A new method to analyze dGEMRIC measurements in femoroacetabular impingement: preliminary validation against arthroscopic findings

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Introduction

In femoroacetabular impingement (FAI), the abnormal contact between the acetabular rim and femoral head-neck junction causes chondral and labral damage, which can progress over time and result in osteoarthritis (OA) of the hip joint if the underlying cause of impingement is not addressed surgically. Corrective surgical procedures, aimed at removing the bony abnormalities of FAI and treating the associated labral and cartilage lesions, have been proposed in order to delay or prevent OA. However, for extensive articular cartilage injuries corrective treatments are less likely to be successful and total hip replacement will be the only viable option as the disease progresses. Preoperative assessment of the hip articular cartilage is therefore critical to discriminate between surgical decisions in patients with FAI.

FAI usually presents with slow onset of an intermittent groin pain, which can be exacerbated by athletic activities or prolonged walking. Physical examination often reveals limited range of motion in the internal rotation and adduction in flexion. Clinical diagnosis is normally confirmed with conventional radiographs, including the anteroposterior (AP) pelvis and cross-table lateral view of the hip. Magnetic Resonance Imaging (MRI) has emerged as the preferred diagnostic modality to confirm morphologic findings of FAI and determine the presence and extent of lesions in the articular cartilage and acetabular labrum, due to its multiplanar image acquisition capability and its high soft tissue contrast. However, routine MRI can...
diagnose cartilage defects only if there are morphologic changes, whereas cartilage may already be irreversibly compromised at a biochemical level despite appearing as normal. MR-based biochemical imaging techniques, such as T2 mapping, T2* mapping, T1–rho mapping and delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC), have been proposed to detect the earliest signs of cartilage degeneration. Ex-vivo and in-vivo validations have shown that dGEMRIC can visualize and quantify the spatial variation of glycosaminoglycans (GAGs), which represent one of the major solid constituents of cartilage, and which are lost early in the disease process of OA. In dGEMRIC, a negatively charged gadolinium-based contrast agent (Gd-DTPA) is administered and the T1 of a tissue is calculated as an indirect measure of the local distribution of GAGs, as Gd-DTPA diffuses into areas in cartilage that are depleted of GAG at a higher concentration than in areas of high GAG. Following the development in recent years of a fast 2-angle 3D T1 mapping (F2T1) pulse sequence and a rapid B1-insensitive 2D T1 mapping pulse sequence, dGEMRIC in the hip joint has become clinically feasible and it has been proposed for assessment of early cartilage degeneration in FAI. However, despite the proven capability to map GAG concentration in the cartilage, it is still unclear how to best interpret dGEMRIC T1 values in order to impact clinical decisions.

A recent study based on 20 symptomatic FAI patients, indicated that at 1.5 T, T1 < 500 ms is a suitable threshold to define damaged cartilage. However, the same study reported a large inter-subject variability of the T1 values in the hip articular cartilage, ranging from 441 ms to 750 ms. A global threshold will therefore lead to erroneous assessment of individual cases. Furthermore, the threshold is specific for 1.5 T. Other authors have proposed to normalize regional T1 values by dividing them by the average T1 of the whole joint including the space between the acetabular and femoral cartilage. Such patient-specific normalization compensates for the effect of magnetic field strength on T1 and for variations in GAG concentration due to patient’s age and sex, or diffusion and transport rates of gadolinium contrast. In their study on 32 asymptomatic subjects at 3 T, these authors found that the normalized T1 values for the anterior—superior cartilage were on average 13.1% lower in the central and peripheral compartments on all patients, using the CAM-type FAI deformities and the rest of the joint. We therefore assume that the central portion of the femoral cartilage is healthy in the early stages of FAI. The aim of this study is to validate our hypothesis using intraoperative findings as the reference. We also compared the results with those obtained by using a fixed threshold of 500 ms (hereinafter referred to as single-threshold dGEMRIC) and we assessed whether our proposed method to analyze dGEMRIC data could improve cartilage evaluation in FAI compared to T1-weighted morphologic MR images alone.

Method

Study population

We performed a retrospective review of 10 hips (four left, six right) in 10 patients (nine females, one male) who underwent hip arthroscopy after being diagnosed with symptomatic FAI, based on clinical examination and plain radiographic findings. None of the patients had previous hip surgery, associated dysplasia or other hip problems. The mean age at surgery was 19.9 ± 5.1 years, ranging from 13.5 to 31.9 years. Informed consent was obtained in all cases and this study was approved by the local ethics committee.

