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Poor Sensitivity of Magnetic Resonance Arthrography to Detect Hip Chondral Delamination: A Retrospective Follow-Up of 227 FAI-Operated Patients

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Abstract

Objective. The purpose of this study was to retrospectively assess the frequency and characteristics of acetabular cartilage delamination (CD) in femoroacetabular impingement (FAI) patients and to assess the sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of magnetic resonance arthrography (MRA) in detecting CD based on the radiologist report. *Design*. This is a single-center retrospective review of consecutive patients operated for symptomatic FAI. All of the patients had a 1.5-T MR-arthrogram within 12 months preoperatively. MRA reports of these patients were compared with operation notes and surgical videos of all patients by two trained assessors. *Results*. At surgery, CD of the acetabulum was present in 169 patients out of a total of 229 patients (74%). Only 6.5% (11 patients) of CD was described on the MRA reports preoperatively. The mean age of the patients was 37.6 $\pm$ 13.3 years. The average extent of delamination was 3.12 $\pm$ 1.5 cm^2 with a mean coronal $\times$ sagittal extent of 0.68 $\times$ 4.33 cm. There was a significant difference regarding age ($P = 0.002$), alpha angle from frog view ($P = 0.002$), and alpha angle from anteroposterior view ($P = 0.012$) between the patients with delamination and without delamination. The majority of labral tears and cartilage damage were located in the anterosuperior quadrant. MRA sensitivity was 6%, specificity 98%, NPV 27%, and PPV 91% based on the radiologist report. *Conclusion*. The CD in patients with FAI can be severely underdiagnosed with MRA. There is a need for better standard diagnostic criteria to detect CD in patients with FAI.

Keywords

cartilage delamination, magnetic resonance arthrography, epidemiology, diagnostic value

Introduction

Delamination of the acetabular cartilage is commonly presented in patients suffering from femoroacetabular impingement (FAI). The reported incidence in the literature varies from 31.5% to 86.5%.[1-6] It occurs between the cartilage and the subchondral plate, with or without disruption of the cartilage surface.[7] These lesions are often associated with different abnormalities in the hip such as labral injuries and cam deformities.[8]

The detection of articular cartilage involvement in FAI is important and has a direct relationship to surgical outcomes.[9] Early surgical intervention may prevent cartilage loss and development of osteoarthritis, if performed before the onset of cartilage breakdown. On the other hand, in patients with advanced cartilage damage, joint-preserving surgical procedures may no longer be possible.[10] Preoperative evaluation of the cartilage is therefore important for the hip surgeon in planning joint-preserving treatment options to delay early hip osteoarthritis.[11]

The findings and diagnostic performance of magnetic resonance arthrography (MRA) in acetabular cartilage delamination (CD) are largely unknown because there are only a few and contradicting reports on this subject in the literature. There is no consensus in regard to the accuracy of MRA in the detection of cartilage lesions in FAI patients. The MRA has been referred to be the gold standard of diagnosis with a high sensitivity 97% and specificity 84% for

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CD.[12] However, several studies showed poor sensitivity and specificity for cartilage lesions of the femoral head and the acetabulum due to the limited joint distensibility.[1,2,5]

There is a need for better understanding of the epidemiology of hip CD in FAI patients and the pathological characteristics which may contribute to the development of substantial cartilage damage in order to establish appropriate treatment guidelines.[13] Furthermore, the diagnostic accuracy of MRA should be further investigated in order to be able to identify this "hidden enemy" in FAI patients. Thus, the purpose of our study was to assess the diagnostic accuracy of MRA for the detection of acetabular CD in FAI patients based on the radiologist reports in our center and to report the characteristics of CD on intraoperative and imaging findings in FAI patients.

Methods

This is a single-center, retrospective review of 229 hips in 227 Canadian consecutive patients operated for symptomatic FAI. All patients underwent a standard radiographic preoperative assessment protocol that included anteroposterior (AP), frog leg lateral, and false profile views. Computed tomography (CT) scans included standard axial, sagittal, and coronal reformatted views. Three-dimensional CT images were also used in order to identify and characterize the extent of the bony morphology. A preoperative 1.5-T MR-arthrogram was also performed for all patients.

