Is the Damage of Cartilage a Global or Localized Phenomenon in Hip Dysplasia, Measured by dGEMRIC?

Andreas Hingsammer MS, Jenny Chan MS,
Leslie A. Kalish ScD, Tallal C. Mamisch MD,
Young-Jo Kim MD, PhD

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Abstract

Background The mechanism of damage in osteoarthritis is believed to be multifactorial where mechanical and biological factors are important in its initiation and progression. Hip dysplasia is a classic model of increased mechanical loading on cartilage attributable to insufficient acetabular coverage that leads to osteoarthritis. If the

damage is all attributable to direct mechanical damage then one initially would expect only local, not global changes.

Questions/purposes We hypothesize that in hip dysplasia although the elevated cumulative contact stresses are localized, the damage to cartilage is biologically mediated, therefore, biochemical changes will be global.

Methods Thirty-two patients with symptomatic hip dysplasia were scanned using a 1.5-T MRI scanner. We used a high-resolution three-dimensional dGEMRIC technique to characterize the distribution of cartilage damage in dysplastic hips. High-resolution isotropic acquisition was reformatted around the femoral neck axis and the dGEMRIC index was calculated separately for femoral and acetabular cartilages. Joint space widths also were evaluated in each reformatted slice. Each hip was characterized by the presence or absence of joint migration and by Tönnis grade.

Results The global dGEMRIC index correlated with the dGEMRIC indices of individual regions with the highest correlations occurring in the anterosuperior to posterosuperior regions. The corresponding correlations for joint space width were uniformly lower, suggesting that tissue loss is a more local phenomenon. Higher Tönnis grades and hips with joint migration were associated with lower dGEMRIC indices.

Conclusions The dGEMRIC index shows a global decrease, whereas tissue loss is more localized. This suggests that hip osteoarthritis in acetabular dysplasia is a biologically mediated event that affects the entire joint.

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Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

This work was performed at the Children's Hospital Boston, Boston, MA, USA.

A. Hingsammer, J. Chan, Y.-J. Kim (✉)
Department of Orthopaedic Surgery, Boston Children's
Hospital, Harvard Medical School, 300 Longwood
Avenue, Hunnewell 225, Boston, MA 02115, USA
e-mail: young-jo.kim@childrens.harvard.edu

L. A. Kalish
Clinical Research Program, Boston Children's Hospital,
Harvard Medical School, Boston, MA, USA

T. C. Mamisch
Department of Orthopaedic Surgery, Inselspital Bern,
University of Bern, Bern, Switzerland

Introduction

Abnormal morphologic features of the hip such as developmental dysplasia of the hip (DDH) contribute to the

development of osteoarthritis (OA) [2]. In patients with DDH, the shallow acetabulum is believed to abnormally increase cartilage contact stress [23] and eventually results in cartilage degeneration [12]. It is the ultimate goal of surgical techniques such as pelvic osteotomies to correct the mechanics and thereby slow the progression of arthritis [28, 29]. The rate of conversion to arthroplasty and progression of OA for these procedures depend on the severity of preexisting OA [24, 28]; therefore, the ability to accurately assess the extent and pattern of damage in the joint is essential for the treatment of DDH [31].

Although the common feature of OA is the destruction of cartilage, it is increasingly believed to be a disease of the entire joint [8, 9]. At an *in vitro* level, the role of mechanics in the initiation and progression of cartilage damage is becoming clear: however, it does not appear to be a simple wear and tear phenomenon resulting from the abnormal mechanics but rather a cellularly mediated event [18, 26]. Chondrocytes are believed to play an important role in mediating cartilage destruction, perhaps by expressing a range of inflammatory mediators in response to the abnormal mechanical load [1].

In DDH, the shallow acetabulum results in a reduced load-transferring articular area, resulting in abnormal load distribution and increased stress on the cartilage [13, 21]. Arthroscopic studies reporting cartilage damage in DDH have shown that cartilage lesions are commonly seen in the acetabular anterosuperior aspect of the joint. Fujii et al. [10] reported cartilage lesions in 14 of 18 hips in prearthritic cases with 11 located in the anterosuperior part of the acetabulum in patients younger than 20 years. McCarthy and Lee [22] confirmed this pattern of early cartilage damage. They reported that 100 (59%) of 170 hips with DDH had chondral defects situated in the anterior quadrant and concomitant anterior labral lesions were as frequent as 66%. Labrochondral damage initiating delamination and rapid progression of the defects resulting from the oscillating hydrodynamic pressure dynamics of the joint fluid were considered to lead to the high proportion of deep defects [7].

