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Diagnostic and Prognostic Value of Delayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC) in Early Osteoarthritis of the Hip

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Abstract

Background: Delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) can detect glycosaminoglycan loss in the acetabular cartilage of asymptomatic individuals with cam morphology. The aims of this study were to explore the relationship between cam morphology and dGEMRIC values, and to explore whether baseline dGEMRIC can predict the development of radiographic hip osteoarthritis.

Methods: Prospective cohort (SibKids) study with clinical, radiographic, and MRI assessment at baseline and five-year follow-up (n=34). The dGEMRIC values of cartilage regions were correlated with measures of cam morphology. ROC analysis was applied to baseline variables to predict radiographic loss of joint space width.

Results: Superoanterior acetabular cartilage dGEMRIC values were significantly lower in participants with cam morphology ($p<0.001$), defined as an alpha angle greater than 60 degrees. There was a negative correlation between alpha angle and the dGEMRIC value of adjacent acetabular cartilage. This relationship was strongest superoanteriorly ($r=-0.697$ $p<0.001$). There was a positive correlation between baseline dGEMRIC and the magnitude of joint space width narrowing ($r=0.398$ $p=0.030$). ROC analysis of combined baseline variables (positive impingement test, alpha angle, dGEMRIC ratio) gave an AUC of 0.75 for predicting joint space width narrowing greater than 0.5mm within five years.

Conclusions: The size and position of cam morphology determines the severity and location of progressive cartilage damage, supporting the biomechanical aetiology of this condition. Baseline dGEMRIC is able to predict the development of radiographic osteoarthritis. Compositional MRI offers the potential to identify patients who may benefit from early intervention to prevent the development of osteoarthritis.

Keywords

1. Femoroacetabular Impingement
2. Hip
3. dGEMRIC
4. MRI
5. Osteoarthritis

Introduction

Diagnosing osteoarthritis at an early stage is critical for the development of therapies aimed at preventing disease progression. Sensitive diagnostic tools may permit the identification of patients who would benefit from intervention at a stage when their degenerative change is potentially reversible, and may also facilitate the evaluation of treatment efficacy within short timeframes. Compositional MRI offers this diagnostic potential, and delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) is able to detect glycosaminoglycan depletion(1) seen in early osteoarthritis(2). However, it remains uncertain whether compositional MRI offers prognostic value(3).

Cam morphology femoroacetabular impingement (FAI) is increasingly recognised as a risk factor for the development of hip osteoarthritis(4). Individuals with cam morphology have lower dGEMRIC values than healthy controls in the absence of radiographic osteoarthritis(5). dGEMRIC values also correlate with the magnitude of cam morphology in both patients with symptomatic FAI(6) and asymptomatic volunteers(7). In hip dysplasia, dGEMRIC correlates with pain and severity of dysplasia, supporting its role as a sensitive marker of early osteoarthritis(8).

It may be feasible to select asymptomatic individuals at greatest risk of future osteoarthritis for early preventative intervention. At present, there remains only limited evidence that baseline dGEMRIC values predict future disease. In patients with hip dysplasia, dGEMRIC predicted the success of peri-acetabular osteotomy within 24 months(5). However, hip dysplasia has a higher predictive value for osteoarthritis than cam morphology, hence the prognostic value of dGEMRIC in patients with cam morphology may be of greater clinical utility(9).

We report five-year follow-up data from a cohort of individuals with a high prevalence of cam morphology who underwent dGEMRIC at baseline(7, 10). Our aims were to a) explore whether dGEMRIC values correlate with the size and position of cam morphology and b) investigate whether baseline dGEMRIC predicts the development of radiographic osteoarthritis.

Methods

Population

At baseline, participants were selected from a prospective longitudinal study of individuals at high risk of developing osteoarthritis (SibKids)(10, 11). SibKids are the offspring of families where at least two siblings received total hip arthroplasty for end-stage osteoarthritis, with their spouses recruited as controls(12). SibKids and spouse controls were selected for baseline dGEMRIC if both hips fulfilled the criteria:

1) No investigation or treatment for hip pain within the previous two years.
2) Minimum joint space width greater than 2.5mm and Kellgren-Lawrence Grade less than two on anteroposterior pelvis radiographs.
3) No radiographic evidence of dysplasia or pincer morphology.

Each participant received dGEMRIC evaluation of a single hip based upon the greatest suspicion of FAI on clinical assessment and radiographic appearance(7). Participants who received baseline dGEMRIC assessment were invited for repeat assessment. Ethical approval was granted by Oxfordshire Research Ethics Committee B (07Q1605/26).

