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SYNOVITIS IN KNEE OSTEOARTHRITIS: A PRECURSOR OF DISEASE?

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Abstract

Objectives—It is unknown whether joint inflammation precedes other articular tissue damage in osteoarthritis. Therefore, this study aims to determine if synovitis precedes the development of radiographic knee OA (ROA).

Methods—The participants in this nested case-control study were selected from knees in the Osteoarthritis Initiative (OAI) that had a Kellgren Lawrence grading (KLG)=0 baseline (BL). These knees were evaluated annually with radiography and non contrast-enhanced magnetic resonance imaging (MRI) over 4-years. MRIs were assessed for effusion-synovitis and Hoffa-synovitis. Case knees were defined by radiographic knee osteoarthritis (ROA) (KLG >=2) on the postero-anterior knee radiographs at any assessment after baseline. Radiographs were assessed at P0 (time of onset of radiographic knee OA), 1 year prior to P0 (P-1) and at BL. Controls were participants who did not develop incident ROA (iROA) from baseline to 48 months).

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Author Contributions

IA and DJH conceived and designed the study, supervised its conduct, drafted the manuscript and take responsibility for the integrity of the work as a whole, from inception to finish. CKK, AG, FR, RMB and MJH were also involved in the design and conduct of the POMA study. All authors contributed to acquisition of the data and its interpretation. All authors critically revised the manuscript and gave final approval of the article for submission.

Competing interest

Drs. Atukorala, Hunter, Boudreau, and Mr. Hannon report no competing interest.

Ali Guermazi is President and co-owner of the Boston Core Imaging Lab (BICL), a company providing MRI reading services to academic researchers and to industry. He has provided consulting services to Novartis, Merck Serono, Sanofi-Aventis, TissueGene and Genzyme.

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C. Kent Kwoh has provided consulting services to Novartis and has received research support from Astra-Zeneca.

Results—133 knees of 120 persons with ROA (83 females) were matched to 133 control knees (83 females). Odds ratios (OR) for occurrence of iROA associated with the presence of effusion-synovitis at BL, P-1 and PO were 1.56 (95% CI 0.86–2.81), 3.23 (1.72–6.06) and 4.7(1.10–2.95), respectively. The ORs for the occurrence of iROA associated with the presence of Hoffa-synovitis at BL, P-1 and P0 were 1.80 (1.1–2.95), 2.47 (1.45–4.23) and 2.40 (1.43–4.04), respectively.

Conclusions—Effusion-synovitis and Hoffa-synovitis strongly predicted the development of incident ROA.

Keywords

Osteoarthritis; Knee; Magnetic Resonance Imaging; Synovitis

INTRODUCTION

Osteoarthritis (OA) is the commonest joint disease worldwide and is a major cause of pain and disability. Despite increased prevalence of this disease (1), there is at present no therapy that prevents or cures knee OA. Therefore, the current focus is on developing drugs to arrest the progression of this disease. In order to facilitate this process it is imperative that the tissue targets in pathogenesis are identified.

In contrast to earlier paradigms, OA is now perceived as joint failure which is the result of complex interactive disease processes in multiple articular and peri articular structures. These tissues include synovium, cartilage, muscle, subchondral and cortical bone (2). However, there is ongoing debate as to which tissue structures change first in OA. The pathogenic role of bone, the meniscus and hyaline cartilage have been extensively examined (3) previously. However, there is increasing evidence that inflammation, particularly synovitis, plays a role in the pathogenic process of OA. Therefore, synovitis is no longer perceived as an innocent bystander in OA (4–6).

Previously, synovitis in OA was believed to be a consequence of underlying joint damage, with synovial inflammation resulting from macrophage phagocytosis of intra-articular cartilage or bone debris, calcium pyrophosphate dihydrate or calcium hydroxyapatite crystals with release of soluble cartilage matrix macromolecules (5, 7).

Furthermore, an overwhelming majority of persons with OA have synovitis (4). There is ample evidence that inflammation is present in the synovium in all stages of OA (2, 5, 8) including those with early disease (9). Moreover, synovitis is associated with pain, disease severity, and progression of knee OA (10). Given these findings, it is likely that synovitis has an aetio-pathogenic role in OA and that it may be a precursor rather than just a consequence of joint failure (11, 12).