MRI is increasingly used to identify damage in the hip resulting from OA because of its ability to directly image the morphologic changes and biochemical changes in soft tissue structures, including cartilage. The delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) technique has been used to assess the biochemical changes of articular cartilage [7, 14]. By measuring the pattern of Gd-DTPA²⁻ penetration into the joint, the loss of glycosaminoglycans (GAGs) from the tissue's extracellular matrix can be estimated quantitatively [3]. The concentration of GAGs affects the cartilage's ability to withstand compression [5] and thus can be an indicator for the tissue's overall integrity [17]. dGEMRIC measurements have

correlated well with clinical pain scores [17] and have been used to predict the outcomes of periacetabular osteotomies performed as part of treatment for dysplasia [6, 15]. Additionally, the average T1 value (ie, dGEMRIC index) in the weightbearing region correlates with the severity of dysplasia and is substantially lower in patients with dysplasia than in healthy volunteers. These biochemical changes are believed to occur during early OA, preceding the joint space narrowing seen on radiographs [17].

Hip dysplasia is a model system of abnormally elevated cartilage contact stress attributable to the reduced load-transferring area leading to OA. If OA relates primarily to mechanics, then we would anticipate cartilage damage, as assessed using the dGEMRIC technique, would be localized to the weightbearing region. If, however, degradation is primarily biologically mediated, the biochemical changes in the hip would be global. The difference in pattern of damage between dysplastic and impingement hips was described by Domayer et al. [7]. They noted that in dysplastic hips the change in dGEMRIC was global compared with impingement hips. A possible artifact that may explain this finding would be the inclusion of joint fluid in the dGEMRIC measurement, especially in the unstable dysplastic hip. The dGEMRIC value of the joint fluid is low; therefore, inclusion of joint fluid in the dGEMRIC measurement as the joint migrates anteriorly in dysplasia may artificially decrease the dGEMRIC index posteriorly. Therefore, we sought to further analyze the dysplastic hip dGEMRIC findings.

We therefore asked: (1) when the dGEMRIC index of femoral and acetabular cartilages are analyzed separately in regions around the joint, how does it relate to changes in the anterosuperior part of the joint; and (2) if we separated the joints with and without joint migration, does the correlation of dGEMRIC findings in the joint change. In addition, (3) we wanted to confirm whether changes in dGEMRIC correlated with Tönnis grade and joint migration since these also are measures of cartilage damage severity.

Patients and Methods

We retrospectively assessed 32 hips in 28 females and four males. All patients were diagnosed with DDH by an orthopaedic surgeon (YJK) and underwent clinical MRI between January 2007 and March 2008. As part of our clinical routine, patients about to have a periacetabular osteotomy for a painful dysplastic hip underwent clinical MRI as long as there was no contraindication to MRI or contrast injection. During this time, one of our clinical scanners had this dGEMRIC protocol available; whether a patient was scanned using this scanner was determined by

the radiology department. During that same time, we performed 93 periacetabular osteotomies in patients with DDH. Subjects had nearly closed triradiate cartilages and showed no signs of neuromuscular disorders or skeletal dysplasia. The mean $\pm$ SD age of these patients was 31.0 ± 11.3 years (range, 11–51 years). We obtained Institutional Review Board approval for this study.

All scans were performed using a 1.5-T MRI system with a flexible surface coil (Magnetom Avanto; Siemens, Erlangen, Germany). Patients received a 0.2 mmol/kg intravenous injection of Gd-DTPA²⁻ (Magnevist; Bayer HealthCare, Wayne, NJ, USA) and then were required to walk for 15 minutes before imaging. We performed a T2-weighted true fast imaging with steady-state precession sequence with slices oriented parallel to the femoral neck axis (repetition time 12.57 ms, echo time 5.48 ms, 256×256 matrix, 16-cm field of view, 144 slices, voxel size of $0.625 \times 0.625 \times 0.63$ mm³). Two images using isotropic dual flip angle gradient echo sequence with volumetric interpolated breath-hold examination were performed approximately 30 minutes after injection with slices oriented parallel to the femoral neck axis (repetition time 15 ms, echo time 3.27 ms, flip angles 4.1° and 23.5°, 192×192 matrix, 16-cm field of view, 96 slices, voxel size of $0.83 \times 0.83 \times 0.83$ mm³) to calculate the T1 map (dGEMRIC) using the dual flip angle technique [20].