Preoperative MRI

All patients underwent an MRI scan of the symptomatic hip less than 4 months before surgery on a 1.5 T MR system (Avanto, Siemens Medical Solutions, Erlangen, Germany). A screening for the risk of Nephrogenic Systemic Fibrosis (NSF) was conducted using a questionnaire and patients at risk were not included in the study. The enrolled patients received a double dose (0.2 mmol/kg) intravenous injection of Gd-DTPA (Magnevist, Bayer Healthcare) prior to imaging and walked for 15 min on a treadmill at controlled speed. T1-weighted coronal spin echo (SE) images were acquired with fat suppression using the following imaging parameters: matrix size = 512 × 512, in-plane spatial resolution = 0.4 × 0.4 mm², slice thickness = 3 mm, TR/TE = 530/11 ms, Flip Angle (FA) = 90°. A fast 2-angle 3D T1 mapping method was used to acquire coronal dGEMRIC T1 maps, approximately 30 min after administration of Gd-DTPA. dGEMRIC pulse sequence had: matrix size = 512 × 512, in-plane spatial resolution = 0.3 × 0.3 mm², slice thickness = 4 mm, TR/TE = 20/4.86 ms, FA = 6° and 20°.

Intraoperative analysis

The same surgeon (YJK) performed routine hip arthroscopy of the central and peripheral compartments on all patients, using the anterolateral, posterolateral, anterior and modified anterior portals with the patient in the supine position. Location of tears and articular cartilage injury/defects were documented on a post-operative descriptive hip form. Cartilage status was reported using a scale from 0 to 5, where 0 corresponded to intact cartilage, 1–4 to Outerbridge scores I–IV and 5 to delaminated cartilage.

dGEMRIC analysis

Image processing was performed using in-house developed software. For each patient, DICOM images were de-identified by removal of name, gender and age. We then selected three coronal slices sections from the 3D slab, showing the anterior—superior, superior and posterior—superior regions of the hip articular cartilage (30 slices in total). For each slice location, a dGEMRIC T1 map and the two gradient echo (GRE) images (FA = 6° and 20°) used to calculate T1 were available. The GRE image with the largest FA (i.e., higher signal) was used to guide cartilage segmentation on the dGEMRIC T1 map. In cases for which it was possible to accurately register the GRE image with a corresponding T1-weighted fat-suppressed coronal MR image with matching slice location, also the latter was employed to improve segmentation. A region of interest (ROI) – femoral ROI – was manually defined in all cases over the central portion of the femoral cartilage (Fig. 1), which we assumed to be healthy in the early stage of FAI. A parametric map was then generated for each dGEMRIC T1 map, by transforming the T1 values (x) to standard scores (z) using:

\[
z = \frac{(x - \mu)}{\sigma}
\]

where \(\mu\) and \(\sigma\) are the mean and the standard deviation of \(T1\) in the femoral ROI. The weight-bearing portion of the hip articular
cartilage, extending from the lateral bony edge, not including the labrum, to the edge of the acetabular fossa was manually segmented on each parametric map and superimposed to the corresponding morphologic GRE image [Fig. 1(d)]. In the resulting standardized dGEMRIC maps, \( z < 0 \) indicates T1 lower than in normal cartilage and therefore a reduced concentration of GAGs. For each map, we assessed whether regions with negative \( z \) values and extending over the full thickness of the acetabular cartilage [Fig. 1(d)] corresponded to cartilage reported as damaged during arthroscopic evaluation (Outerbridge score I or greater). As small variations in GAG concentration are physiologic and do not necessarily indicate cartilage injuries, we compared the diagnostic performance of the standardized dGEMRIC when using \( z < -1, z < -2 \) and \( z < -3 \), as the threshold between damaged and healthy cartilage. The results obtained with our patient–specific analysis method were compared with those obtained by using an absolute T1 threshold of 500 ms in all cases, which was proposed by other authors.\(^2\) In order to facilitate such comparison, the original dGEMRIC T1 maps were normalized by 500 ms and the weight-bearing portion of the hip articular cartilage was segmented on each slice, using the same ROIs defined for the standardized dGEMRIC analysis.

Morphologic evaluation

Two blinded fellowship trained musculoskeletal radiologists (CP and KD) independently reviewed MR images of the 10 hips used in this study. MR images were de-identified, cleared of demographic information and randomized. Readers were aware that patients had had arthroscopy but had no knowledge of the results at the time of interpretation. For each patients, only three T1-weighted fat-suppressed coronal MR images, corresponding to the anterior–superior, superior and posterior–superior regions of the hip articular cartilage and matching the slice locations of the dGEMRIC maps, were provided for interpretation. For every section, each radiologist independently assessed the presence (yes/no) of cartilage defects and the consensus decision among the two was validated against the arthroscopic findings.