Clinical Assessment

An academic orthopaedic clinician measured passive range of movement and assessed for impingement indicated by groin discomfort on flexion, adduction, and internal rotation. Two Patient Reported Outcome Measures (PROMs) questionnaires were completed on the day of assessment (Non-Arthritic Hip Score(13) and Oxford Hip Score(14)).

Radiographic Assessment

Standing anteroposterior and cross-table lateral radiographs were acquired at baseline and follow-up with the hip in 15 degrees of internal rotation. Radiographs were analysed non-sequentially using OxMorf 2.1.0 software by two observers. The development of osteoarthritis was assessed on anteroposterior radiographs using minimum joint space width (minJSW) and joint space width at the medial sourcil (medJSW) and lateral sourcil (latJSW). Regional JSW measurements were adopted since cam lesion FAI results in chondropathy at the lateral acetabulum(7, 15). JSW values were corrected using a 20mm calibration ball. The smallest detectable difference in JSW was calculated as 1.96 x standard deviation of the mean difference in JSW between two readings from the same radiograph. A clinically relevant reduction in JSW was taken to be greater than 0.5mm(16). Cam morphology was evaluated on anteroposterior and lateral radiographs using the alpha angle(17) and was defined as an alpha angle greater than 60 degrees on anteroposterior radiographs(18).

MRI Protocol

The imaging protocol adopted at baseline was repeated at follow-up using the same 3 Tesla Philips Achieva X-series platform (Philips Healthcare, Netherlands) and two flexible surface coils (medium and large)(7).

Morphology:

Prior to administering contrast for dGEMRIC, the hip was imaged with a 3D-gradient-echo sequence (WATSf) with repetition time (TR) 13.65ms, echo time (TE) 6.9ms, flip angle 30 degrees, bandwidth 145Hz/pixel, field of view 150mm x 150mm x 70mm, acquisition matrix 248 x 188 x 88 (interpolated to 512 x 512 x 175), acquired in a true sagittal orientation. Scan time was 8 minutes. Three-dimensional

multiplanar reconstructions were produced as radial slices around the axis of the femoral neck at 30 degree intervals. The coronal axis (12 o'clock position) was positioned parallel to the axis of the proximal femur diaphysis. Cam morphology was quantified using the alpha angle on each of the radial slices.

dGEMRIC:

0.2mM/Kg of Magnevist (dimeglumine gadopentetate [Gd-DTPA^{2-}], Bayer Schering Pharma, Germany) was administered intravenously. An exercise protocol was completed with 10 minutes of walking on a treadmill at 4km/hour followed by 150 hip movements (50 flexion, 50 internal rotation, 50 external rotation) to ensure full perfusion of the gadolinium into the articular cartilage(19). 75 minutes after contrast administration the dGEMRIC sequence was commenced. Sequence parameters comprised sagittal inversion-prepared 3D-turbo-field-echo (TFE) with repetition time (TR_{TFE}) 6.0ms, echo time (TE) 2.9ms, flip angle 12 degrees, bandwidth 289Hz/pixel, inversion times (Tis) 2100, 1200, 600, 250, and 105ms, field of view 180mm x 180mm, slice thickness 3mm, acquisition matrix 208 x 209 (interpolated to 512 x 512). The first slice was aligned with the most medial aspect of the femoral head and the remaining slices extending laterally with no gap between slices. To attain sufficient signal-to-noise at short Tis, the total time between inversion pulses (TR_{TOTAL}) was held constant at 2200ms. Scan time was 45 minutes. Quantitative T1 maps were generated by averaging signal intensity from segmented areas on co-registered images and fitting a mono-exponential T1 recovery curve using a non-linear algorithm (MATLAB, MA, USA).

Segmentation

Sagittal dGEMRIC images were manually segmented using OsiriX Software (Version 6.0.2 64 Bit, Pixmeo, Geneva, Switzerland) by a single academic orthopaedic clinician

blinded to the timepoint of the scan and the presence of cam morphology. Averaging relaxation times across the entire joint is insufficiently sensitive to detect early disease and prior studies demonstrate the superiority of regional evaluation(20). Regions of interest (ROI) were developed based on a clockface around the centre of the femoral head at 30 degree intervals (Table 1 & Figure 1). Regions were referenced from the 12 o'clock position that passes through the centre of the femoral head parallel to the axis of the proximal femur diaphysis. The 3 o'clock position lies perpendicular to this line and represents the anterior position. Slices between the centre of the femoral head and the superior chondrolabral junction were selected for segmentation and an equal number of slices were then segmented medially. The total number of segmented slices ranged from four to six depending on femoral head size. Mean T1 relaxation time was calculated for each clockface ROI averaged across the medial or lateral slices. Femoral and acetabular cartilage was segmented separately (Figure 1). T1 values within each ROI were expressed as a ratio of the mean T1 relaxation time for all segmented cartilage outside of the ROI. This technique overcomes physiological variables that influence the delivery of contrast agent to the joint(21) and limit the ability to investigate longitudinal change or compare absolute values between participants. Each hip therefore acts as an internal control(7).