To evaluate the T1 distribution and joint space width around the joint, we reformatted isotropic data sets (T2 true fast imaging with steady-state precession sequence, gradient echo, and T1 maps) using a Leonardo workstation (Siemens, Erlangen, Germany). A reference plane tangent to the acetabular rim in the parasagittal and coronal planes was established (Fig. 1), and nine slices (anteroinferior, anterior, anterosuperior, superoanterior, superior, superoposterior, posterosuperior, posterior, and posteroinferior) subsequently were constructed at 30°-intervals around the center of the acetabulum.

For each radial reformat, we drew a region of interest (ROI) between the edge of the fossa and the lateral edge of the acetabulum using bony landmarks (Fig. 2). In a previous unpublished study we found the intraclass correlation coefficient for measuring dGEMRIC index to be approximately 0.9. Femoral and acetabular cartilage layers were included and the labrum was excluded. The dGEMRIC index was defined as the average T1 value of the ROI, which ranged from 30 mm² to 40 mm². We also calculated a global dGEMRIC index as the average dGEMRIC index across the nine slices. The minimum joint space width was measured for each of the nine regions using the T2-weighted true fast imaging with steady-state precession sequence data set. On each reformat, one of us (JC) determined the minimum distance between the bony contours of the femoral head and acetabulum in the ROI and

recorded it as the minimum joint space width. Research staff performed all measurements after a series of training sessions by the senior researcher (YJK). In severely dysplastic hips or hips with anterosuperior cartilage loss, the joint may be subluxated anteriorly at rest. Inclusion of the joint fluid in the dGEMRIC measurement may lead to a falsely low T1 values. The bright joint fluid was identified visually and care was taken to include only the acetabular and femoral cartilages when calculating the dGEMRIC index in these hips. Additionally, joint migration was noted for hips with fluid visible between cartilage layers and the pattern of dGEMRIC values in hips with and without joint migration was compared. The average $\pm$ SD global dGEMRIC score was 462 ± 108 ms and joint space width was 3.6 ± 0.8 mm (Table 1). Ten of the 32 hips studied had evidence of joint migration.

The severity of OA was evaluated for each patient by the senior author (YJK). A standing AP or supine radiograph was used and level of OA was determined based on the Tönnis grading scale (0 = no arthritis, 1 = bony sclerosis, 2 = mild joint space narrowing, 3 = focal joint space loss) [27]. Of the 32 hips in this study, nine had a Tönnis grade of 0, 17 had Grade 1, and six had Grades 2 to 3 disease.

We summarized dGEMRIC T1 and joint space width values in each region with means and standard deviations. Global dGEMRIC and joint space width values were calculated by averaging across the nine regions. We used Pearson correlations to assess the associations between pairs of regions and between each region and the global average. Subjects with versus without joint migration were compared with the two-sample t-test. Tests for violations of normality in each joint migration subgroup, and for equal variances between groups, were almost all nonsignificant. In the few cases where parametric assumptions were in question, we performed nonparametric Wilcoxon tests to check the sensitivity of our analyses. In all cases the conclusions were similar. To test whether the pattern of damage across regions differed between hips with versus without joint migration, we fit a repeated measures model with region as a repeated measure, joint migration as a fixed effect, and their interaction. An interaction would suggest that the pattern differed by joint migration. We used ANOVA and the Tukey-Kramer post hoc tests to compare dGEMRIC indices between Tönnis groups. The same sensitivity analysis was conducted as for joint migration; again there was little evidence that assumptions were violated and conclusions were robust to the method of analysis. All p values are two-sided.