After ethical approval from the institutional review board of the local health authority, all demographic data were collected; preoperative radiographs, CT and MRA scans, arthroscopic video recordings, patients' charts, and radiologist reports of the MR-arthrograms. The radiological reports of the MRA were reviewed independently by two orthopedic surgeons (GK, IW) with sports medicine fellowships and advanced training. From these sources, the FAI bone and soft tissue pathological findings were documented. Similarly, the MRA reports of CD were compared with operative notes and surgical videos for all patients. Findings at surgery served as the reference standard. The sensitivity, specificity, accuracy, negative predictive value (NPV), and positive predictive value (PPV) of MRA for CD in FAI patients was calculated based on the radiological report.

Patients were included if they (a) had hip arthroscopy for symptomatic FAI and (b) had a diagnostic MR-arthrogram within 12 months of surgery with a radiological report that described the acetabular cartilage status. On the other hand, patients were excluded if they had (a) revision surgery, (b) previous hip pathologic conditions, (c) presence of local or systemic infection, or if (d) the original record of intraoperative findings was absent.

The indication for arthroscopic treatment was intra-articular hip pain for more than 6 months that did not improve with physiotherapy or medication. All of our patients had a positive labral tear on the MR-arthrogram of their hip and significant restriction of their activity level. At times there were differences between imaging findings of FAI and the location of symptoms. To confirm an intra-articular source of symptoms and to exclude extra-articular pathologies, a diagnostic ultrasound-guided intra-articular injection was performed preoperatively using local anesthetic.

The magnetic resonance imaging (MRI) was performed with a Siemens 1.5-T Symphony MRI scanner (Erlangen, Germany). All hips under investigation were injected with an anterior approach using ultrasound guidance under sterile conditions. Initially, the femoral neck was localized, and the needle was inserted intra-articularly. The position of the needle was confirmed with the injection of 3 mL of non-ionic iodinated contrast medium. Next, 10 to 20 mL of gadolinium saline solution at a 1:100 dilution was injected in the joint. The spine and body array coils were used for the axial, coronal, and sagittal fat-saturated hip images with repetition time (TR) and echo time (TE) being 630 and 12 ms respectively; 512 × 512 and 256 × 256 matrices for coronal and axial–sagittal images, respectively; 3-mm slice thickness and two interleaved excitations with use of a 200-mm field of view. T2-weighted (fast spin-echo, TR/TE, 2,000-2,500/60-80; field of view, 14-16) images with fat saturation were also used.

Statistical Analysis

SPSS version 24 was used for statistical analysis. Descriptive statistics (mean, standard deviation [SD], and range) were calculated. Two-tailed independent 2-sample *t*-tests were performed at 95% confidence intervals. Moreover, sensitivity, specificity, PPV, and NPV were calculated to assess the diagnostic accuracy of MRA for detecting CD.

Results

Our cohort included 227 patients with 229 hips that underwent arthroscopic surgery for symptomatic FAI between June 2012 and June 2013 (mean ± SD age at surgery of 37.77 ± 13.26). Of these consecutive hips, 109 were from male patients and 120 were from females with mean age of 38.04 (SD± 12.75) and 37.53(SD ±13.75) years, respectively. The majority were left hips (55.9%). The mean ± SD body mass index of the patients at the time of surgery was 26.3 ± 5.2 kg/m^2. Patients were symptomatic for 42.0 ± 38.8 months before surgery (**Table 1**).

All patients in our study during the time of surgery had a labral tear. Psoas release was performed in 77.7%. None of the patients were diagnosed with hip osteoarthritis preoperatively. The mean hip joint space on the AP view was 4.5 ± 0.9 mm. In 38.4% of patients, there were subchondral cystic lesions either in the acetabulum or in the acetabular

Table 1. Summary of Main Demographic Variables and FAI Pathomorphological Characteristics.

