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THE ASSOCIATION OF FEMOROACETABULAR IMPINGEMENT AND DELAYED GADOLINIUM ENHANCED MRI OF CARTILAGE (DGEMRIC): A POPULATION-BASED STUDY

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Abstract

Objective: 1) To assess the association of FAI and dGEMRIC T1 relaxation values (RV). 2) To evaluate whether subtypes of FAI (cam, pincer, mixed) are associated with region-specific dGEMRIC T1 RVs.

Methods: A population-based sample of Caucasian subjects with and without hip pain, aged 20-49, was selected through random digit dialing. A sample of 128 subjects underwent hip joint 3T dGEMRIC scans. Radiographic cam FAI was defined as an alpha angle >55°, while pincer FAI was defined by a lateral center edge angle >40° or a positive cross-over sign. Mixed impingement was defined by the presence of both cam and pincer impingement. Overall and region-specific T1 RVs were compared between all FAI subtypes using weighted linear regression analysis to account for sampling design of the study.

Results: Subjects had mean age of 38 years and 51% were female. We did not find an association of FAI with overall hip T1 RV (mean difference =-15.5, 95% CI -77.23, 47.14). Significant associations of cartilage degeneration in anterior superior and central superior regions were found in subjects with mixed FAI compared to other FAI subtypes and non-FAI subjects.

Conclusion: Subjects with mixed FAI had reduced T1 RVs compared other FAI subtypes. No substantial cartilage degeneration was found in pure cam or pincer FAI compared to non-FAI hips. These results indicate that the presence of cam or pincer impingements alone does not suggest the beginning of cartilage degeneration. In contrast, the presence of both FAI subtypes is a risk factor for early cartilage damage.

Significance and Innovations

- The presence of any FAI (cam, pincer or mixed) was not associated with T1 relaxation values on dGEMRIC for the hip as a whole in this young population-based cohort.
- In region-specific analyses, subjects with mixed FAI had reduced T1 relaxation values, i.e. worse cartilage scores, compared to those with no FAI and those with cam or pincer FAI alone in the anterosuperior and central superior regions, whereas pure cam and pure pincer FAI, compared to non-FAI, was not significantly associated with cartilage degeneration.
- These findings indicate a synergistic effect of cam and pincer FAI on cartilage degeneration in early hip disease.

Femoroacetabular impingement (FAI) is a condition in which the proximal femoral head abuts against the acetabular rim, leading to damage to surrounding tissues and underlying cartilage (1). There is evidence that the presence of FAI strongly associates with early development of hip osteoarthritis (OA) (2-6). Cam and pincer impingement are the two main variations of FAI. Cam usually occurs in young active men (1, 7, 8) and is caused by an enlarged femoral head-neck junction, which abuts against the acetabular rim (9). This abnormal contact leads to delamination and damage of the labrum (10). Pincer impingement is more common in middle-aged active women (1) and is caused by the over-coverage of the femoral head by the acetabulum. The continuous loading of the acetabular rim may result in chronic degenerative changes such as labral degeneration, intra-substance ganglion formation, ossification of acetabular rim, and deepening of the acetabulum (1, 11, 12). Cam and pincer morphology can occur as separate conditions, but, more commonly, occur as mixed cam and pincer impingement (1).

Delayed gadolinium enhanced MRI of cartilage (dGEMRIC) is an imaging technique used to identify early degenerative changes in cartilage. It can characterize cartilage quality in earlier phases of OA, when it may be potentially reversible (13). The negative charge of glycosaminoglycan (GAG), an essential component of aggrecan for maintenance of cartilage homeostasis, attracts water into the cartilage to create a hyperosmotic pressure (14, 15). GAG loss occurs as a result of cam and pincer FAI, leading to structural degeneration of articular cartilage (16). Patterns of cartilage change in FAI patients are more accurate and better visualized in dGEMRIC, suggesting a higher sensitivity compared to standard MRI (17, 18). dGEMRIC has been validated by previous studies, showing that it is able to detect patterns of cartilage changes in patients with and at risk of hip and knee OA (19-22). T1 relaxation value (RV) is the primary measure of GAG concentration in cartilage.

Although most studies of FAI have focused on symptomatic patients, the FAI hypothesis has been extended to propose that FAI is the single most common cause of hip pain in non-dysplastic hips and to propose that FAI is the explanation for the majority of primary hip OA (3, 23, 24). However, establishing definitively the relationships between FAI deformities, hip pain and OA requires population-based studies. To date there have been few population-based studies assessing the relationships between FAI, pain and cartilage degeneration (7, 8, 25, 26). Most studies of cartilage changes in FAI have been of symptomatic patients, although one study of 19 asymptomatic cam subjects (mean age =52, SD =8) found significant reduction in GAG content in cam hips compared to normal hips (P =0.0008) using dGEMRIC(19). It is unclear whether all FAI deformities, including mixed type, increase the risk of hip pain and cartilage degeneration. The objective of this study was to evaluate the association of radiographic FAI with total hip dGEMRIC RV and with regional hip dGEMRIC RVs in a population-based cohort of subjects with and without hip pain.

Methods

Subjects

Subjects were recruited from the Investigations of Mobility, Physical Activity, and Knowledge Translation in Hip Pain (IMPAKT-HiP) study, which is a population-based study of 500 Caucasian subjects with and without hip pain (27). Subjects in the IMPAKT-HiP study were recruited through random digit dialing of households in a large city as a method of random population sampling. The parent study's purpose was to recruit a population-based cohort with and without hip pain in order to examine the association of activities and hip pain (27). In order to keep the same population characteristics, the current study utilized the same subject selection criteria. Inclusion criteria for the IMPAKT-HiP study were 1) age 20-49 years; 2) ability to attend a two-hour assessment, consisting of questionnaires, physical examination of the hip and hip x-rays. Exclusion criteria were pregnancy and bilateral hip replacements.

All Caucasian subjects enrolled in the IMPAKT-HiP study were invited to return to the study centre for participation in an MRI and dGEMRIC study (27). To be eligible for the dGEMRIC study, subjects had to have completed all IMPAKT-HiP study assessments. Subjects with contraindications to MRI or gadolinium contrast administration were excluded. The study was conducted in accordance with the declaration of Helsinki and subjects gave written, informed consent. The University of British Columba Clinical Research Ethics Board approved the study.