Results

All regional indices correlated ($r = 0.93$ – 0.97) with the global dGEMRIC index with the highest correlations

Fig. 1A–D The selection of radial slices for reformatting (white lines indicate plane selection) are shown. First, the plane across the acetabular opening is selected in the (A) parasagittal and (B) coronal views. In the resulting (C) axial plane, slices are chosen at

30°-intervals around the joint: 1 = anteroinferior; 2 = anterior; 3 = anterosuperior; 4 = superior; 5 = superoanterior; 6 = superoposterior; 7 = posterosuperior; 8 = posterior; 9 = posteroinferior. (D) The bone structure of the acetabulum is shown for reference.

occurring in the superoanterior to posterosuperior regions (Table 2). In contrast, the correlations between the joint space width of individual regions and the global joint space width were uniformly lower (Table 2; $r = 0.56$ – 0.77) than for dGEMRIC. These results suggest that actual tissue loss as measured by joint space width is localized in early OA, whereas biochemical changes to the cartilage (dGEMRIC index) often are generalized throughout the joint.

dGEMRIC indices were generally lower in hips with joint migration with the most notable differences occurring in the posterosuperior to posteroinferior regions ($p = 0.03$, 0.05 , and 0.02 , respectively) (Table 3). We found no difference in the pattern of damage between hips with and

without joint migration (repeated measures model interaction test $p = .41$) (Fig. 3). In both groups the dGEMRIC index follows a global damage with generally lower values in hips with joint migration.

Hips of Tönnis Grade 1 generally had lower global T1 values as compared with hips of Tönnis Grade 0 (Fig. 4). The differences in T1 values between hips of Tönnis Grades 1 and Grades 2 to 3 were less distinct, although T1 values for Tönnis Grades 2 to 3 values tended to be lower than for Grade 1. T1 values with Tönnis Grade 1 were lower than with Grade 0 in the superior ($p = 0.03$) and superoposterior ($p = 0.02$) regions. Tönnis Grade 2 levels were lower than Grade 0 levels in the superoanterior ($p = 0.03$), superior ($p = 0.02$),

Fig. 2A–B A region of interest that includes the femoral and acetabular cartilages was selected by including all cartilage from the medial subchondral edge of the acetabular sourcil to the lateral edge. (A) The dGEMRIC color map and (B) the corresponding true-FISP slice are shown.

Table 1. Mean ($\pm$ SD) dGEMRIC and joint space width measurements

Region	dGEMRIC (ms)	Joint space width (mm)
Anteroinferior	424 ($\pm$ 115)	.41 ($\pm$.16)
Anterior	431 ($\pm$ 119)	.37 ($\pm$.13)
Anterosuperior	438 ($\pm$ 126)	.37 ($\pm$.14)
Superoanterior	462 ($\pm$ 114)	.34 ($\pm$.11)
Superior	490 ($\pm$ 118)	.33 ($\pm$.10)
Superoposterior	496 ($\pm$ 112)	.36 ($\pm$.08)
Posterosuperior	491 ($\pm$ 102)	.38 ($\pm$.10)
Posterior	480 ($\pm$ 103)	.37 ($\pm$.11)
Posteroinferior	446 ($\pm$ 112)	.35 ($\pm$.11)
Overall	462 ($\pm$ 108)	.36 ($\pm$.08)

superoposterior ($p = 0.05$), posterior ($p = 0.04$), and posteroinferior ($p = 0.008$) regions.

Discussion

Patients with DDH are considered to be at risk for having OA develop owing to the loss of GAG as an early event in the development of hip OA [16]. Therefore, observation of cartilage integrity and the amount of GAG is important in evaluating the effect of joint-preserving hip surgery on OA progression [17, 25]. We therefore asked: (1) when the dGEMRIC index of femoral and acetabular cartilages are analyzed separately in regions around the joint, how does it relate to changes in the anterosuperior part of the joint; and

Table 2. Correlation between each regional score and the overall global score

Region	dGEMRIC (ms) (95% CI)	Joint space width (mm) (95% CI)
Anteroinferior	.93 (.86, .96)	.69 (.43, .83)
Anterior	.95 (.89, .97)	.65 (.38, .81)
Anterosuperior	.95 (.89, .97)	.70 (.46, .84)
Superoanterior	.96 (.92, .98)	.76 (.55, .87)
Superior	.96 (.91, .98)	.77 (.57, .88)
Superoposterior	.97 (.93, .98)	.73 (.50, .85)
Posterosuperior	.96 (.91, .98)	.74 (.52, .86)
Posterior	.95 (.89, .97)	.60 (.32, .78)
Posteroinferior	.93 (.85, .96)	.56 (.25, .75)

(2) if we separated the joints with and without joint migration, does the correlation of dGEMRIC findings in the joint change. In addition, we wanted to confirm that changes in dGEMRIC correlated with Tönnis grade and joint migration since these also are measures of cartilage damage severity.