Variables	Values
Total no. of patients/hips (n/n)	227/229
Male, n (%)	109 (47.6)
Female, n (%)	120 (52.4)
Right side, n (%)	101 (44.1)
Left side, n (%)	128 (55.9)
Age at surgery, years, mean ± SD	37.8 ± 13.3
Body mass index, kg/m^2, mean ± SD	26.3 ± 5.2
Duration of symptoms, months, mean ± SD	42.0 ± 38.8
Delamination presence, n (%)	169 (73.84)
Male (%)	87 (51.5)
Female (%)	82 (48.5)
Right side (%)	68 (40.2)
Left side (%)	101 (60.8)
Delamination size, cm^2, mean ± SD	3.12 ± 1.5
Joint space, mm, mean ± SD	4.5 ± 0.9
Alpha angle frog view, deg, mean ± SD	53.2 ± 15.8
Alpha angle AP view, deg, mean ± SD	58.4 ± 20.0
LCEA, deg, mean ± SD	34.3 ± 8.1

AP = anteroposterior; FAI, femoroacetabular impingement; LCEA = lateral center edge angle; SD = standard deviation.

rim; which could indicate some localized cartilage damage. With regard to the FAI characteristics of our sample, exclusively cam or pincer pathomorphology was present in 10.0% and 18.3% of all cases, respectively. Mixed type FAI was present in 67.7% of cases. The mean alpha angle from the frog leg and AP X-ray views were 53.2° ± 15.8° and 58.4° ± 20.0°, respectively. Finally, patients underwent an MR-arthrogram on average 8.4 ± 3.5 months before surgery (**Table 1**).

Cartilage delamination was present in 73.8% of our sample. Male and female patients presented CD at 51.5% and 48.5%, respectively. Cartilage delamination was more common on the left hips (60.8%) in comparison with the right hips (40.2%). The mean size of CD based on the measurements intraoperatively was 3.12 ± 1.5 cm^2 with a mean coronal × sagittal extent of 0.68 cm × 4.33 cm (**Tables 1** and **2**). In most of the cases, the location of the CD was at the anterosuperior quadrant of the acetabular rim between 2.6 o'clock and 11.9 o'clock position. The mean patient age of the delamination and nondelamination patient group was 39.4 ± 13.0 and 33.2 ± 12.8 years, respectively. Both patient groups had similar mean waite times for surgery and similar mean lateral center edge angles (LCEA; 33.7° ± 8.1° and 35.9° ± 8.0°, respectively). The cam deformity measured by the alpha angle was larger on the sagittal and coronal level in the delamination group. The mean joint space on the AP weightbearing pelvic view was similar in both groups of patients. A significant difference was seen regarding age ($P = 0.002$), alpha angle frog view ($P = 0.002$), and alpha angle AP view ($P = 0.012$) between the delamination and non delamination group. (Table 2).

Based on the radiologist report for CD, the sensitivity of an MR-arthrogram result positive for delamination for patients with described delamination during arthroscopic surgery was 6%. The specificity of an MR-arthrogram accurately reporting no delamination was 98%. A patient with an MR-arthrogram describing CD (according to the MRA report) had a 91% chance of having delamination found intraoperatively. Conversely, a patient with an MRA report not reporting CD had a 27% chance of not having delamination as an intraoperative finding. The overall prognostic accuracy of MRA in our series was 30% (**Table 3**).

Further analysis of the detection of CD by MRA, based on the size of the cartilage lesion, showed low sensitivity and NPV while the specificity and PPV of MRA were high (**Table 4**).

Discussion

According to our study, CD in patients undergoing surgery for FAI is a common finding. The incidence of CD in our case series of 229 hips (mean age 37.7 years) was 73.8%. There are contradicting prevalence rates of CD in the literature ranging from 31.5% to 86.5%.[1-6] Fontana *et al*.[2] reported the lowest incidence (31.5%) in a sample of 359 patients with a mean age 38.8 years. Anderson *et al*.[1] reported an incidence of 44% in a sample of 64 hips with a mean age of 28 years. A higher percentage (52%) was reported by Pfirrmann *et al*.[5] in a series of 130 hips with mean patient age of 30.7 years. Johnston *et al*.[3] reported 79% CD in 82 hips with a mean age of 25 years. An article coming from the Swedish registry reported 53% CD in 606 hips and a mean patient age of 36.6 years.[6] Our findings are more in accordance with a recent publication coming from the Danish registry (86.5%) in 2000 patients who underwent arthroscopic FAI surgery (mean age 37.5 years).[4]

The variation of CD incidence between patient cohorts could be explained by differences in demographic and FAI characteristics of each group. CD is known to be positively associated with increased age, male gender,[1,3] cam characteristics[1,3] (increased alpha angle), and osteoarthritic changes (subchondral cysts[14] presence). On the contrary, there is a possible negative association of CD presence with increased LCEA[1] in patients with symptomatic FAI. In our study male and female patient populations were almost equal. Cystic subchondral lesions were present in 38.4% of the patients on the plain X-rays and the mean hip joint space was 4.5 ± 0.9 mm on the standing AP X-ray view. The location of the cystic lesions was at the lateral aspect of the acetabular roof and at the acetabular rim. According to Gdalevitch *et al*.,[14] subchondral cysts at the lateral aspect of the acetabular roof can be caused by labral tears and were

Table 2. Major Characteristics of Delamination Versus Nondelamination Patient Groups.