Synovial inflammation manifests as synovial membrane thickening or joint effusion. However conventional knee radiographs are unable to visualize the synovial membrane. Though ultrasonography is useful in imaging synovitis, it has not yet been used in large scale studies of osteoarthritis (13). Therefore, the best imaging method to identify synovial inflammation is by magnetic resonance imaging (MRI). MRI demonstrates synovitis as

thickening and enhancement after intravenous contrast administration or as an effusion (13). Accordingly, MRI is useful to investigate early “preclinical” disease before radiographic changes occur. Furthermore, the MRI is invaluable to examine and delineate pathologies in all structures associated in the pathogenesis of OA. This is due to the ability of MRI to visualize deeper structures and examine the knee in its entirety in 3 dimensions unlike any other imaging modality (13).

Large scale epidemiological studies have established the validity of semi-quantitative assessment of synovitis by non contrast-enhanced MRI (14¯16). Currently, effusion-synovitis or Hoffa-synovitis are the surrogates used to identify synovial inflammation on non contrast-enhanced MRI (13, 17). Effusion-synovitis is defined by the presence of fluid equivalent signal in the joint cavity on T2/IW/PDw magnetic resonance images. Hoffa-synovitis assesses the degree of hyperintensity in Hoffa’s fat pad on T2/PD/Iw-w fat suppressed sequences within the fat pad(18).

This nested case-control study was performed to identify whether synovitis precedes the onset of radiographic OA (ROA). Thus the objective was to identify if synovitis/effusion is more prevalent in knees that develop ROA compared to those that do not.

PATIENTS AND METHODS

Study Design and subjects

The study participants were selected from the Osteoarthritis Initiative (OAI). The OAI is a multi-centre, eight-year prospective observational cohort study that examines the biomarkers and risk factors for causation and progression of knee OA in 4796 individuals.

Details of subject inclusion and exclusion have been described previously (19, 20). The OAI participants are both those with knee OA and those who are at high risk of developing knee OA.(21). The participants were of all ethnicities with 59% being female and 18% were non-white.

Study subjects were assessed annually by radiography and MRI.

Cases and Controls

Cases knees were those that developed incident ROA (iROA) on or before the 48 month OAI xray and that had baseline Kellgren Lawrence grades (KLG) of 0. All such knees with MRI readings at either of the visits where iROA was first read or the time prior to that were included. iROA was the first occurrence of radiographic findings compatible with OA (KLG of >=2 on the PA view (22)) during the course of study. This time point was called P0 with P-1 being defined as the time point 1 year before ROA was detected on radiographs.

Each case was matched from a sample of knees that were KLG 0 at baseline, did not develop iROA during the study period, who were at risk at the time of case occurrence, had available images at the timepoints where the case had images. The case knees were matched to a single control knee on sex, age (within five years), and contralateral knee OA status (i.e. KLG = 0, 1, or 2 + in the other knee).

Included knees had to have images at baseline and either P0 or P-1, but not necessarily both. The small set of knees where effusion synovitis could be scored and Hoffa synovitis could not were included for the analysis of the former only. Because of the design, an MRI score for both parts of the case-control pair had to be available before it was included in that analysis.

History of joint surgery and previous injury to the knee was evaluated at the enrolment visit by asking the participants whether they have ever injured their knee(s) badly enough to limit their ability to walk for at least two days or whether they have ever had any kind of knee surgery including arthroscopy, ligament repair or meniscectomy. At the same visit, participants' Body Mass Index (BMI) was taken and they were asked about their knee pain in the past 12 months (no pain, infrequent pain [pain not on most days of a month], or frequent pain [pain on most days of at least one month] and the number of knee bending activities in the past 30 days. These activities were: taking more than 10 flights of stairs, kneeling for 30+ minutes, squatting for 30+ minutes, moving a heavy (25 pounds or more) object, or going into/out of a squat more than ten times. A scale from 0 to 5 was created by taking the sum of the number of different activities to which they answered yes.