Statistical Analysis

Statistical analysis was performed using STATA 12.0 (College Station, TX, USA). Longitudinal change in outcome measures was assessed using paired t-tests after confirming normality with kernel density and QQ plots. The Pearson correlation coefficient was used to assess the relationship between continuous variables. Reproducibility was assessed using the intra-class coefficient of correlation (ICC) for absolute agreement. Level of significance was set at $p<0.05$.

Receiver operating characteristic (ROC) analysis was performed on individual variables with a binary outcome of radiographic progression at the lateral sourcil greater than 0.5mm. In addition to individual variables, a combined variable for alpha angle on anteroposterior radiograph, dGEMRIC ratio in SAa, and a positive impingement test was generated. Individual variables were rescaled to have a SD of 1 (denoted by underlining), hence the aggregate biomarker weight gives an estimate of importance(22).

Combined = (0.70 x Radiographic AP alpha angle) + (0.50 x Baseline SAa dGEMRIC ratio) + (0.28 x Positive Impingement)

Results

Cohort Characteristics

At baseline, 34 individuals participated in the study (15 female, 19 male, mean age 52 years, range 36–67) and 29 individuals (14 female, 15 male, mean age 57 years, range 41–72) returned for follow-up. This equates to a 14.7% loss to follow-up (two patients geographically relocated and three were not contactable). Average time between assessments was 58 months (range 52–62).

Two participants who attended follow-up did not receive a repeat dGEMRIC scan (one developed a medical contra-indication to MRI and the other developed impaired renal function precluding contrast administration). Scans from two follow-up patients were not interpretable due to a technical failure of MRI scanner hardware.

Defining cam morphology as an alpha angle greater than 60 degrees on the baseline anteroposterior radiograph of the index hip(18), the cohort at baseline included 26 individuals with cam morphology and 8 with normal morphology. At follow-up, there were 23 individuals with cam morphology and 6 with normal morphology. The cohort with follow-up dGEMRIC scans comprised 20 individuals with cam morphology and 5 with normal morphology.

Within the cohort (n=29), minJSW fell from mean 3.70mm (SD 0.80) to 3.41mm (SD 0.90) (paired t-test p=0.013). Defining progression as reduction minJSW greater than 0.5mm, 8 participants displayed radiographic disease progression (28%). LatJSW fell from mean 4.80mm (SD0.90) to 4.43mm (SD1.19) (paired t-test $p<0.001$), with nine participants displaying progression (31%). Baseline Kellgren-Lawrence grade was '0' (no osteoarthritis) in 17 participants and '1' (possible osteophytes without JSW

narrowing) in 17 participants. At follow-up, Kellgren-Lawrence grade had increased from '1' to '2' (definite osteophytes and JSW narrowing) in one participant and was unchanged in all other participants.

Mean alpha angle on baseline anteroposterior radiographs in participants with greater than 0.5mm minJSW reduction was 84.97 degrees (SD 19.58) compared with 78.74 degrees (SD 21.40) in those without progression (p=0.55). Mean alpha angle on baseline anteroposterior radiographs in participants with greater than 0.5mm latJSW reduction was 88.05 degrees (SD 21.24) compared with 77.04 degrees (SD 18.50) in those without progression (p=0.33). There was no longitudinal change in alpha angle with mean 78.46 degrees (SD 25.64) at baseline and 78.89 (SD 25.76) at follow-up (p=0.67).

Oxford Hip Score fell from mean 46.93 (SD 2.49) at baseline to 45.69 (SD 4.42) at follow-up (p=0.091). Baseline Non-Arthritic Hip Score fell from mean 97.80 (SD 3.62) to mean 94.40 (SD 11.53) (p=0.064). There was no correlation with radiographic or MRI measures of osteoarthritis.

Regional Variation in dGEMRIC Values

T1 relaxation times for each ROI are expressed as absolute values and as a ratio of the mean value for all segmented cartilage outside of that ROI (Table 2). Participants with cam morphology had lower mean dGEMRIC ratios in the lateral acetabular cartilage compared with medial acetabular cartilage that reached statistical significance within superoanterior acetabular cartilage (SAa) (p=0.002).