Statistical analysis

Two regions were defined for the hip articular cartilage on the three dGEMRIC maps and the three T1-weighted images that were selected for each patient: the peripheral region, extending from the lateral edge of the acetabulum to half distance between the labrum...
and the fovea, and the central region, bounded by the medial edge of the peripheral region and the fovea. These two regions were evaluated separately, resulting in six observations per patient for each of the diagnostic methods, for a total of 60 observations.

Logistic regression for correlated data was used to assess and compare standardized dGEMRIC (three cases corresponding to \( z < -1 \), -2 and -3), single-threshold dGEMRIC and morphologic assessments in terms of accuracy for the detection of cartilage abnormalities relative to the reference standard (i.e., arthroscopy). The logistic model was estimated using generalized estimating equations (GEE) with empirical standard errors and exchangeable working correlation structure to account for the correlations among multiple assessments derived for the same patient. Statistical significance was defined as \( P < 0.05 \). SAS 9.3 (SAS Institute, Cary, NC) was used for all computations.

**Results**

Table I reports \( T_1 \) values in the healthy femoral cartilage ROI for each case. Average \( T_1 \) in the femoral ROI (i.e., healthy cartilage) was consistent for each patient among the anterior—superior, superior, posterior—superior regions, with differences ranging from 2 to 110 ms (6 ± 4% variation). However, it varied among patients, with the average \( T_1 \) in the femoral ROI ranging from 544 ms to 900 ms (mean/stddev = 663 ± 80 ms). The average \( T_1 \) value in the femoral ROI is plotted in Fig. 2, where the error bars indicate intra-patient variability based on the three selected slices. Figure 3 shows standardized dGEMRIC maps in the global ROI for one representative patient, superimposed to one of the two GRE coronal images used to calculate the \( T_1 \) map. The color scale has been adjusted to highlight regions where GAG concentration is lower than the normal (i.e., where \( z < 0 \)). In this particular case, \( z \) was low in the peripheral portion of both the anterior—superior and superior acetabular cartilage, which was intraoperatively evaluated as Outletbridge score IV and III, respectively, whereas \( z \) was normal in the peripheral portion of the posterior acetabular cartilage, which the surgeon ruled as intact. Figure 4 compares the standardized dGEMRIC map, single-threshold dGEMRIC and the \( T_1 \)-weighted fat-suppressed MR image, used for the evaluation of the anterior—superior cartilage of the same representative patient. In this patient, the average \( T_1 \) in the femoral ROI was 806 ms, \( T_1 \) of degenerated cartilage was lower than average but not below 500 ms, resulting in incorrect diagnosis for the threshold method (central image in Fig. 4). The cartilage was incorrectly reported as intact also by morphologic assessment, based on the rightmost image in Fig. 4. Table II shows an estimate and the 95% confidence limits for the overall diagnostic performance of the three methods for the detection of abnormal cartilage relative to arthroscopic findings. The sensitivity of standardized dGEMRIC was the highest for all three \( z \) values considered as the threshold between normal and injured cartilage, with the cases of \( z = -1 \) and \(-2 \) significantly different (\( P < 0.05 \)) than single-threshold dGEMRIC and morphologic evaluation. Specificity and accuracy for standardized dGEMRIC using \( z = -1 \) was significantly lower (\( P < 0.05 \)) than for all other methods, ruling out the possible use of such value for clinical diagnosis. The difference between the accuracy of standardized dGEMRIC using \( z = -3 \) (65%) and that of single-threshold dGEMRIC (55%) was statistically significant (\( P < 0.05 \)).

![Average T1 in Healthy Femoral Cartilage](image)

**Discussion**

This study describes a new method to analyze dGEMRIC measurements for improved evaluation of the hip cartilage in FAI patients. Standardized dGEMRIC maps are generated by converting \( T_1 \) values to \( z \) values, using the \( T_1 \) in the central region of the femoral cartilage as an internal reference, corresponding to healthy cartilage. The importance of standardizing dGEMRIC values on a patient-specific basis is confirmed by Fig. 2, which shows that baseline cartilage \( T_1 \) values vary significantly among patients. Although Table I suggests that such variability does not depend on patient’s age, this preliminary study included only 10 young patients (13–31 y/o) and therefore a larger number of patients, representing different age groups, is needed to assess if such correlation exists.