All Hips	Delamination Present (n = 169)	Delamination Absent (n = 60)	*P* (Delamination vs. Non delamination)
Age at surgery, years, mean ± SD	39.4 ± 13.0	33.2 ± 12.8	0.002
Waiting time for surgery, months, mean ± SD	8.7 ± 6.7	8.5 ± 5.8	0.214
AP x-ray LCEA, deg, mean ± SD	33.7 ± 8.1	35.9 ± 8.0	0.201
Alpha angle frog view, deg, mean ± SD	55.1 ± 15.8	47.8 ± 14.6	0.002
Alpha angle AP view, deg, mean ± SD	60.3 ± 19.9	52.8 ± 19.0	0.012
Joint space, mm, mean ± SD	4.4 ± 1.7	4.36 ± 1.0	0.276

AP = anteroposterior; LCEA = lateral center edge angle; SD = standard deviation.

Table 3. Diagnostic Value of Magnetic Resonance Arthrography (MRA) for Detecting Labral Tear.

Variable	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy
Delamination presence according to the MRA report	6	98	91	27	30

Table 4. Diagnostic Accuracy of Magnetic Resonance Arthrography Based on Size of Delamination.

Delamination Size	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
<1 cm^2	8	100	100	21
1-2 cm^2	6	92	75	20
2-4 cm^2	4	100	100	33
>4 cm^2	4	100	100	36

characterized as labral cysts. Subchondral cysts found at the rim were characterized as delamination cysts and were highly associated with CD.[14]

Cam-type FAI was present in 77.7% of the operated hips with a mean alpha angle from the frog leg and AP X-ray view measuring 53.2° ± 15.8° and 58.4° ± 20.0°, respectively. The mean LCEA was 34.3° ± 8.1°. The mean size of CD based on the measurements intraoperatively was 3.12 ± 1.5 cm^2 with a mean coronal × sagittal extent of 0.68 cm × 4.33 cm. Cartilage delamination lesions were primarily located at the anterosuperior quadrant of the acetabular rim between the 2.6 o'clock and 11.9 o'clock position. In the study by Anderson *et al*.[1] (CD prevalence of 44%), 64.1% of patients were male, the mean LCEA was 38.5°, and cam deformities were reported in 77% of their cases. In the study by Pfirrmann *et al*.[5] (CD prevalence of 52%), 70% of the population was male. The coronal extent of the CD was 7.6 mm and the cam deformity prevalence was 72%. In the study by Johnston *et al*.[3] (CD prevalence of 79%), 57% of their population was male and the mean alpha angle was 53.9°. In the Swedish registry (CD prevalence of 53%), 67% of the patients were males and 98% of all patients had a cam pathology.[6] Finally, in the Danish registry[4] (CD prevalence of 86.3%), 44% were male patients with 86.3% of patients having a cam deformity. No osteoarthritic lesions were seen in 60.8% of the patients. Pathologic hip joint narrowing was observed in 33.1% of the cases with a mean hip joint space between 3 and 4 mm. In only 6.1% of the joints, the mean joint space was smaller than 3 mm. With respect to the FAI characteristics, the mean alpha angle was 67° and the mean LCEA was 33°.