Radiographs

Fixed flexion radiographs acquired using the Synaflexor of both knees were performed in all subjects. The radiographs of knees were assessed for their KLG (23) and was found reliable (kappa=0.7 at baseline and 0.78 at 36th month follow up). Radiographs acquired at the baseline, 12, 24, 36 and 48 month visit were read by the OAI central readers.

Magnetic Resonance Imaging

MRI acquisition was done on a 3 Tesla MRI (3T-MRI) machine. Non contrast-enhanced MRIs of both cases and controls were obtained. The OAI MRI protocols and image acquisition techniques were utilized. Semi quantitative tissue scoring was done using coronal intermediate-weighted 2DTSE (slice thickness/in-plane area 3.0/0.37*0.46) and sagittal intermediate-weighted 2TSE images with fat suppression (slice thickness/in-plane area 3.0/0.37*0.51) (20).

The MRI Osteoarthritis Knee Score (MOAKS) instrument was used to assess the whole joint for structural changes compatible with knee OA (18). Knee inflammation was assessed by using surrogates; Hoffa-synovitis in infrapatellar and intercondylar regions and effusion-synovitis. The MRIs were scored semi-quantitatively 0 to 3 as part of the MOAKS scoring system. Hoffa-synovitis score (on sagittal image) and effusion–synovitis (on axial) were assessed for magnitude as follows: 0=normal/no hyperintensity, 1=mild, 2=moderate and 3=severe for Hoffa-Synovitis and 0=physiological amount, 1= small, 2=medium and 3=large respectively effusion-synovitis (Figure 1). For both, any finding (>= 1) was compared to no finding.

MRI readings were performed by AG and FWR with 15 and 12 years experience in MRI semiquantitative assessment respectively. Scores were entered directly into an electronic web-based database. All MRIs were read sequentially, unblinded to timepoint. Inter-rater reliability on a subset of MRIs was performed for MRI reading quality control. Inter-rater

reliability was weighted kappa= 0.68 (95% CI 0.38, 0.99) and 0.95 (95% CI 0.61, 1.00) for synovitis and for effusion respectively. These were calculated using the full range of semiquantitative assessment (0–3 for synovitis, 0–3 for effusion). Subsequently, on going surveillance for measurement drift was carried out by AG by re-reading 5% of the MRIs (24).

Statistical Analysis

Conditional logistic regression models using a GEE (general estimated equations) method with a robust sandwich estimator to account for correlations between case-control pairs and between knees for individuals with bilateral incident OA were employed to model the relationships between the key predictors and OA. Models with only the key predictors were run first, and unadjusted associations with OA were obtained. Then models adjusted for baseline covariates (self-reported injury, self-reported knee surgery, BMI and knee bending activities) were run to see that the findings persisted when these covariates were controlled for. Models were run at three time points: Baseline (time of enrollment in the OAI), P-1 (the year prior to the finding of ROA), and P0 (concurrent with incident ROA).

RESULTS

A total of 133 knees from 120 participants with baseline KLG=0 on knee radiographs developed ROA during the first 48 months. An identical number of matched control knees were selected. The demographics and baseline clinical parameters did not differ significantly between cases and controls (Table 1). All participant radiographs were KLG 0 at baseline. 59 subjects (44.36%) of cases and controls had contralateral OA at baseline. The majority (69.92% of cases and 78.95% of controls) were pain free or had infrequent knee pain at baseline. 40% cases had a frequent knee pain compared to 28% of controls.

The timing of the occurrence of ROA in the cases is shown in Figure 2. At the onset of ROA, 57.1% of cases had frequent knee pain and 25.6% had infrequent pain. Correspondingly, 20.3% and 32.3% of controls showed frequent or infrequent pain. History of injury at baseline was reported by 20.3% of cases and 12.8% of controls. A history of knee surgery (self-reported) at baseline was similarly low; 3.76% of cases and 3.01% of controls. The KLG of cases at point of occurrence of ROA was as follows: KLG 2–75.9%; KLG 3 – 22.6% and KLG 4-1.5%. Only 3 controls (2.3%) reached a KLG 1 grade. The remainder continued to be at KLG 0 at P0.