Clinical assessment

At the initial IMPAKT-Hip enrolment, subjects completed an online questionnaire regarding hip pain, medical and surgical history, and they completed a validated questionnaire ascertaining a detailed life-time history of occupational, domestic, sports and leisure physical activity (28), as

well as the Copenhagen Hip and Groin Outcome Score (HAGOS) questionnaire (29). BMI (kg/m^2) was calculated using self-reported height and weight. Subjects underwent radiographs of both hips. In order to identify pain originating from the hip and to avoid causes due to soft tissue injury, hip pain was defined as pain in the groin or upper thigh that either lasted ≥6 weeks or occurred on ≥3 occasions over the past 12 months.

At the dGEMRIC study visit, subjects completed a self-report questionnaire regarding recent hip pain, injury and function, using the HAGOS and the Western Ontario and McMaster Universities (WOMAC VA3.1) Osteoarthritis Index (30). WOMAC questionnaire was scored using visual analog scale. The HAGOS completed at the IMPAKT-HiP enrolment and the dGEMRIC study was used to assess interim changes.

The study hip was determined based on the presence of radiographic FAI at the time of enrollment into the IMPAKT-HiP cohort. If FAI was detected in both or neither hips, then the hip with more severe pain was selected as the study hip. If equal or no hip pain was reported, the study hip was selected at random.

Radiographic assessment

Radiographs of both hips were obtained using a weight-bearing AP view of the pelvis (hip 15° internal rotation) and supine Dunn views (hip 45° flexion, 20° abduction) (31). Radiographs were read manually for alpha angle, lateral center edge angle and cross-over sign by a trained 3rd year medical student. The trained non-radiologist reader had a sensitivity of 0.83 and specificity of 0.87 for correctly diagnosing FAI compared to a fellowship trained musculoskeletal radiologist with over 20 years of experience (31). Intra-rater agreement for the trained medical student

was very good with kappa of 0.72, and a prevalence-adjusted bias-adjusted kappa of 0.76. Additional details of radiograph reading process are provided in a previously published validation study (31).

Cam was defined as an alpha-angle of >55°; pincer was defined as either a lateral center edge angle of >40° or positive cross-over sign (32). Mixed FAI was defined as the presence of both cam and pincer impingements. FAI was defined as the presence of cam, pincer or both.

dGEMRIC assessment

dGEMRIC images were obtained for the study hip on a 3T scanner (Philips Integra) at a single centre. Subjects received intravenous injection of 0.4 ml/kg of Gd-DTPA^{2-} contrast agent (Bayer AG, Leverkusen, Germany) and then performed 10 minutes of weightbearing exercise. Imaging was started 90 minutes after injection.

Imaging parameters for the three dimensional inversion recovery turbo field echo (3D-IR-TFE) sequences in the sagittal plane included: TRtfe/TE/flip angle = 6.1ms/2.9ms/12°, TRshot = 2200ms, TI = 2100, 1200, 600, 250, 105ms, NSA=2 FOV = 180*180mm, matrix: 208 x 209 * (interpolated to 512 x 512), 3mm slice thickness, 15 slices.

Images were analyzed by a trained imaging scientist using a custom written Matlab program. Femoral and acetabular cartilage was manually segmented and $T1_{overall}$ RVs were calculated for the entire hip. Region-specific T1 RVs were then determined for anterior superior ($T1_{AS}$), central superior ($T1_{CS}$) and posterior inferior ($T1_{PI}$) regions, defined based on the Hip OA MRI Scoring System (HOAMS) (33) (Figure 1). Due to the poor visualization of the medial acetabular

rim, the definition of HOAMS regions were modified compared to the original publication (33). The inter-rater repeatability of this analysis (using Intraclass correlation coefficients) for 10 sets of hip FAI dGEMRIC data was 0.96 when compared to another trained imaging scientist, and the intra-rater repeatability of the reader was 0.99. The reader was blinded to both radiographic and clinical data.

Statistical Analyses

All analyses were conducted using Proc Survey procedures in SAS 9.4 to account for sampling design of the study. Sampling weights accounted for non-response and for post-stratification to match the population of a large city (N= 1,016,990). In particular, the sampling weights were adjusted for non-response for the eligible IMPAKT-HiP cohort with age, gender, and hip pain status. The weights were further revised to reflect the age and gender distribution of the population of interest.

Sampling weighted demographic characteristics were assessed using mean and percentage, as appropriate. Proportions of subjects with no FAI, cam, pincer, and mixed FAI were determined. Descriptive results were compared to the parent cohort (n=500) and those who did not participate in the dGEMRIC study (n=372) for representativeness. Sampling weighted descriptive statistics for dGEMRIC $T1_{overall}$ and $T1_{regional}$ RVs were reported as mean and 95% confidence interval (CI).

In our primary analysis, weighted linear regression analysis was used to determine the association of presence of FAI (independent variable) with $T1_{overall}$ RV (dependent variable). In secondary analyses, we assessed the association of each FAI type with $T1_{AS}$, $T1_{CS}$ and $T1_{PI}$ using

weighted linear regression. For secondary analyses, an interaction term was included to assess the effect modification of pincer and cam FAI. All analyses were adjusted for age, gender, and BMI. We repeated the above analyses stratified for hip pain. Statistical significance was defined as $p<0.05$.