FAI remains a clinical diagnosis that is confirmed with imaging. This imaging includes a number of plain radiographs, CT scans, and MRA. The aim is to identify any symptomatic bony pathology and any chondrolabral lesions preoperatively. Early identification of CD in patients with FAI and early surgical intervention prior to the irreversible progression of osteoarthritis is critical to the long-term success of FAI treatment. Patients with advanced articular cartilage lesions typically do not improve with joint preservation surgery, while those with mild cartilage lesions can benefit significantly.[15] Therefore, the role of imaging is important in planning joint-preserving treatment options to delay early hip osteoarthritis in an active and young population.[16]

While MRA is considered to be a reliable diagnostic tool for osteonecrosis,[17] acetabular labral tears,[18] and meniscal tears of the knee,[19] its diagnostic strength with regard to

articular CD lesions remains uncertain.[20,21] In the literature, the reported sensitivity and specificity of MRA in diagnosing CD in symptomatic FAI patients varies significantly from 22% to 100% and from 40% to 100%, respectively.[1,12,22-24] We report the lowest diagnostic value of MRA for the detection of CD in patients with FAI. We found that the sensitivity of MRA was only 6%. These findings question the efficacy and diagnostic value of MRA in detecting CD for patients with FAI, preoperatively.

Zaragoza *et al*.[12] reported a high sensitivity and specificity of MRA in a study of 48 hips (97% and 84%, respectively), commenting that MRA represents an effective diagnostic tool for the identification of CD. In another study of 42 hips with FAI by Schmid *et al*.,[24] MRA was evaluated to be moderate to good in detecting acetabular CD. They reported a sensitivity and specificity of 65% to 100% and 40% to 80%, respectively. Contrary to those studies, Anderson *et al*.,[1] reported a low to medium performance of the MR-arthrogram as a diagnostic tool for CD, in a study of 64 patients with FAI. They reported 22.2% sensitivity, 100% specificity, NPV 65%, and PPV 100%. The diagnostic accuracy was reported to be 55.6% in a sample of patients with 44% CD. A recent systematic review and meta-analysis[23] included 828 cases from 21 qualitative and 12 quantitative studies, all performed with a 1.5-T MR-arthrogram. The systematic review reported an overall sensitivity of 75% and specificity of 86.6%, for detecting CD in symptomatic FAI patients.[23]

MRA clarity depends on the technique that is used. Its accuracy could be affected by high magnetic resonance field strengths, dedicated cartilage-specific sequences and variable imaging findings in different planes. In our center, an MR-arthrogram was performed with the use of a Siemens 1.5-T Symphony MRI scanner (Erlangen, Germany). The axial, coronal, and sagittal fat-saturated T1- and T2-weighted hip images were reviewed by our radiologists. There are a number of MRA findings described in the literature that could indicate the presence of CD and are commonly used by radiologists and orthopedic surgeons. These include the following: (a) fluid presence under the cartilage delamination ("inverted Oreo cookie" sign; a specific but rare finding),[25,26] (b) hypointense areas in the cartilage layer on intermediate weighted fat-saturated or T1-weighted images,[26,27] (3) low signal intensity curvilinear flap with greater than 1 mm thickness on the T1-weighted images,[1,12,17] and/or (4) a hypointense line in the acetabular cartilage layer parallel to the subchondral plate.[26]

Diagnosis of CD in symptomatic FAI patients remains poor despite the technological advancements of MRA imaging. Pfirrmann *et al*.[27] showed that the sensitivity and specificity among the aforementioned different MRA CD diagnostic descriptions may significantly vary from 22% to 74% and from 57% to 95%, respectively. The hypointense acetabular cartilage on the coronal T1-weighted spin-echo images and in sagittal water excitation 3-dimensional double-echo steady-state images presented the highest sensitivity and accuracy percentage (74% and 82%, respectively). In a recent study, Crespo-Rodrigez *et al*.[28] demonstrated that the 1.5-T MR-arthrogram presents inferior diagnostic strength when compared with the simple 3-T MRI in terms of labral pathology but not for CD. More specifically, in a study of 50 patients who were diagnosed with symptomatic FAI from the acetabular labrum abnormalities, the 3-T MRI outperformed the 1.5-T MR-arthrogram with 88.9% versus 86.1% sensitivity, 78.6% versus 50% specificity, 91.4% versus 81.6% PPV, 73.3% versus 58.3% NPV, and 86% versus 76% accuracy, respectively. With regard to labral-chondral transitional zone lesions, 1.5-T MRA presented slightly superior sensitivity and NPV in comparison with the 3-T MRI while the two techniques had the same accuracy (98%).