Longitudinal Change

In participants with cam morphology, there was a statistically significant decrease in dGEMRIC ratio within the lateral superoanterior acetabular cartilage (SAa) between

baseline and follow-up (p=0.018). The decrease observed in adjacent lateral superoposterior acetabular cartilage (SPa) almost reached statistical significance (p=0.056). There was no statistically significant change in any other region or in participants with normal morphology (Figure 2).

Spatial Localisation of Alpha Angle and dGEMRIC Ratio

To explore the relationship between cam lesion location and follow-up dGEMRIC measurements, three additional regions of interest were devised. These were created to increase sampling area and improve the validity of results since anteversion of the acetabulum means there are fewer anterior acetabular cartilage ROIs as one moves laterally when using true sagittal images. These three regions were anterior (Aa+ASa), anterosuperior (ASa+SAa), and superior (SAa+SPa).

Alpha angle measured in all positions demonstrated a statistically significant correlation with dGEMRIC ratio in the superior acetabulum (SAa+SPa) except when measured at the 2 o'clock position (Table 3). Alpha angles measured anteriorly (3 o'clock MRI and lateral radiograph) but at no other position correlated with dGEMRIC ratio within the anterior acetabulum (Aa+ASa). Alpha angle measurements performed at the 2 o'clock position on MRI did not correlate with the dGEMRIC ratio in any region. The strongest correlation was between average radiographic alpha angle and dGEMRIC ratio in SAa (Figure 3).

Relationship between dGEMRIC and Joint Space Width Narrowing

Baseline dGEMRIC ratio in the lateral superoanterior acetabulum (SAa) and lateral superior acetabulum (SAa+SPa) correlated with change in latJSW (SAa: r=0.392 p=0.032 and SAa+SPa: r=0.398 p=0.030) (Figure 4). These two regions also correlated with the ratio between the change in medJSW and latJSW (SAa: r=0.764 p=0.001 and

SAa+SPa: r=0.387 p=0.046). This demonstrates that patients with a low dGEMRIC ratio in SAa or SAa+SPa experience a reduction in latJSW relative to medJSW. No region demonstrated a statistically significant correlation with change in minJSW.

Predictive Models for Future Osteoarthritis

A reduction in latJSW of 0.5mm was used for differentiating individuals with or without evidence of developing osteoarthritis and 9 out of 29 participants exceeded this threshold[14]. Measurements selected as potential predictors of future osteoarthritis were dGEMRIC ratio in region SAa, positive impingement test on hip examination, and alpha angle. Alpha angle measured on an anteroposterior radiographs performed best at identifying progression with a ROC Area Under the Curve (AUC) 0.694 (95% CI: 0.472-0.917). Alpha angles exceeding 88.65 degrees can predict the development of clinically relevant osteoarthritis with a sensitivity 77.8% and specificity of 75.0% where 75.9% of individuals are classified correctly. The ROC AUC for average alpha angle on MRI radial slices was 0.600 (95% CI 0.376-0.824) and average alpha angle on anteroposterior and lateral radiographs was 0.561 (95% CI 0.336-0.786). Alpha angle on an anteroposterior radiograph also outperformed the ROC AUC for SAa dGEMRIC ratio of 0.617 (95% CI: 0.398-0.836) and positive impingement on hip examination of 0.542 (95% CI: 0.352-0.732).

A combined variable consisting of anteroposterior radiographic alpha angle, SAa dGEMRIC ratio, and a positive impingement test performs better than any individual variable with a statistically significant ROC AUC of 0.750 (95% CI: 0.541 – 0.959). It offers a sensitivity of 55.6% and specificity of 90.0% where 79.3% of individuals are classified correctly (Figure 5).

Reproducibility

The primary observer repeated all morphological measurements and segmentation of ten randomly selected hips six months after the original readings. A second observer performed the same measurements. Intra-observer ICCs were 0.983 for radiographic alpha angle, 0.962 for MRI alpha angle, 0.990 for minJSW, 0.993 latJSW, and 0.990 for the mean T1 value in each ROI. Inter-observer ICCs were 0.830 for radiographic alpha angle, 0.956 for MRI alpha angle, 0.932 for minJSW, 0.990 for latJSW, and 0.980 for the mean T1 value in each ROI. The smallest detectable difference was 0.21mm for minJSW and 0.41mm for latJSW.