Results

Of 500 Caucasian subjects in the IMPAKT-HiP study, 85 (17%) were unable to be contacted, 171 (34%) were not interested, 45 (9%) were ineligible due to MRI contraindications, and 7 (1%) had moved away. Of 182 that agreed to return to the study centre for MRI, 128 agreed to undergo dGEMRIC. The sampling weighted mean age was 38.0 years, mean BMI was 25.5 kg/m^2 and mean WOMAC pain was 8.1. The sampling weighted percent of FAI was 50.8%, including 16.6% with mixed, 13.5% with cam and 20.7% with pincer FAI (Table 1). Descriptive characteristics were similar in the dGEMRIC and the IMPAKT-HiP cohorts, with the exception of a higher proportion of mixed FAI in the dGEMRIC cohort of 16.6% compared to only 10% (left hip) and 8.3% (right hip) in the IMPAKT-HiP cohort. Age, gender, and BMI were similar across all FAI subtypes, with the exception of a lower percentage of females in the cam group (Table 2). Age, sex, BMI and hip pain frequency were similar in the dGEMRIC subjects (n=128) and those who did not participate in the dGEMRIC study (n=372) (Supplemental table 1). There was a higher prevalence of hip pain in the pincer and no FAI groups, whereas cam and mixed FAI has a lower prevalence of hip pain (Table 2). Sampling weighted descriptive T1 results are shown in Figure 2. Mean T1 RVs were generally quite high ranging from 780.9 to 907.6 in the overall analysis. Mean T1 RVs tended to be lower in the mixed FAI group for overall and regional analyses, although considerable variations existed for cam, pincer, and no FAI hips (Figure 2).

Pain assessment using select HAGOS questions showed that the majority of subjects reported improvement or no change between initial assessment in the IMPAKT-HiP study and assessment in the dGEMRIC study (mean = 1.2 years, SD= 0.53). Pain on walking on a hard surface (1-5 scale) improved or remained unchanged in 103 (82.4%) and worsened in 22 (17.6%). Pain severity walking up or downstairs (1-5 scale) improved or remained unchanged in 106 (84.8%), while it worsened in 19 (15.2%). General difficulty with hip and/or groin improved or remained unchanged in 108 (86.4%) and worsened in 17 (13.6%). No interim injuries were reported at the MRI study visit.

We found no statistically significant association between presence of FAI and overall hip T1 (mean difference (MD) =-15.5, 95% CI -77.2, 47.1).

Using weighted linear regression analysis, $T1_{AS}$ was significantly lower in the mixed FAI hips than in no FAI hips (MD =-138.0, 95% CI -213.5, -62.6), cam hips (MD =-208.5, 95% CI -304.7, -112.2) and pincer hips (MD =-116.2, 95% CI -211.6, -20.7) (Figure 3). We found no statistically significant differences in $T1_{AS}$ RVs between cam and no FAI hips (MD =70.5, 95% CI -5.01, 146.5) and between pincer and no FAI hips (MD =-21.9, 95% CI -92.4, 48.7) (Figure 3). There was a significant interaction (P =0.003) between cam and pincer indicating a synergistic effect of cam and pincer FAI on cartilage loss.

$T1_{CS}$ RVs were significantly lower in the mixed FAI hips than in the no FAI hips (MD =-195.8, 95% CI -299.3, -92.3), cam hips (MD =-276.5, 95% CI -415.4, -137.6) and pincer hips (MD =-172.4, 95% CI -290.1, -54.7) (Figure 3). We found no significant differences in $T1_{CS}$ between cam and no FAI hips (MD =80.7, 95% CI -25.1, 186.5), and between pincer and no FAI hips (MD =-

23.4, 95% CI -112.2, 65.5). Similar to the AS region, a significant interaction (P= 0.002) was found between cam and pincer FAI.

In the posterior inferior region, no statistically significant differences were seen for $T1_{PI}$ RVs for mixed FAI hips compared to no FAI hips (MD =-29.2, 95% CI -127.9, 69.3), cam hips (MD =-123.6, 95% CI -267.6, 20.3) or pincer hips (MD =24.0, 95% CI -106.3, 154.3), nor for the comparison of cam versus no FAI hips (MD =94.4, 95% CI -30.6, 219.5), and pincer versus no FAI hips (MD =-53.2, 95% CI -146.6, 40.2) (Figure 3). No significant interaction (P =0.42) was found between cam and pincer FAI in this region.

Stratification by pain status did not substantially change the results, although the statistical significance was reduced for some associations due to smaller sample sizes (Table 3).

In the hip pain stratified group, mixed FAI vs. cam was significant in $T1_{AS}$, $T1_{CS}$ and T_{PI} (P =0.001, 0.002 and 0.005 respectively). Mixed FAI was also observed to be significantly different from pincer in $T1_{AS}$ (p=0.046). Cam vs. no FAI was significant, but it became non-significant in a sensitivity analysis in which one subject with extremely large sampling weight and large T1 RV was excluded. Differences in RVs were not statistically significant between mixed FAI vs. no FAI in all regions of interest.

In the no-hip pain group, significant results were found between mixed FAI vs. cam FAI in $T1_{AS}$ (P =0.002) and in $T1_{CS}$ (P =0.002). Furthermore, significant differences in cartilage content were also found between Mixed FAI vs. no FAI in $T1_{AS}$ (P =0.005) and $T1_{CS}$ (P =0.012). There were no statistically significant comparisons in $T1_{PI.}$

Discussion

In this population-based cohort of young adults with and without hip pain, we found no statistically significant association of FAI with $T1_{overall}$ dGEMRIC RVs. In region-specific analyses, mixed FAI was significantly associated with reduced T1 RVs in anterior superior and central superior regions compared to those with no FAI and compared to those with only cam or only pincer FAI. No significant differences were seen in T1 RVs in those with cam or pincer FAI compared to those without FAI in any of the three regions analyzed.

Our finding of an overall cam FAI prevalence of 30.2% (the sum of the isolated cam FAI prevalence of 13.6% and mixed FAI prevalence of 16.6%) is in the range of cam FAI prevalence reported in the literature. Hack et al. (8) reported a cam prevalence of 34% in a cohort of 200 asymptomatic volunteers in Canada (mean age =29, range 21-51 years). Gosvig et al. (7) conducted a cross-sectional radiographic assessment of 3202 symptomatic and asymptomatic subjects in Denmark (mean age =60, range 22-90 years). Using an alpha angle cutoff of 57^0 in females, cam prevalence was determined to be 3.5%. Compared to the estimated female cam prevalence of 19.2% in the current study, Gosvig et al. applied more strict exclusion criteria, such that subjects with various past or current hip diseases were excluded. Thus, selecting for a healthier cohort will lead to decreased rates in cam FAI detection. In a meta-analysis reported by Vasco et al.(34), the mixed prevalence was determined to be 8.8 ±5.1% in the asymptomatic population and 40.2 ±18.0% in the symptomatic population. With the inclusion of both symptomatic and asymptomatic subjects, the mixed prevalence of 16.6% in the current study falls within the above range.