The low diagnostic sensitivity found in our study could be explained by the difficulty in the early diagnosis of CD in FAI patients in general. This could be due to a number of factors such as the thinness of the acetabular cartilage (1-3 mm) and its arrangement as a spherical surface deep in the body. In order to be effective, MRA needs high resolution and a high signal-to-noise ratio.[29] The initial loosening of the cartilage, which is presented arthroscopically with the "wave sign", or the debonding lesion which appears in the later stages of delamination can be missed from gadolinium not penetrating beneath the lesion. The hypointense signal at delaminated areas is more obvious on the T1-weighted images and could be best identified on planes of the section that would be oriented perpendicular to the involved cartilage.[30] Large lesions can be identified in both sagittal and coronal views bur smaller lesions are not always visible on the MR-arthrogram films and could be easily missed.[27] To some extent, there is also susceptibility to artifacts when reading an MR-arthrogram.

The main limitation of this study is that there is no adequate explanation for the low MRA-detection of CD. One reason might be inattention to the acetabular cartilage when the MR-arthrogram is read or a lack of training to identify the lesions. Another possible explanation is that the interpretation of the images was not always being performed under consideration of the patient history, clinical examination, and morphological MRI findings. A further factor that could bias the outcome of this study is that there was some delay between the MR-arthrogram and the operation that could allow cartilage lesions to develop or even aggravate during that time. However, that was unavoidable due to the long elective surgical waitlist of the sports department in our hospital. It would be interesting to see if this delay changed the incidence/progression of CD. This factor could be mitigated if we were able to ensure that the MR-arthrogram was performed closer to

surgery. Another possible factor for the low diagnostic sensitivity of MRA could be the design of this study. We only compared the MRA reports of the patients with operative notes and surgical videos. We did not review the MRA films in a systematic manner with defined criteria by two or more trained orthopedic surgeons with musculoskeletal radiologists as it happens in the majority of the relevant published literature. This clearly demonstrates the underdiagnosis of CD in FAI patients in MRA reports and indicates the need for better standard diagnostic criteria to detect CD using an MR-arthrogram. Both orthopedic surgeons and radiologists need to be alert when examining an MR-arthrogram for the identification of this pathology in FAI patients. In a future study, radiologists could review the MRA films while actively trying to identify any CD lesions. If the diagnostic sensitivity remains low, it could indicate that MRA is weak in diagnosing this common pathology.

The high prevalence of CD in symptomatic FAI patients and the low diagnostic sensitivity of MRA identifies CD as a "hidden enemy". It is hard to definitively diagnose CD with MRA, especially if small cartilage lesions or early degenerative cartilage changes are present. Two elements are important for a successful early diagnosis. One is the high image quality of MRA for the optimal cartilage delineation. This can be achieved with high cartilage contrast and image resolution settings. The second is the awareness of this "sneaky" pathology when only minor imaging characteristics suggesting CD are present. New MRI advancements include delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), T1ρ (T1rho), T2/T2* mapping, and several others. MR-arthrograms performed under traction may present a better diagnostic efficiency for CD diagnosis. Schmaranzer et al.[31] reported that the sensitivity and the specificity in detecting acetabular CD using traction was 85% to 88% and 78% to 96%, respectively, between two readers. The hip under axial traction allows the contrast agent to better penetrate the interface of the detached cartilage and the subchondral bone.[32-34] Even if the initial results are promising, further studies are needed to confirm the efficacy and accuracy of this technique. These recent developments may prove to be promising diagnostic tools that could depict extracellular matrix changes of the cartilage and potentially isolate early cartilage degeneration. Furthermore, they could improve the diagnostic ability to accurately and reproducibly identify CD in symptomatic FAI patients, which may help surgeons improve their clinical decision making, treatment prognosis of a joint preservation surgery, and preoperative planning.

Conclusion

This is the first study to report such a low sensitivity (6%) of MRA in the diagnosis of CD based on the radiologists' reports. This fact suggests the need for better standard diagnostic criteria to detect CD using MRA. Both orthopedic surgeons and radiologists need to be alerted when examining an MR-arthrogram for the identification of this pathology in symptomatic FAI patients. New technologies may also prove to be helpful in accurately diagnosing this "hidden enemy" but more studies will need to be done in the future.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Ethical approval for this study was obtained from the Nova Scotia Health Authority Research Ethics Board (NSHA-RS/2015-331).

Informed Consent

Written informed consent was obtained from all subjects before the study.

Trial Registration

Not applicable.

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