At baseline, there was no significant association between effusion-synovitis and subsequent iROA (37.59% vs. 30.08%. OR = 1.56, CI 0.86–2.81). However, effusion-synovitis in the year prior to the finding of iROA (P-1) was associated with subsequent iROA (52.80% in cases vs. 29.60% in controls, OR = 3.23, CI 1.72–6.06). At the time point when iROA was read (P0), the relationship was still present (OR = 4.70, CI 2.35–9.34).

Hoffa-synovitis showed a similar set of associations except that the difference at baseline was significant (46.21% vs. 30.83%, OR 1.80, CI 1.10–2.96). At P-1, Hoffa-synovitis continued to be associated with subsequent iROA (53.23% in cases vs. 30.40% in controls,

OR = 2.47, CI 1.45–4.23). At P0, the relationship between Hoffa-synovitis and iROA was still found (OR = 2.40, CI 1.43–4.04) (Table 2).

The association between synovitis/effusion-synovitis with the occurrence of ROA persisted in a sensitivity analysis where we adjusted for potential covariates (Table 2).

DISCUSSION

This study demonstrates that synovial inflammation and effusion is associated with the later occurrence of ROA.

The first finding is that the presence of synovial inflammation; effusion-synovitis or Hoffa-synovitis; is associated with increased odds of developing iROA. Inflammation has been postulated to play a role in the occurrence of knee OA (2) and is believed to be a consequence of underlying damage in the knee joint (5,7). However, our study suggests that synovial membrane inflammation plays a role early in the disease. These findings are further supported by previous research on knees without OA which show synovitis and effusion increases risk for cartilage loss (25). Therefore, our findings concur with previous findings which indicate at least an accelerating role of inflammation in disease initiation (25)(9). An additional strength of this study is that we used MRI, which has previously been proven to be a sensitive tool to detect synovitis (13).

The second observation is that the occurrence of synovial inflammation is more marked in the year preceding the occurrence of ROA. This association was demonstrated with both surrogates of inflammation; effusion-synovitis and Hoffa-synovitis. The risk of incident OA from synovitis/effusion was greatest when the visit was immediately proximate to the case defining time point with both parameters. This suggests that occurrence of synovitis not only predates but is also associated with the development of ROA. However, approximately one third of the control group had effusion synovitis and Hoffa synovitis without subsequent consequence. It is possible that the controls will subsequently develop ROA at a slower rate than the cases. This is best explained by the fact that all the individuals who were selected to the OAI are those at high risk of KOA. It is likely that different individuals will develop OA at different rates.

This cohort contained relatively small numbers of participants who had injury or surgery to that knee prior to the onset of ROA. However, the association between synovial inflammation and the occurrence of ROA persisted in models adjusted for history of knee injury and history of knee surgery at baseline. The fact that majority of participants developed synovial inflammation independent of a documented insult to the knee suggesting that inflammation may occur either independently or as a result of a clinically insignificant pathology within the knee. But the current study is not able to prove whether synovitis or effusion precedes structural joint damage or is a result of early intrinsic tissue alterations such as meniscal or cartilage damage.

The next observation is that the strength of associations at each time point was greater for effusion-synovitis than for Hoffa-synovitis. This may be due to the reduced sensitivity of Hoffa-synovitis as a measure of synovial inflammation (26). Effusion-synovitis on non

contrast-enhanced MRI is perceived as a better assessment of synovial inflammation, as it circumvents the lack of specificity of using Hoffa-synovitis as an index of synovial inflammation (13).

The following limitations were identified in this research project. The gold standard of identifying synovitis on imaging is contrast-enhanced MRI. However, because of possible side effects, ethical considerations and increased expense, contrast-enhanced MRI is not routinely used in the assessment of pre-symptomatic OA in large-scale clinical and epidemiological research. Instead synovial inflammation is assessed in non contrast-enhanced MRI using surrogate signal changes in Hoffa's fat pad (Hoffa-synovitis) and by effusion-synovitis (27, 28). We assert that the non contrast-enhanced MRI is a useful tool in the detection of the onset of synovial inflammation in pre-symptomatic OA, particularly in the face of ethical and practical considerations in using contrast in pre-symptomatic OA cohorts. In addition, this study retrospectively assessed subjects who did not have ROA at baseline. The retrospective study design is a disadvantage, but it was the most feasible to use in this previously unexplored area of research.