Our finding that there was no statistically significant association between FAI and dGEMRIC $T1_{overall}$ RVs is inconsistent with some previous studies. Zilkens et al. (35) reported a statistically significant decrease in hip joint dGEMRIC T1 RVs. Mean T1 RVs ranged from 476.7±125.2ms to 349.4±123.7ms in symptomatic patients. Asymptomatic volunteers had mean T1 RVs that

ranged from 595.1±134.5ms to 463.8±45.9ms. Zilkens et al used a small sample of volunteers of 35 symptomatic FAI patients (mean age 32.8±10.2 years) and compared to asymptomatic volunteers with a much lower mean age (mean age: 24.5±1.8 years). Using dGEMRIC, Mamisch et al. (16) recruited 6 symptomatic cam FAI patients (mean age =33, range =17-43), 7 symptomatic pincer patients (mean age =36.29, range =22-49) and 12 asymptomatic volunteers (mean age =25.25, rage =23-31). Mean T1 RVs was 643.3 (range =297.9-775.4) for asymptomatic controls, 488.13 (range =297.9-775.4) for the cam group, and 462.0 (range =300.8-640.7) for the pincer group. Statistically significant decreases for both cam and pincer groups were detected compared to the control group ($P < 0.00001$ and $P < 0.00001$, respectively). Compared to these previous studies, the current study used a population-based, randomly recruited cohort. Furthermore, these previous studies compared symptomatic FAI patients against asymptomatic volunteers, whereas the current study compared subjects based strictly on radiographic findings of FAI. We may have identified subjects at an earlier stage of cartilage degeneration in which GAG content has not yet substantially decreased, as evidenced by our high mean T1 RVs, compared to the patient cohorts in the above-mentioned studies, who may be at a later stage of cartilage degeneration.

Our finding that cartilage damage associated with FAI, when found, was isolated to certain regions is in agreement with previous studies. Mamisch et al. (16) found cartilage degradation that was concentrated centrally in the anterior portion. Bittersohl et al. (18) compared T1 RVs in 26 young symptomatic FAI patients to 10 asymptomatic volunteers using 1.5T dGEMRIC. They found a significant decrease in T1 in the anterior to superior portion of cam hips ($P =< 0.05$). Similarly, Domayer et al. (36) assessed 20 FAI cases retrospectively (mean age =29.6 ±11.7, range =15-52) using dGEMRIC and found localized decrease of T1 in the anterior superior quadrant compared to other regions. We did not, however, find the pattern of cartilage damage in the posterior inferior region with pincer type deformities that has been previously

reported (37). It has been proposed that in pincer FAI, the persistent contact and deepening of the acetabulum may cause chondral damage to the posterior aspect of the femoral head, known as the "contre-coup" mechanism (3). It is possible that many of the cases of pincer impingement in our study had not yet progressed to cartilage degeneration.

A number of longitudinal studies reported an association between FAI and development of hip OA (5, 6, 38). The Chingford study investigated the relationship between hip deformities and 19-year risk of total hip arthroplasty in a cohort of 1003 females (age 44 -67)(6). Results showed a positive association between cam FAI and hip OA requiring THA (P=0.001). The current study shows that cartilage damage does not result from cam nor pincer alone, but from a combination of both. This difference in findings can be explained by the cross-sectional design of the current study and the difference in the subject characteristics, such that the former study used an older and all female cohort. To the best of our knowledge, no longitudinal study to date has investigated mixed FAI and its outcomes.

Region specific analyses at the anterior superior and central superior regions showed an interaction effect between cam and pincer type impingements. This may cause GAG content to decrease significantly in subjects with mixed types FAI compared to either cam or pincer FAI alone. Similar effects were not seen in the posterior inferior region. To the best of our knowledge, there is no existing literature that reported such effects in mixed FAI.

In our hip pain stratification analysis, a decrease in cartilage content was observed in mixed FAI, compared to other types of FAI or no FAI in certain regions in the hip pain and also in the no hip pain group. Our findings are supported by previous studies reporting poor associations

between pain and radiographic measures of OA in other joints (39), including Gosvig et al. (7), who did not find significant correlation between cam FAI and hip pain.

One current limitation is the cross-sectional nature of the study. We are unable to determine whether subjects with FAI will progress to radiographic hip OA in the future. Similarly, we could not determine whether mixed-type FAI detected in our subjects were preceded by the progression of a pre-existing cam or pincer impingement. It is also not clear whether low dGEMRIC T1 RVs ultimately lead to radiographic OA. A longitudinal follow-up study is needed to further elucidate the clinical course of FAI. Another limitation is the use an alpha angle of >55° to define presence of cam FAI. A much stronger association between cam and no FAI would have been elicited if a more strict definition of alpha angle was applied (i.e. alpha angle >70°). However, significant results were found in the regional analysis despite the less strict definition, suggesting the strong validity of the current study. In the hip pain stratified analysis, we had a small number of subjects in the pain group, which may have limited our power to detect weaker associations. Lastly, this study was restricted to a Caucasian population. The prevalence of FAI and its association with regional dGEMRIC RVs may vary in other ethnic groups.

A major strength of this study is the recruitment through random population sampling of the parent cohort and application of population weights to ensure generalizability of results. As such, findings from this study provide a realistic estimate of the expected prevalence of FAI and mean dGEMRIC RVs in the Caucasian population residing within a major city.

In summary, in this population-based study of young adults with and without hip pain, we found no association of FAI with total hip T1 dGEMRIC RV. We found significantly lower dGEMRIC RVs in the anterior superior and central superior regions for mixed FAI, but no significantly reduced

regional T1 RVs for isolated cam or pincer FAI. These results indicate that the presence of cam or pincer impingements alone does not suggest the beginning of cartilage degeneration. In contrast, the presence of a combination of both cam and pincer impingement is a risk factor for early cartilage damage, assessed on dGEMRIC.