Discussion

Results from this exploratory study suggest that cam size and position determines the severity and location of progressive cartilage damage. In addition, baseline dGEMRIC offers the potential to predict radiographic osteoarthritis progression within five years.

Cam morphology is prevalent within the general population(23). It can give rise to pain and confers up to a ten-fold increased risk of developing end-stage hip osteoarthritis within five years(4). However, the positive predictive value for developing osteoarthritis may be as low as 6% and it is not currently possible to identify individuals most likely to benefit from intervention(4). Hip arthroscopy is adopted with increasing frequency to excise the cam deformity and restore a normal femoral head-neck contour. This surgical intervention can improve symptoms and potentially delay joint degeneration(24, 25), however, it is ineffective in the presence of osteoarthritis(26). The success of preventative strategies requires the ability to identify patients at greatest risk of developing osteoarthritis, and to diagnose pre-structural degenerative change whilst it remains reversible(27).

In order to explore the potential value of compositional MRI for predicting the development of radiographic hip osteoarthritis, a cohort of individuals was followed up five years after initial assessment. Consistent with the cohort having been selected as an at-risk population, participants demonstrated disease progression with reduced average joint space width between baseline assessment and follow-up. The prevalence of cam morphology in this cohort was significantly greater than within the general population(28) and joint failure commencing at the lateral acetabular margin was supported by our dGEMRIC data.

Our relaxation times are comparable to those reported in other studies(29, 30), acknowledging differences in the disease severity between cohorts, specific pulse sequences employed, and post-processing methodology. Previous analysis of the baseline dGEMRIC values gave higher average values due to different post-processing methodology(7).

Cam morphology gives rise to degenerative change at the anterosuperior lateral acetabulum(15). This region (SAa) demonstrated the greatest longitudinal change in dGEMRIC values. Comparable MRI studies also identified this region as the primary location of chondropathy in patients with cam morphology(29, 30). We therefore adopted this region as a biomarker of degenerative change secondary to cam morphology.

Osteoarthritis secondary to cam morphology is thought to develop when the aspherical femoral head enters the acetabulum on flexion and internal rotation(31) leading to damage of the chondrolabral junction and adjacent articular cartilage(32). The location of cam lesion on the femoral neck varies between individuals and the resultant labral and chondral damage is expected to develop in corresponding regions of the acetabulum(33). Our data supports this pathogenesis, where only alpha angles measured anteriorly correlated with dGEMRIC values in the anterior acetabulum. Furthermore, the magnitude of alpha angles measured superiorly correlated with dGEMRIC values in the superior but not anterior acetabulum (Table 3). This co-localisation provides further support to the proposed biomechanical aetiology of osteoarthritis development.

Interestingly, the dGEMRIC ratio in the superior acetabulum correlated with alpha angles measured at all positions and suggests this region rarely escapes damage.

Possible explanations are that alpha angles are on average greatest at the 12 o'clock and 1 o'clock positions (Table 3), that even very anterior cam lesions abut the superior acetabulum when the hip lies in a flexed and internally rotated impingement position, or that this region of cartilage is more vulnerable to injury.

There was no correlation between dGEMRIC ratio and reduction in minJSW in any region. The majority of dGEMRIC studies report the same observation(6, 8) and this is expected given the hip joint has different modes of failure(34) and minJSW is not co-localised to the segmented dGEMRIC regions of interest. Joint failure secondary to cam morphology commences within the superior lateral acetabulum(35), and accordingly dGEMRIC values in this region (SAa and SAa+SPa) correlate with a reduction in JSW at the lateral sourcil.

This study suggests that dGEMRIC can predict the development of clinically relevant osteoarthritis within five years. Alpha angle measured on anteroposterior radiographs displayed the greatest predictive value for clinically relevant joint space loss. This finding is consistent with large cohort studies(4). We found that alpha angles exceeding 88.65 degrees predict the development of clinically relevant osteoarthritis progression with a sensitivity 77.8% and specificity 75.0%. This threshold is higher than the 60 degrees often used to define the presence of a cam deformity and more similar to the pathological threshold of 78 degrees proposed in large longitudinal studies(18).

A combination of baseline variables consisting of the dGEMRIC ratio in region SAa, alpha angle on anteroposterior radiographs, and clinical impingement test, performed better than any individual variable at predicting osteoarthritis development. The combined variable provides an AUC of 0.75 with a sensitivity of

363 55.6% and specificity of 90.0%. Our sample size is small and confidence intervals are
364 wide. However, this exploratory data provides impetus to study the predictive value
365 of compositional MRI in a larger cohort of patients with FAI. In developmental
366 dysplasia of the hip, dGEMRIC was shown to predict failure after peri-acetabular
367 osteotomy with an AUC of 0.977(5). This superior performance may reflect a later
368 stage of disease in a symptomatic cohort.