The use of a local reference defined in a region of healthy cartilage allowed us to clearly separate out zones with a low GAG concentration, compared with the case of a global reference value averaged over the whole joint of the patient. However, due to the limited number of patients, the optimal threshold between normal and degenerated cartilage is not clear yet. As sensitivity is important for early diagnosis, our results suggest that \( z = -2 \) (sensitivity = 88%, specificity = 51%) may represent a good choice, although some of the sensitivity could be traded off by choosing \( z = -3 \) (sensitivity = 71%, specificity = 63%), when increased specificity is needed. In both cases, standardized dGEMRIC was more accurate (62% and 65% vs 55%) than single-threshold dGEMRIC. Neither sensitivity (47%) nor specificity (58%) was high for the latter. A previous study validating dGEMRIC in the hip at 1.5 T against arthroscopy, based on 16 FAI patients, also reported a weak correlation between dGEMRIC prediction of abnormal cartilage based on 500 ms threshold and intraoperative findings. Analysis of the data presented in that paper revealed that the sensitivity and the specificity were 75% and 37%, respectively. The relatively low specificity of dGEMRIC, also found in our study, may...
be artefactual, as dGEMRIC can detect biochemical changes in the articular cartilage before macroscopic effects occur. Therefore, dGEMRIC may be detecting chondral abnormalities earlier than possible with arthroscopy, which is our current “gold standard”. Furthermore, the surgeon might have missed lesions in regions where he did not visualize the cartilage directly during hip arthroscopy.

Bittersohl et al.\textsuperscript{26} also evaluated the diagnostic performance of morphologic assessment based on the same FAI patient population. From their Table II, sensitivity and specificity can be calculated to be 60\% and 91\%, respectively. In our study we also found specificity (79\%) to be higher than sensitivity (47\%) with standard MRI analysis. The superior performance in their study compared with the current study might be due to their use of radial imaging planes\textsuperscript{37}, which minimize volume-averaging effects and allow orthogonal display of the whole acetabular rim around its circumference, whereas in this study we used coronal images, in which the extent of cartilage damage might be misinterpreted\textsuperscript{22}. A study by Pfirrmann et al.\textsuperscript{28}, based on 46 FAI patients that underwent MR arthrography at 1.5 T prior to hip arthroscopy, reported that the sensitivity and specificity when using T\textsubscript{1}-weighted images with conventional imaging planes were 35\% and 90\%, and 61\% and 95\%, for two experienced radiologists, respectively. Other authors found sensitivity and specificity to be 81\% and 81\%, and 62\% and 100\% for two readers, respectively, based on T\textsubscript{1}-weighted coronal images of the hip in 21 symptomatic patients who underwent MR arthrography at 1.5 T\textsuperscript{29}. However, in this case the comparison is limited by the fact that the contrast agent was injected intra-articularly and patients underwent open surgery, which allowed complete inspection of the articular cartilage, and therefore a more reliable validation of imaging findings. Morphologic assessment in our study was limited by the available data, which included only T\textsubscript{1}-weighted SE fast-suppressed MR images at slice locations matching dGEMRIC maps. In fact, other clinical MR pulse sequences, such as T\textsubscript{1}-weighted Steady State Free Precession (SSFP)\textsuperscript{30}, or fat-suppressed Turbo SE\textsuperscript{31,32} allow for better depiction of the articular cartilage and will be employed in future validation studies.

In this study we showed that standardized dGEMRIC could improve the sensitivity of cartilage assessment compared to morphologic imaging. As our approach relies on the identification of healthy cartilage over the central region of the femoral cartilage, it is expected to be less accurate for patients with advanced cartilage degeneration or other pathologies (e.g., dysplasia) for which the femoral cartilage is compromised. The medial femoral cartilage may provide an alternative and reliable choice for standardization in a wider population, because it is probably preserved longer than superior cartilage as chondral degeneration associated with FAI progresses. However, high-resolution three-dimensional isotropic dGEMRIC acquisitions would likely be needed in order to define an ROI over the medial femoral cartilage without being severely affected by partial volume averaging. For this study, both dGEMRIC and morphologic analysis were based on coronal sections, which are susceptible to partial volume averaging along some imaging sections, due to the hip joint’s position and orientation within the pelvis.