Reference

1. Banerjee P, McLean CR. Femoroacetabular impingement: a review of diagnosis and management. Curr Rev Musculoskelet Med. 2011;4(1):23-32.

2. Wilson AS, Cui Q. Current concepts in management of femoroacetabular impingement. World J Orthop. 2012;3(12):204-11.

3. Ganz R, Parvizi J, Beck M, Leunig M, Notzli H, Siebenrock KA. Femoroacetabular impingement - A cause for osteoarthritis of the hip. Clinical Orthopaedics and Related Research. 2003(417):112-20.

4. Wagner S, Hofstetter W, Chiquet M, Mainil-Varlet P, Stauffer E, Ganz R, et al. Early osteoarthritic changes of human femoral head cartilage subsequent to femoro-acetabular impingement. Osteoarthritis Cartilage. 2003;11(7):508-18.

5. Gregory JS, Waarsing JH, Day J, Pols HA, Reijman M, Weinans H, et al. Early identification of radiographic osteoarthritis of the hip using an active shape model to quantify changes in bone morphometric features: can hip shape tell us anything about the progression of osteoarthritis? Arthritis Rheum. 2007;56(11):3634-43.

6. Nicholls AS, Kiran A, Pollard TCB, Hart DJ, Arden CPA, Gill T, et al. The Association Between Hip Morphology Parameters and Nineteen-Year Risk of End-Stage Osteoarthritis of the Hip A Nested Case-Control Study. Arthritis and Rheumatism. 2011;63(11):3392-400.

7. Gosvig KK, Jacobsen S, Sonne-Holm S, Gebuhr P. The prevalence of cam-type deformity of the hip joint: a survey of 4151 subjects of the Copenhagen Osteoarthritis Study. Acta Radiol. 2008;49(4):436-41.

8. Hack K, Di Primio G, Rakhra K, Beaule PE. Prevalence of Cam-Type Femoroacetabular Impingement Morphology in Asymptomatic Volunteers. Journal of Bone and Joint Surgery-American Volume. 2010;92A(14):2436-44.

9. Byrd JW, Jones KS. Arthroscopic management of femoroacetabular impingement in athletes. Am J Sports Med. 2011;39 Suppl:7S-13S.

10. Ito K, Minka-Ii MA, Leunig M, Werlen S, Ganz R. Femoroacetabular impingement and the cam-effect - A MRI-based quantitative anatomical study of the femoral head-neck offset. Journal of Bone and Joint Surgery-British Volume. 2001;83B(2):171-6.

11. Dorrell JH, Catterall A. The torn acetabular labrum. J Bone Joint Surg Br. 1986;68(3):400-3.

12. Klaue K, Durnin CW, Ganz R. The acetabular rim syndrome. A clinical presentation of dysplasia of the hip. J Bone Joint Surg Br. 1991;73(3):423-9.

13. Burstein D, Bashir A, Gray ML. MRI techniques in early stages of cartilage disease. Invest Radiol. 2000;35(10):622-38.

14. Maroudas AI. Balance between swelling pressure and collagen tension in normal and degenerate cartilage. Nature. 1976;260(5554):808-9.

15. Maroudas A, Venn M. Chemical composition and swelling of normal and osteoarthrotic femoral head cartilage. II. Swelling. Ann Rheum Dis. 1977;36(5):399-406.

16. Mamisch TC, Kain MS, Bittersohl B, Apprich S, Werlen S, Beck M, et al. Delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) in Femoacetabular impingement. J Orthop Res. 2011;29(9):1305-11.

17. Lattanzi R, Petchprapa C, Ascani D, Babb JS, Chu D, Davidovitch RI, et al. Detection of cartilage damage in femoroacetabular impingement with standardized dGEMRIC at 3 T. Osteoarthritis and Cartilage. 2014;22(3):447-56.

18. Bittersohl B, Steppacher S, Haamberg T, Kim YJ, Werlen S, Beck M, et al. Cartilage damage in femoroacetabular impingement (FAI): preliminary results on comparison of standard diagnostic vs delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC). Osteoarthritis and Cartilage. 2009;17(10):1297-306.

19. Pollard TCB, McNally EG, Wilson DC, Wilson DR, Madler B, Watson M, et al. Localized Cartilage Assessment with Three-Dimensional dGEMRIC in Asymptomatic Hips with Normal Morphology and Cam Deformity. Journal of Bone and Joint Surgery-American Volume. 2010;92A(15):2557-69.

20. Cunningham T, Jessel R, Zurakowski D, Millis MB, Kim YJ. Delayed gadolinium-enhanced magnetic resonance imaging of cartilage to predict early failure of Bernese periacetabular osteotomy for hip dysplasia. J Bone Joint Surg Am. 2006;88(7):1540-8.

21. Kim YJ, Jaramillo D, Millis MB, Gray ML, Burstein D. Assessment of early osteoarthritis in hip dysplasia with delayed gadolinium-enhanced magnetic resonance imaging of cartilage. J Bone Joint Surg Am. 2003;85-A(10):1987-92.

22. McKenzie CA, Williams A, Prasad PV, Burstein D. Three-dimensional delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5T and 3.0T. J Magn Reson Imaging. 2006;24(4):928-33.

23. Beck M, Kalhor M, Leunig M, Ganz R. Hip morphology influences the pattern of damage to the acetabular cartilage - Femoroacetabular impingement as a cause of early osteoarthritis of the hip. Journal of Bone and Joint Surgery-British Volume. 2005;87B(7):1012-8.

24. Allen D, Beaule PE, Ramadan O, Doucette S. Prevalence of associated deformities and hip pain in patients with cam-type femoroacetabular impingement. J Bone Joint Surg Br. 2009;91(5):589-94.

25. Reichenbach S, Juni P, Werlen S, Nuesch E, Pfirrmann CW, Trelle S, et al. Prevalence of Cam-Type Deformity on Hip Magnetic Resonance Imaging in Young Males: A Cross-Sectional Study. Arthritis Care & Research. 2010;62(9):1319-27.

26. Dickenson E, Wall PD, Robinson B, Fernandez M, Parsons H, Buchbinder R, et al. Prevalence of cam hip shape morphology: a systematic review. Osteoarthritis Cartilage. 2016;24(6):949-61.

