patients and ten asymptomatic controls, Bittersohl et al. revealed a trend of lower $T_{1\beta}$ mean values in the entire joint as compared to asymptomatic volunteers.21 Furthermore, a

![Figure 1](https://example.com/figure1.png)

**Figure 1.** After intravenous injection and systemic circulation, the negatively charged contrast agent diethylene triamine pentaacetic acid (Gd-DTPA2) penetrates into the cartilage in an inversely proportional manner to the negatively charged glycosaminoglycan (GAG) content. According to the decrease of GAG within cartilage degeneration, more Gd-DTPA2 penetrates into the cartilage, which will cause reduction of $T1$ relaxation time. Note: Coll indicates collagen fiber, Chon indicates chondrocyte.
pattern of zonal variation that seems to be unique for a sub-group of FAI lesions could be revealed (Figure 4).

The zonal distribution of 3D $T_1$ mapping in the hip joint of asymptomatic adult volunteers at 1.5 Tesla has been recently characterized. This study included ten volunteers (3 males and 7 females with a mean age of 26.5 years; range, 24-31 years). MRI protocol included standard sequences for hip imaging and a dual-flip-angle 3D gradient-echo (GRE) sequence with volumetric interpolated breath-hold examination (VIBE) post-contrast administration. Analysis of the radial distribution revealed an increase of $T_1$ values toward the superior regions. $T_1$ values differed between the peripheral and central portions. The standard deviation (SD) ranged from 76.2 ms to 124.1 ms in the peripheral zone, and from 69.1 ms to 112.9 ms in the central zone. In both zones, SD was low in the superior regions compared with the anterior and posterior regions of the joint. Based on the high intra-(0.95) and interobserver (0.87) agreement, normative data obtained from this study will prepare the foundation for further studies of dGEMRIC and $T_1$ measurement in the hip. These findings are critical while outlining future studies for detailed objective evaluation of zonal cartilage lesions due to varying pathologies.

Domayer et al. have outlined the pattern of cartilage damage in symptomatic cases of developmental dysplasia of the hip (DDH) and of femoroacetabular impingement (FAI) with a 3D dGEMRIC technique. After clinical diagnosis with conventional radiographs, two consecutive series of each 20 patients with DDH or FAI were assessed with 3D dGEMRIC. Radial $T_1$ maps were reconstructed and region of interest analysis of the central and peripheral cartilage was carried out. The dGEMRIC index was mean 531±92.7 (391-729) ms in DDH and 551±95.7 (372-694) ms in FAI, respectively ($P=0.507$). Subgroup analysis showed higher $T_1$ in the weight-bearing areas and significantly higher values in the central areas (DDH $P$-value <0.0001, n=11; FAI $P$-value=0.036, n=14) of the acetabulum in pre-arthritic cases (dGEMRIC index >500 ms) both in DDH and FAI. A breakdown of this distribution was noted both in DDH and FAI cases with an dGEMRIC index <500 ms. Pearson correlation analysis demonstrated the dGEMRIC index had a poor predictive value for the anterior-superior quadrant of the hip joint in FAI ($r=0.482$, $P=0.031$, $r^2=0.233$).

Polland et al. investigated the potential of dGEMRIC to detect cartilage disease in asymptomatic hips with cam deformities compared with morphologically normal hips to establish whether dGEMRIC could identify advanced disease in hips with positive clinical findings, and establish whether cartilage damage correlated with the severity of the cam deformity. Subjects were recruited from a prospective study of individuals with a family history of osteoarthritis and their spouses who served as control subjects. dGEMRIC was performed on a 3T system, studying two regions of interest: the anterosuperior aspect of the acetabular cartilage ($T_1_{acetabular}$) and the total femoral and acetabular cartilage ($T_1_{total}$). The cohort was placed in subgroups by joint morphology, impingement test status, and genetic predisposition. The mean $T_1$ scores were compared, and the alpha angle and $T_1$ were correlated. Hips with a cam deformity had

![Figure 2. Morphological hip assessment (A) revealing cartilage grade 2 changes and cyst formation (arrow) at the superiolateral aspect of the hip joint. Corresponding $T_1$Gd map (B) clearly depicting severe acetabular $T_1_{Gd}$ decrease (arrow) pointing towards major GAG loss in the same area.](image)

![Figure 3. Reformatting of radial $T_1$Gd planes for 3D dGEMRIC assessment. Note the homogenous $T_1_{Gd}$ signal in all planes in this asymptomatic normal adult hip joint with normal $T_1_{Gd}$ values displayed by the green cartilage coloring.](image)
reduced acetabular glycosaminoglycan content compared with normal hips (mean $T1_{acetabular}/T1_{total} = 0.949$ and 1.093, respectively; $P = 0.0008$). Hips with a positive impingement test result had global depletion of glycosaminoglycan compared with hips with a negative result (mean $T1_{acetabular}$=625 ms versus 710 ms; $P=0.0152$). $T1_{acetabular}$ inversely correlated with the magnitude of the alpha angle ($r=-0.483$, $P=0.0038$), suggesting that the severity of cartilage damage correlates with the magnitude of the cam deformity.