369 A salient finding is that dGEMRIC did not appear to offer a large improvement over
370 alpha angle for predicting the development of osteoarthritis. The performance of
371 dGEMRIC may improve with higher in-plane resolution or radial imaging planes to
372 limit the partial volume effect when imaging thin and spherical hip cartilage. In
373 order to account for variables that influence the delivery of contrast agent to joint
374 cartilage, dGEMRIC was expressed as a ratio of mean T1 relaxation times within a
375 ROI (numerator) to the mean T1 relaxation times of all segmented cartilage outside
376 of this ROI (denominator). The limitation of this technique is that sensitivity may be
377 reduced by cartilage degeneration adjacent to the ROI. An alternative strategy is to
378 select femoral cartilage from a distant region of the joint as the denominator, since
379 this cartilage is usually preserved in early disease. However, reducing the sampling
380 area makes results more susceptible to measurement artefact or distant cartilage
381 lesions. Adopting central femoral cartilage as the denominator in this study gave
382 comparable results, likely reflecting the localised early disease in this cohort. The
383 selection of an appropriate denominator should be considered in all studies.

384 The salient strength of this study is longitudinal data acquisition, hence the imaging
385 protocol adopted at baseline was not modified. Given dGEMRIC requires potentially
386 nephrotoxic intravenous contrast agent(36, 37), long scan times with imaging pre and
387 post contrast delivery, and complex post-processing image analysis at significant

388 expense, its role may be limited to a research setting. However, alternative non-
389 invasive compositional MRI sequences such as T2 mapping and T1 Rho may offer
390 superior performance and greater clinical utility(3). Future research should therefore
391 focus on alternative compositional MRI sequences with validation against
392 dGEMRIC.

393 Limitations to this study include the small sample size, which was dictated by the
394 number of patients assessed at baseline. This study must therefore be considered
395 exploratory and further work is required to validate the results. Nevertheless, our
396 data suggests that compositional MRI in may play a valuable role in predicting
397 future osteoarthritis in asymptomatic populations. Our outcome measure for
398 identifying participants who developed clinically relevant degenerative change
399 secondary to cam morphology was a reduction in radiographic JSW at the lateral
400 sourcil. MRI measurements of cartilage morphology may represent a superior
401 outcome measure(38), however, our MRI protocol already exceeded 60 minutes and
402 we did not wish to add additional sequences to ensure acceptability to participants.
403 The nature of this exploratory study meant that a large number of statistical tests
404 were performed, increasing the risk of false positives. After adjustment using
405 Bonferroni methodology, our salient results remained statistically significant.

406 ## Conclusions

407 The results of this study confirm that cam morphology is associated with progressive
408 localised cartilage damage within the superior lateral acetabulum. The severity and
409 location of degenerative change within the acetabulum is correlated with the size
410 and position of a cam lesion upon the femoral head-neck junction. This adds further
411 support to a biomechanical aetiology of osteoarthritis secondary to cam morphology,

412 which may represent a target for joint-preserving strategies. Baseline dGEMRIC
413 offers the potential to predict radiographic osteoarthritis progression in non-
414 dysplastic hips. The predictive value increases when combined with alpha angle and
415 clinical findings. This suggests that compositional MRI has the potential to identify
416 high-risk patients for inclusion into clinical trials, and may also facilitate the
417 evaluation of new preventative strategies for osteoarthritis. Although the complex
418 protocol and requirement for intravenous contrast may prevent the adoption of
419 dGEMRIC in routine clinical care, an increasing number of alternative compositional
420 MRI sequences are available that may offer superior performance and warrant
421 further investigation. The demand for diagnostic and predictive tools in early
422 osteoarthritis is likely to intensify given the increasing number of proposed
423 treatment strategies.

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434 Conflicts of Interest

Nil declared

Author Contributions

AJRP: Study conception/design, Data acquisition, Data analysis and interpretation, Drafting of manuscript, Critical Revision

SF: Data acquisition, Data analysis and interpretation, Drafting of manuscript, Critical Revision

IR: Statistical expertise, Data analysis and interpretation, Critical Revision

DP: Data analysis and interpretation, Critical Revision

TP: Study conception/design, Data acquisition

JB: Data analysis and interpretation, Critical Revision

NB: Data analysis and interpretation, Critical Revision

AC: Study conception/design, Critical Revision

SGJ: Study conception/design, Critical Revision

Tables and Figures:

Table 1: Regions of interest for MRI segmentation.