27. Kopec JA, Cibere J, Li LC, Zhang C, Barber M, Qian H, et al. Relationship between physical activity and hip pain in persons with and without cam or pincer morphology: a population-based case-control study. Osteoarthritis Cartilage. 2017;25(7):1055-61.

28. De Vera MA, Ratzlaff C, Doerfling P, Kopec J. Reliability and validity of an internet-based questionnaire measuring lifetime physical activity. Am J Epidemiol. 2010;172(10):1190-8.

29. Thorborg K, Holmich P, Christensen R, Petersen J, Roos EM. The Copenhagen Hip and Groin Outcome Score (HAGOS): development and validation according to the COSMIN checklist. Br J sports Med. 2011;45(6):478-91.

30. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15(12):1833-40.

31. Ratzlaff C, Zhang C, Korzan J, Josey L, Wong H, Cibere J, et al. The validity of a non-radiologist reader in identifying cam and pincer femoroacetabular impingement (FAI) using plain radiography. Rheumatol Int. 2015.

32. Tannast M, Siebenrock KA, Anderson SE. Femoroacetabular impingement: Radiographic diagnosis - What the radiologist should know. American Journal of Roentgenology. 2007;188(6):1540-52.

33. Roemer FW, Hunter DJ, Winterstein A, Li L, Kim YJ, Cibere J, et al. Hip Osteoarthritis MRI Scoring System (HOAMS): reliability and associations with radiographic and clinical findings. Osteoarthritis and Cartilage. 2011;19(8):946-62.

34. Mascarenhas VV, Rego P, Dantas P, Morais F, McWilliams J, Collado D, et al. Imaging prevalence of femoroacetabular impingement in symptomatic patients, athletes, and asymptomatic individuals: A systematic review. Eur J Radiol. 2016;85(1):73-95.

35. Zilkens C, Miese F, Kim YJ, Hosalkar H, Antoch G, Krauspe R, et al. Three-dimensional delayed gadolinium-enhanced magnetic resonance imaging of hip joint cartilage at 3 T: A prospective controlled study. European Journal of Radiology. 2012;81(11):3420-5.

36. Domayer SE, Mamisch TC, Kress I, Chan J, Kim YJ. Radial dGEMRIC in developmental dysplasia of the hip and in femoroacetabular impingement: preliminary results. Osteoarthritis and Cartilage. 2010;18(11):1421-8.

37. Pfirrmann CWA, Mengiardi B, Dora C, Kalberer F, Zanetti M, Hodler J. Cam and pincer femoroacetabular impingement: Characteristic MR arthrographic findings in 50 patients. Radiology. 2006;240(3):778-85.

38. Agricola R, Heijboer MP, Bierma-Zeinstra SMA, Verhaar JAN, Weinans H, Waarsing JH. Cam impingement causes osteoarthritis of the hip: a nationwide prospective cohort study (CHECK). Annals of the Rheumatic Diseases. 2013;72(6):918-23.

39. Hunter DJ, Guermazi A, Roemer F, Zhang Y, Neogi T. Structural correlates of pain in joints with osteoarthritis. Osteoarthritis Cartilage. 2013;21(9):1170-8.

Table 1 – Sampling weighted demographics and clinical characteristics of the study population

	All	Female (n= 85)	Male (n= 43)
Age (years)	38.0 (35.2, 40.9)	38.2(34.6, 41.9)	37.8 (33.5, 42.2)
BMI (kg/m^2)	25.5 (24.0, 26.9)	25.5 (23.7, 27. 4)	25.4 (23.2, 27.6)
WOMAC, pain (0-100)	8.1 (4.1, 12.2)	6.9 (3.7, 10.2)	9.4 (1.7, 17.0)
Hip pain (%)	28.0 (15.9, 40.1)	29.4 (12.6, 46.3)	26.4 (9.3, 43.5)
Mixed FAI (%)	16.6 (1.7, 31.5)	12.3 (0, 28.7)	21.2 (0, 45.9)
Cam FAI (%)	13.5 (5.3, 21.7)	6.9 (0, 15.1)	20.6(5.6,35.5)
Pincer FAI (%)	20.7 (9.0, 32.3)	24.1(6.7, 41.4)	17.0 (2.2, 31.9)
No FAI (%)	49.2 (33.7, 64.7)	56.8 (37.0, 76.6)	41.2 (16.9, 65.5)

One hip per subject (index hip)

Values are means, unless otherwise indicated, and 95% confidence interval.

Based on the dGEMRIC samples (n=128), with sampling weights applied.

Table 2 – Sampling weighted demographics of the study population by FAI subtype

	Mixed FAI (n=10)	Cam FAI (n=20)	Pincer FAI (n=31)	No FAI (n=67)
Age (years)	31.6 (26.0, 37.2)	44.1 (40.6, 47.7)	37.8 (33.1, 42.5)	38.6 (34.8, 42.5)
Female (%)	38.0 (0, 85.8)	26.1 (0, 53.4)	59.8 (30.5, 89.2)	59.3 (37.0, 81.5)
BMI (Kg/m^2)	23.7 (21.4, 26.1)	25.9 (23.9, 28.0)	25.5 (23.6, 27.5)	25.9 (23.4, 28.5)
Hip Pain (%)	12.5 (0, 31.5)	21.7 (0.58, 42.8)	27.8 (4.6, 51.1)	34.9 (15.6, 54.3)

Values are means, unless otherwise indicated, and 95% confidence interval

Based on the dGEMRIC Samples (N=128), with sampling weights applied

Table 3 – Association of FAI with T1 relaxation values using weighted linear regression analysis stratified by pain.