We recognize limitations to our study. First, all identification of ROIs were done visually and may be prone to error. It is relatively easy to separate the cartilage from bone; however, separating the boundary between joint fluid and cartilage and labrum and cartilage is more difficult. Fortunately, the change in dGEMRIC values across these different regions is monotonic and smooth; therefore, we previously found that small errors in classification of tissue did not cause large changes in dGEMRIC value of the ROI. Second, we assumed dGEMRIC is a reflection of GAG

Table 3. Mean dGEMRIC measurements (ms), by joint migration, and mean difference between groups

Region	Joint migration		Difference mean (95% CI)	p value*
	No (N = 22)	Yes (N = 0)		
Anteroinferior	441	385	-56 (-145, 33)	.21
Anterior	452	385	-67 (-158, 23)	.14
Anterosuperior	466	376	-90 (-184, 4)	.06
Superoanterior	488	406	-82 (-167, 3)	.06
Superior	510	445	-66 (-156, 25)	.15
Superoposterior	518	448	-70 (-155, 15)	.10
Posterosuperior	517	433	-84 (-159, -10)	.03
Posterior	504	427	-76 (-153, 1)	.05
Posteroinferior	475	381	-94 (-176, -13)	.02
Overall	486	410	-76 (-157, 4)	.06

* 2-sided independent samples t-test

Fig. 3 Distribution of mean T1 values for hips with and without joint migration is shown. The horizontal lines indicate the mean global index for hips with and without joint migration. The mean T1 for each regions of the hips (AI = anteroinferior; A = anterior; AS = anterosuperior; SA = superoanterior; S = superior; SP = superoposterior; PS = posterosuperior; P = posterior; PI = posteroinferior) are given. The overall pattern of higher T1 in the weightbearing region of the joint is preserved but hips with joint migration had a globally decreased T1 value.

tissue concentration based on prior validation studies. However, whether this is true in this particular scenario remains to be proven. Third, we did not use the other side as a contralateral control in patients with unilateral DDH. These were clinically obtained scans and we did not have funding to obtain contralateral scanning. Thus we cannot say whether or how the findings might differ in a normal hip in the same patient.

We found high correlations between the dGEMRIC indices of each region of a patient's hip and the global score, suggesting biochemically the entire joint is affected

Fig. 4 Distribution of mean T1 values for hips grouped by Tönnis grade is shown. The horizontal lines indicate the mean global index for each group. AI = anteroinferior; A = anterior; AS = anterosuperior; SA = superoanterior; S = superior; SP = superoposterior; PS = posterosuperior; P = posterior; PI = posteroinferior.

although the mechanical overload in dysplastic hips is more localized. However, the tissue loss as measured by joint space width is more localized to the superior and superoanterior regions. This may suggest that although the initiating cause of OA in DDH is a mechanical event, there may be a biologic factor that may mediate the degradative process. Mechanical injury induces chondrocytes to synthesize and secrete cartilage degrading proteases, cytokines, and other inflammatory mediators and has been proposed as the critical signal for the initiation and progression of OA [11]. In vitro models of cartilage injury have shown that injurious compression promotes cell death, predominantly by apoptosis [19]. Our in vivo data using dGEMRIC suggest that the mechanically driven OA in dysplastic hips may have a biologic mediator and is not a simple mechanical wear and tear phenomenon.

We found the lowest dGEMRIC index at the anteroinferior, anterior, and anterosuperior regions of the hip and generally higher values in the weightbearing areas of the hip. This agrees with the T1 distribution in healthy volunteers [4] and with histologic data on GAG distribution in the acetabulum [30]. We attempted to see if the global change in dGEMRIC index could be the result of inclusion of joint fluid in our measurements. In general, hips with more severe OA and severe dysplasia will have anterior joint migration. However, when we separated the hips with joint migration, we still were able to see the global change in the dGEMRIC map suggesting this phenomenon is not an artifact.

Three-dimensional dGEMRIC analysis of dysplastic hips suggests that although the mechanical insult leading to cartilage damage is often focal, the biochemical change in the joint is global. Femoral and acetabular cartilages are

affected in all regions. This suggests that there may be a biochemical event that is triggered by the mechanical stimuli causing the cartilage damage.

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