Table 2: T1 relaxation times in milliseconds displayed as absolute values and as a ratio to the mean relaxation time of all segmented cartilage.

Table 3: Relationship between follow-up dGEMRIC ratio and alpha angle measurements (shaded regions denote statistical significance).

Figure 1: Regions of interest for MRI segmentation.

Figure 2. Longitudinal change in dGEMRIC ratio in participants with cam morphology in the medial and lateral acetabular cartilage.

Figure 3: Scatterplot of SAa dGEMRIC versus average radiographic alpha angle with 95% confidence intervals.

Figure 4: Scatter Plot of change in JSW at lateral sourcil (latJSW) versus SAa dGEMRIC ratio with 95% confidence intervals.

Figure 5: ROC plots of predictive factors for clinically significant loss of JSW at lateral sourcil (latJSW).

Tables:

Table 1:

Region of Interest	Description
Aa	Anterior Acetabular Cartilage
ASa	AnteroSuperior Acetabular Cartilage
SAa	SuperoAnterior Acetabular Cartilage
SPa	SuperoPosterior Acetabular Cartilage
PSa	PosteroSuperior Acetabular Cartilage
Pa	Posterior Acetabular Cartilage
Af	Anterior Femoral Cartilage
ASf	AnteroSuperior Femoral Cartilage
SAf	SuperoAnterior Femoral Cartilage
SPf	SuperoPosterior Femoral Cartilage
PSf	PosteroSuperior Femoral Cartilage
Pf	Posterior Femoral Cartilage

473 Table 2:

Baseline																
	Lateral Half of Joint								Medial Half of Joint							
Region	Normal Morphology				Cam Morphology				Normal Morphology				Cam Morphology			
	Mean T1 Relaxation Time		Standard Deviation		Mean T1 Relaxation Time		Standard Deviation		Mean T1 Relaxation Time		Standard Deviation		Mean T1 Relaxation Time		Standard Deviation	
	ms	ratio	ms	ratio	ms	ratio	ms	ratio	ms	ratio	ms	ratio	ms	ratio	ms	ratio
Aa	391.46	0.8128	43.15	0.0934	396.58	0.9029	49.36	0.0831	395.98	0.8234	46.86	0.1019	403.91	0.9197	51.91	0.0886
ASa	466.69	0.9476	102.50	0.0694	428.11	0.9397	82.49	0.0815	446.04	0.8870	145.69	0.1221	531.89	0.9713	82.83	0.2327
SAa	514.15	1.0571	119.45	0.0863	448.39	0.9912	80.44	0.0901	460.03	0.9220	160.09	0.1933	440.87	0.9980	69.53	0.2194
SPa	519.51	1.0735	102.95	0.0588	465.27	1.0331	84.42	0.0856	467.21	0.9597	119.56	0.2354	451.96	1.0259	74.76	0.2281
Psa	489.96	1.0172	71.76	0.1309	463.90	1.0308	82.73	0.0893	470.59	0.9739	103.76	0.2381	457.52	1.0426	75.38	0.2440
Pa	455.53	0.9446	47.74	0.0462	441.30	0.9801	62.68	0.0940	433.72	0.8894	70.45	0.1608	431.98	0.9852	60.08	0.2457
Af	480.91	1.0274	76.30	0.1784	480.47	1.1316	81.51	0.1009	438.73	0.8952	84.62	0.0969	495.51	1.1931	89.51	0.4118
ASf	525.52	1.0942	123.15	0.2143	495.96	1.1496	91.25	0.3237	549.58	1.1559	137.96	0.2648	492.12	1.1411	108.05	0.3715
SAf	507.71	1.0468	145.27	0.2459	467.37	1.0704	78.99	0.2825	524.33	1.0779	163.81	0.2263	458.22	1.0514	98.72	0.3415
SPf	479.80	0.9841	129.34	0.2268	443.92	1.0062	69.66	0.2406	486.78	0.9879	149.77	0.1772	441.97	1.0006	80.81	0.2598
PSf	443.84	0.9115	74.14	0.1594	433.74	0.9807	69.30	0.2296	467.49	0.9529	111.98	0.1490	450.34	1.0263	85.82	0.2925
Pf	411.47	0.8352	61.18	0.1130	403.37	0.9002	52.81	0.1708	421.72	0.8352	130.42	0.1089	395.10	0.9083	121.46	0.3632
Five Year Follow-Up																
	Lateral Half of Joint								Medial Half of Joint							
	Normal Morphology				Cam Morphology				Normal Morphology				Cam Morphology			
	Mean T1 Relaxation Time		Standard Deviation		Mean T1 Relaxation Time		Standard Deviation		Mean T1 Relaxation Time		Standard Deviation		Mean T1 Relaxation Time		Standard Deviation	
	ms	ratio	ms	ratio	ms	ratio	ms	ratio	ms	ratio	ms	ratio	ms	ratio	ms	ratio
Aa	350.72	0.9313	29.73	0.0320	380.50	0.9239	18.61	0.0791	350.72	0.9313	29.73	0.0320	386.07	0.9400	21.77	0.0936
ASa	403.97	0.9511	52.48	0.0755	493.45	0.9379	47.40	0.0734	374.28	0.8780	45.89	0.1122	396.73	0.9476	45.33	0.0789
SAa	447.93	1.0666	67.80	0.0646	404.59	0.9659	51.36	0.0574	404.02	0.9528	74.25	0.1362	411.29	0.9891	50.05	0.1173
SPa	442.38	1.0493	71.42	0.0488	421.58	1.0127	50.73	0.0502	406.85	0.9612	59.07	0.1079	425.84	1.0277	51.93	0.1045
PSa	416.18	0.9839	49.75	0.0561	420.04	1.0090	49.34	0.0529	389.20	0.9151	45.95	0.0891	431.66	1.0442	50.95	0.1034
Pa	401.37	0.9431	48.85	0.0346	407.05	0.9755	43.48	0.0677	383.97	0.9023	44.17	0.0946	408.76	0.9834	47.39	0.1175
Af	428.56	1.1289	42.15	0.0519	450.77	1.1236	37.76	0.1446	458.32	1.0922	42.15	0.0519	451.40	1.1327	32.38	0.1001
ASf	433.28	1.0362	72.29	0.1663	456.35	1.1164	54.62	0.1495	438.49	1.0506	83.50	0.1875	453.47	1.1037	59.07	0.1126
SAf	405.48	0.9572	78.66	0.1543	431.53	1.0438	52.29	0.1115	411.47	0.9703	89.07	0.1579	435.07	1.0500	60.19	0.0914
SPf	397.39	0.9361	69.25	0.1374	411.10	0.9858	48.95	0.0785	397.24	0.9343	77.67	0.1460	417.38	1.0010	57.72	0.0764
PSf	381.36	0.8953	46.95	0.1040	405.25	0.9692	51.00	0.0726	401.55	0.9452	61.87	0.1049	417.21	1.0008	56.21	0.0741
Pf	359.14	0.8401	31.06	0.1006	390.55	0.9319	47.63	0.0909	367.77	0.8607	34.45	0.0903	406.79	0.9734	51.21	0.0730