Mamisch et al. compared the dGEMRIC indices in a group of six cam and seven pincer patients to a control group (n=12) of asymptomatic controls that had no plain MRI findings of osteoarthritis. The superior portion of the hip joint was divided into seven regions from 9 to 3 o'clock. These regions were then subdivided into peripheral and central regions. The cam and pincer groups both had statistically lower dGEMRIC values compared to the control group. The cam group demonstrated not only peripheral but also central involvement of the joint and this was concentrated in the anterior portion of the joint. The pincer group exhibited more global hip involvement with all areas of the hip aging a dGEMRIC index 28% less than controls. The authors concluded that the use of dGEMRIC can elicit more specific patterns of cartilage wear in patients with impingement, which may improve patient selection and help better understand the progression of osteoarthritis throughout the hip joint.

dGEMRIC combined with MRA
dGEMRIC works on the principle of decreased $T1$ relaxation time due to the infiltration of the anionic, negatively charged contrast Gd-DTPA into the cartilage in an inversely proportional manner to the negatively charged glycosaminoglycan (GAG) content ($T1_{cartilage}$). In contrast to the MRA technique, which includes the direct fluoroscopic-guided intra-articular Gd-DTPA injection, the intravenously syringed Gd-DTPA in dGEMRIC reaches the joint after systemic circulation in a lower amount providing only an indirect MR arthrogram of the hip joint and achieves less cartilage delineation and contrast-to-noise ratio (CNR). In a pilot study we investigated the feasibility of cartilage assessment in symptomatic FAI patients using intra-articular delayed Gadolinium Enhanced MRI of Cartilage (ia-dGEMRIC) instead of intravenous gadolinium dGEMRIC (iv-dGEMRIC). We hypothesized that a biochemically sensitive MRI technique complemented with the benefits of a direct arthrogram of the hip would provide better and more accurate information that an MR arthrogram alone. Based on a previous study we were aware that penetration of the cartilage differs with intravenous than intra-articular administration of Gadolinium. In this study, Bashir et al. measured the penetration of Gd-DTPA into the articular cartilage following both intra-articular and intravenous injection. For intra-articular Gd-DTPA it took up to seven hours for penetration into 4 mm of articular cartilage. Otherwise, cartilage penetration of 4 mm was completed after 2.5 hours subsequent to intravenous of Gd-DTPA administration. However, this study was performed in knee joint cartilage of two healthy volunteers only. Recently, new data addressing the transport of Gd-DTPA over time into various depths of knee joint cartilage after iv- Gd-DTPA administration including subchondral T1 assessment and pre-contrast analyses was presented. In this yet unpublished study the authors report an ongoing Gd-DTPA transport towards the deep cartilage zone and a washout after time at the superficial zone whereas T1 measurement within the subchondral region revealed no T1 variation over time leading to the conclusion that the amount of Gd-DTPA entering cartilage from the subchondral bone is negligible.

To examine the contrast infiltration process into hip joint cartilage (via MR arthrogram) we initially assessed T1 at sequential time intervals in nine patients. Twenty seven patients were subsequently scanned with ia-dGEMRIC 45 minutes post Gd-DTPA injection. These $T1_{cartilage}$ findings were correlated to the morphological extent of cartilage damage. In this study, we noted significant difference between the $T1$ values measured pre-contrast ($T1_0$) and the $T1$ values measured 15 minutes post-contrast ($T1_{15}$). The mean values then continued to remain almost constant until about 45 minutes following the intra-articular contrast injection. Thus, $T1_{cartilage}$ analysis as early as 15 minutes post Gd-DTPA injection may be possible. After 45 minutes post-injection, the $T1_{cartilage}$ values then increased suggesting washout of the contrast agent from the cartilage. Furthermore, there...
was a significant change in the $T_{1\text{Gd}}$ values with varying extent of cartilage damage (none to $>0.75$ cm to $>0.75$ cm) depicting the ability of $T_{1\text{Gd}}$ after intraarticular Gd-DTPA$^\text{2-}$ injection to pick up different severities in damage of cartilage in many regions (Figure 8).

In a further study comparing $T_{1\text{Gd}}$ mapping with both these techniques (iv and ia), the ia-dGEMRIC findings while assessing the cartilage status of symptomatic patients with FAI were similar to those from iv-dGEMRIC in a demographically comparable group of patients. Mapping with both iv-dGEMRIC and ia-dGEMRIC demonstrated obvious differences between various grades of cartilage degeneration.

Conclusions

With the increasing understanding of hip joint pathologies such as hip dysplasia and FAI, which may be clinically less symptomatic in the early stages but which can lead to early osteoarthritis of the hip in the follow-up if proper treatment is not provided in sufficient time, it is understandably critical for the treating clinician to be able to detect hip joint pathology not only in detail but also at an early stage to maximize the patient benefit. Aids to diagnosis include a detailed medical history and physical examination, radiographs and MR arthrography with radial scanning. Current advances in cartilage imaging continue to demonstrate an increasing interest in techniques that are sensitive to biochemical changes as this remains the final bridge of communication between pre-operative analysis and intra-operative assessment, information that is key and critical in decision making as well as prognostication of joint outcomes. Several techniques have been in various stages of development in recent years that have attempted biochemical evaluation of both healthy and damaged cartilage. dGEMRIC has been proven accurate and reliable for hip joint assessment. Developments in the dGEMRIC techniques such as 3D dGEMRIC and ia-dGEMRIC imaging further underline the potential of this technique that may become a standard for hip joint analysis in the daily clinical setup.