The validation of the proposed method was limited by the use of 1.5 T MRI in this study, which made it difficult to delineate the border

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**Fig. 3.** Standardized dGEMRIC maps of the weight-bearing portion of a representative hip articular cartilage, superimposed to GRE coronal images. Values smaller than zero indicate GAG concentration lower than normal. The black arrows point to the central region of the femoral cartilage used to transform T\textsubscript{1} values into z values for each slice. The white arrows point to the peripheral region of the acetabular cartilage, which is associated to early cartilage injuries in FAI. The anterior–superior (left) and the superior (center) cartilage regions were degenerated (i.e., z < 0), whereas the posterior–superior cartilage (right) was intact (i.e., z ≥ 0), matching the arthroscopic findings.

**Fig. 4.** Standardized dGEMRIC map (left), dGEMRIC map obtained normalizing the corresponding T\textsubscript{1} map by 500 ms (center) and T\textsubscript{1}-weighted image (right), showing for a coronal plane the weight-bearing portion of the anterior–superior cartilage for a representative hip. The dGEMRIC maps have been segmented and superimposed to GRE coronal images. Compared to intraoperative assessment, the peripheral acetabular cartilage was correctly identified as degenerated in the standardized dGEMRIC map (z < 0), whereas it resulted normal in the single-threshold dGEMRIC map (T\textsubscript{1}/500 > 1) and was reported as intact by morphologic evaluation.
between femoral and acetabular cartilage layers. We decided to use a single ROI that included both layers, which resulted, for some cases, in a dark band (i.e., region of low z values) over the joint space. However, that did not affect the analysis for standardized dGEMRIC, as we reported abnormal cartilage only when the region with low z extended over the full thickness of the acetabular cartilage. On the other hand, the interface between bone and cartilage was clearly identifiable, so that in each case it was possible to reliably drawing an ROI on the central femoral cartilage, by including only the layer just above the bony surface of the femoral head.

This work was a preliminary validation of the new method and the generality of the conclusions is limited by the retrospective nature of the study and by the small number of patients. The sample size was not determined on the basis of statistical power considerations, as the aim of this study was to assess the potential of the standardized dGEMRIC analysis using the available data, in order to justify a larger validation study. Although the confidence levels reported in Table II show that there is some variability in the results, note that the sample size had sufficient statistical power to detect differences between analysis methods in terms of diagnostic accuracy, as evidenced by the number of significant differences identified that are reported in Results section.

Given the encouraging results of this preliminary study, future work will include a prospective validation study, based on a larger number of patients and 3 T MR acquisitions, for improved signal-to-noise and contrast-to-noise ratios. Furthermore, we will employ a new rapid 2D T1 mapping pulse sequence that allows performing dGEMRIC analysis along radial imaging planes of the hip, in order to avoid partial volume averaging. Note that our method to standardize dGEMRIC can be applied at any magnetic field strength, allowing for direct comparison of results. Once an optimal threshold between normal and degenerated cartilage is established based on a large patient population, the color scale in the standardized dGEMRIC maps can be adjusted accordingly to allow areas of abnormal cartilage to stand out to further improve clinical interpretation. Although a similar contrast may be achieved in the original dGEMRIC T1 maps by carefully adjusting the color scale based on the T1 values in the central femoral cartilage, it would be difficult to define a reliable threshold value for separating normal from abnormal cartilage, due to the larger dynamic range of T1 values compared to z values.

In conclusion, this preliminary validation study suggests that the proposed standardized dGEMRIC may be able to predict cartilage abnormalities with high sensitivity and accuracy in FAI patients. The results presented here suggest that adding standardized dGEMRIC to morphologic cartilage evaluation could be useful to guide surgical decisions in FAI, following more extensive calibration and validation.

### Table II

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<th>dGEMRIC</th>
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<td>Accuracy</td>
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<td>(27–55%)</td>
<td>62%</td>
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<td>88%</td>
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<td>92%</td>
<td>(74–98%)</td>
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PPV = positive predictive value, NPV = negative predictive value.

### Contributions

RL conceived and designed the study, drafted the manuscript and takes responsibility for the integrity of the work as a whole. CG, CP, KD, HR and MR were also involved in the conception and design of the study. AK, CG and RL were responsible for cartilage segmentation and analysis of the data. AVM and YJK were responsible for acquiring the MRI and surgical data. CP and KD were responsible for the morphologic evaluation. All authors critically revised the manuscript and gave final approval of the article for submission. The corresponding author (RL) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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### Conflict of interest

The authors certify that they have no financial conflict of interest with the subject matter, nor materials discussed in this manuscript.

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