474 Table 3:

Position of Measurement	Mean Alpha Angle Measurement [SD]		Aa + ASa Lateral Joint	ASa + SAa Lateral Joint	SAa + SPa Lateral Joint		SAa Lateral Joint	SPa Lateral Joint
MRI 12 O'Clock	70.37 [22.79]	R Value	-0.002	-0.251	-0.425		-0.412	-0.322
		P Value	0.497	0.113	0.017		0.020	0.058
MRI 1 O'Clock	73.44 [15.04]	R Value	-0.16	-0.458	-0.513		-0.522	-0.355
		P Value	0.222	0.011	0.004		0.004	0.041
MRI 2 O'Clock	69.18 [9.84]	R Value	-0.096	-0.056	-0.096		0.029	0.029
		P Value	0.324	0.394	0.324		0.446	0.446
MRI 3 O'Clock	60.77 [13.94]	R Value	-0.362	-0.465	-0.505		-0.415	-0.481
		P Value	0.038	0.01	0.005		0.020	0.008
Anteroposterior Radiograph	79.47 [21.72]	R Value	-0.056	-0.408	-0.57		-0.617	-0.347
		P Value	0.396	0.021	0.001		0.001	0.045
Lateral Radiograph	56.39 [14.26]	R Value	-0.398	-0.407	-0.337		-0.302	-0.288
		P Value	0.024	0.022	0.050		0.071	0.082
Average MRI: Clockface Positions	68.44 [10.15]	R Value	-0.273	-0.579	-0.677		-0.597	-0.562
		P Value	0.094	0.001	<0.001		0.001	0.002
Average Radiograph AP and Lateral	68.26 [14.44]	R Value	-0.221	-0.516	-0.663		-0.697	-0.459
		P Value	0.144	0.004	<0.001		<0.001	0.011

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