	Interaction term	Mixed vs. no FAI [MD (95% CI)]	Mixed vs. Cam [MD(95% CI)]	Mixed vs. pincer [MD (95% CI)]	Cam vs. no FAI [MD (95% CI)]	Pincer vs. no FAI [MD (95% CI)]
Hip Pain Group						
Anterior Superior	P = 0.006	-113.3 (-252.6, 26.1) P=0.11	-254.3 (-397.3, -111.4) P=0.001	-142.5 (-282.4, -2.6) P=0.046	141.1* (17.5, 264.6) P=0.03	29.3 (-100.6, 159.1) P=0.66
Central Superior	P = 0.009	-153.3 (-336.5, 30.0) P=0.10	-312.7 (-507.7, -117.6) P=0.002	-164.4 (-354.4, 25.6) P=0.09	159.4* (32.1, 286.6) P=0.01	11.1 (-116, 138.5) P=0.86
Posterior Inferior	P = 0.006	-109.4 (-255.6, 36.8) P=0.14	-420.9 (-712.3, -129.5) P=0.005	-181.1 (-331.1, -31.0) P=0.02	311.5* (30.5, 592.5] P=0.03	71.7 (-86.9, 230.3) P=0.37
No-hip pain Group						
Anterior Superior	P = 0.048	-138.7 (-234.1, -43.4) P=0.005	-190.2 (-310.4, -69.9] P=0.002	-97.1 (-215.7, 21.5) P=0.11	51.4 (-32.9, 135.7) P=0.23	-41.6 (-126, 43.1) P=0.33
Central Superior	P = 0.02	-214.9 (-346.3, -83.4) P=0.002	-269.4 (-436.9, -102.0) P=0.002	-171.2 [-321.3, -21.1) P=0.03	54.6 (-57.3, 166.4) P=0.34	-43.6 (-156.9, 69.6) P=0.45
Posterior Inferior	P = 0.52	-14.6 (-131.2, 102.0) P=0.81	-42.7 (-196.6, 111.2) P=0.58	86.2 (-58.1, 230.5) P=0.24	28.1 (-87.0, 143.2) P=0.63	-100.8 (-206.8, 5.3) P=0.06

MD = Mean Difference

FAI = Femoroacetabular Impingement

CI = Confidence Interval

Interaction term = A synergistic effect between cam and pincer FAI, such that the presence of both leads to increased cartridge damage, more than that of expected in an additive effect.

* Analyses became nonsignificant in a sensitivity analysis in which one subject with extremely large sampling weights and large T1 RV was excluded.

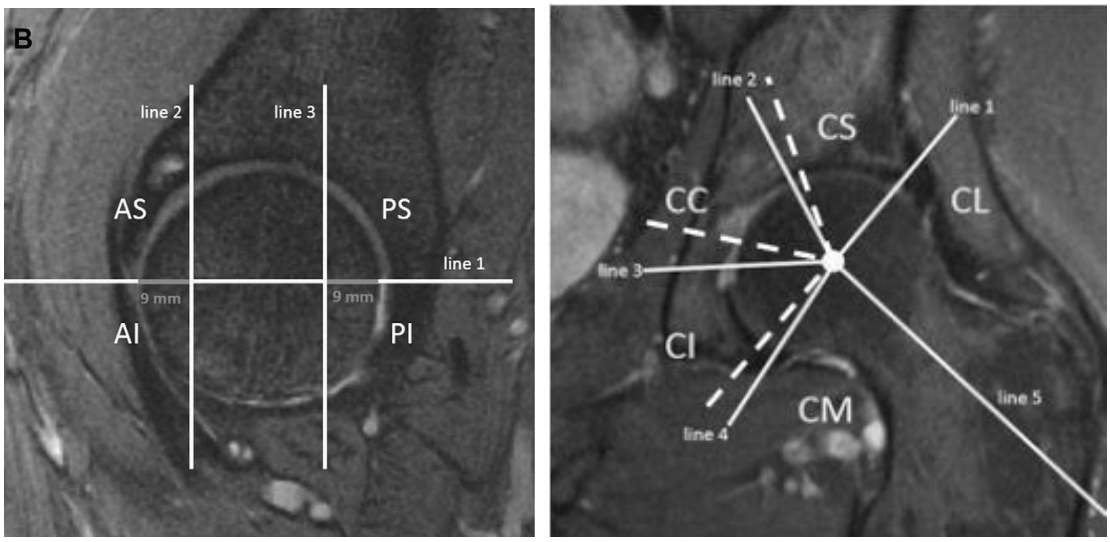

Fig. 1 – Definition of HOAMs regions in sagittal and coronal scans - Solid lines indicates the original coronal HOAMs. Dashed lines indicates the modified definition of HOAMs

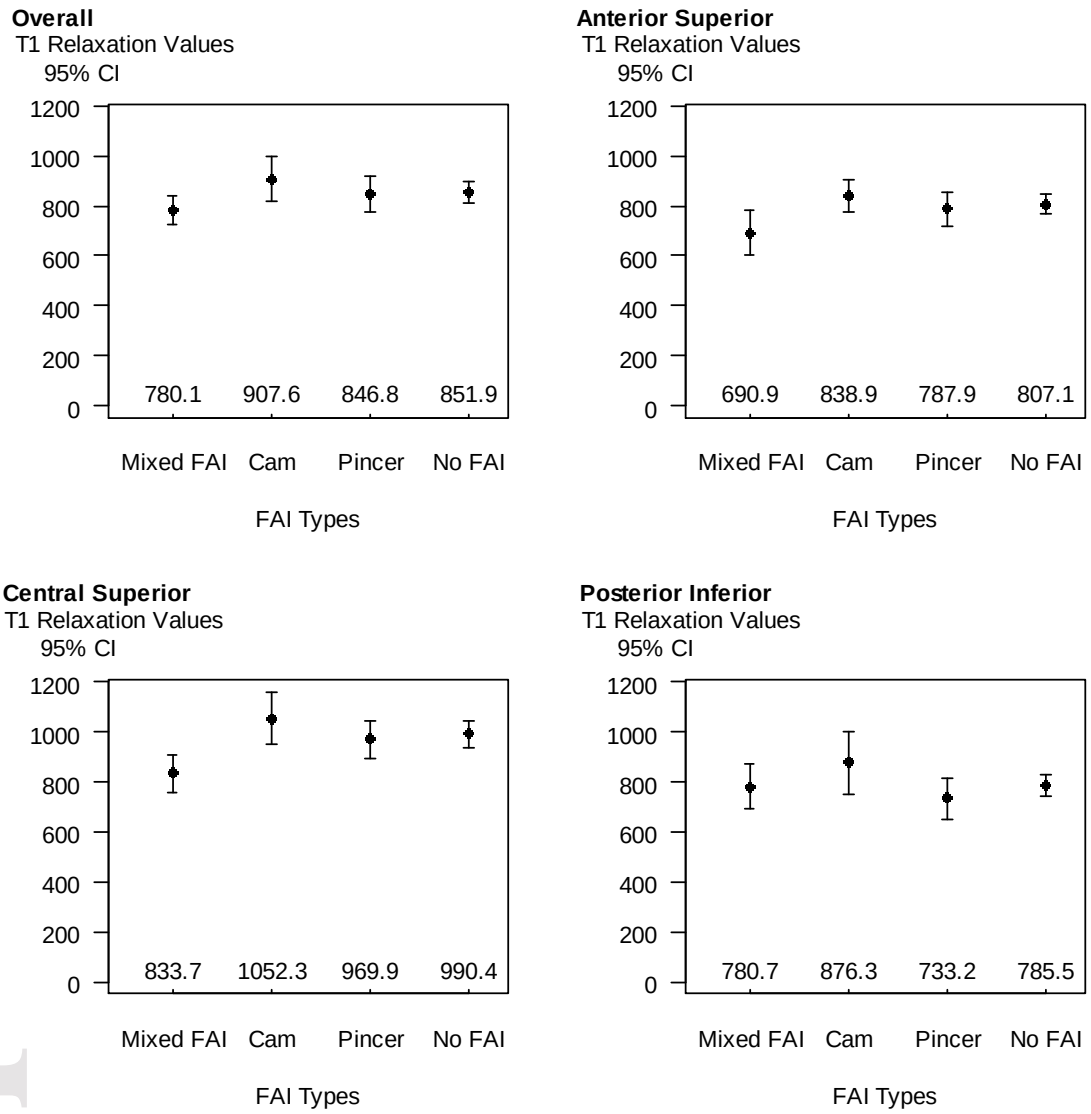

Fig. 2 -Region specific dGEMRIC T1 relaxation values for mixed, cam, pincer and no FAI subgroups

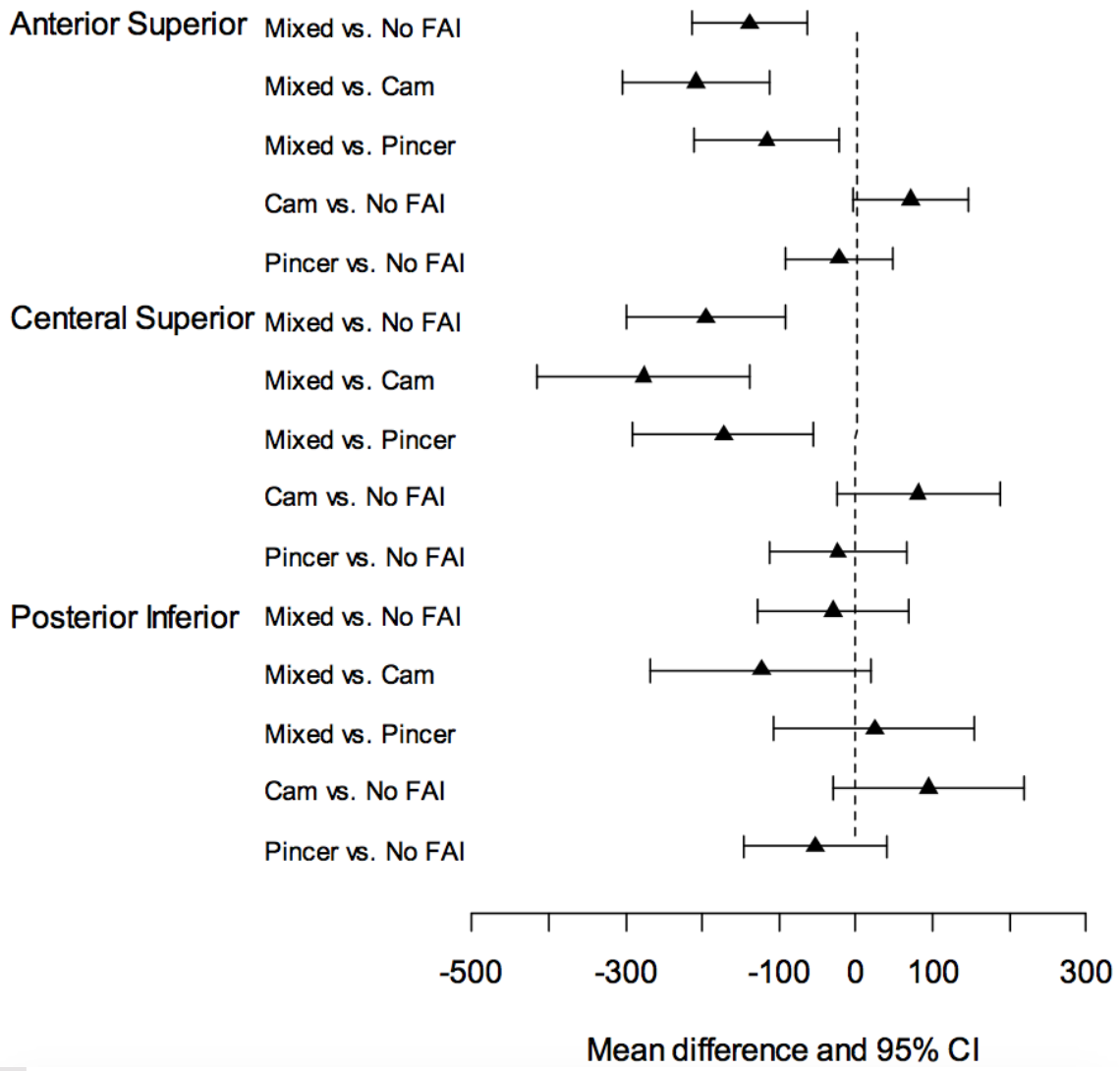

Fig. 3 – Association of FAI with T1 relaxation values using weighted linear regression analysis.

FAI = Femoroacetabular Impingement