Furthermore, Hoffa's fat pad synovitis on non contrast-enhanced MRI has been shown to correlate histologically with synovitis in the same location (29). Intra articular fluid signals are assessed using non contrast-enhanced MRI according to the extent of capsular distension (30). This has been shown to be a composite of true joint effusion and synovial thickening and may underestimate synovial inflammation (31). This study used these previously validated tools to identify synovitis. However, it is possible that synovitis may be underestimated in the non contrast-enhanced MRIs (32). Therefore, we reiterate that the use of contrast-enhanced MRI would likely strengthen rather than diminish any association detected by non contrast-enhanced MRI in this study (27).

The OAI study population contains persons at high risk of KOA and both cases and controls in this study were predominately overweight or obese (24% of cases and 29% of controls were in normal BMI ranges). Therefore, this study is unable to identify whether Hoffa synovitis and effusion synovitis is associated with increasing weight.

This study is the first, to the best of our knowledge, which demonstrates the association of synovitis with incident knee osteoarthritis. These findings concur with previous research findings which demonstrated the pivotal role of synovitis in development and prevalence of symptoms and progression of knee OA. It is noteworthy that these studies demonstrated the association of clinical features of joint inflammation with radiological progression in knee OA (33). Further, an MRI study has demonstrated a strong and unique association between synovitis, capsular thickening and the severity of knee pain (32). In addition, higher grades of synovitis conferred an increased risk of painful knee OA (9). Similarly an increase in levels of synovial biomarkers associated with synovial activity, serum hyaluronan, have demonstrated an association with radiographic progression of the knee (10). Laboratory studies have established that pro- inflammatory cytokines contribute to OA pathogenesis by increasing cartilage degradation. Furthermore inflammation produces pain and hyperalgesia in OA via multiple mechanisms (34). Several inflammatory markers including IL-1, IL-6, TGF-beta, TNF-a. IL-17 and VEGF are increased in the synovium in OA (12). And

increasing synovial IL-17 levels has been shown to correlate with knee OA severity and progression (35). In addition, inhibitors of the growth factors, TG-beta and BMP, reduced synovial thickening and osteophyte formation (36). Therefore, it is intuitive that treatment of synovitis may improve symptoms and disease progression.

There is evidence to support the postulate that treatment of synovitis may improve symptoms. Yttrium -90 synovectomy (38) used in treating painful knee OA showed a better response in early knee OA. Therefore, treating synovitis in knee OA may have a role in reducing progression of the disease and provide symptom relief. Therefore, the results of this study are useful in identifying a targeted therapy to alter the pathogenesis of knee OA.

Our study has demonstrated that synovitis is a precursor of radiographic OA. These findings if confirmed by similar studies including those with synovial biopsies will establish the role of inflammation in the pathogenesis of OA. The findings have the potential to be translated towards developing targeted therapies to prevent the development of knee OA.

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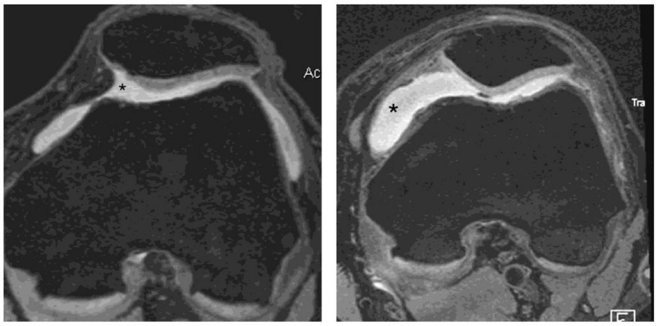

Figure A. Effusion-synovitis. A. Axial dual echo at steady state (DESS) image shows grade 1 effusion synovitis. Intra-articular fluid and synovial thickening is depicted as hyperintensity (asterisk). B. Axial DESS image shows marked distension of the joint capsule representing grade 3 effusion-synovitis (asterisk).

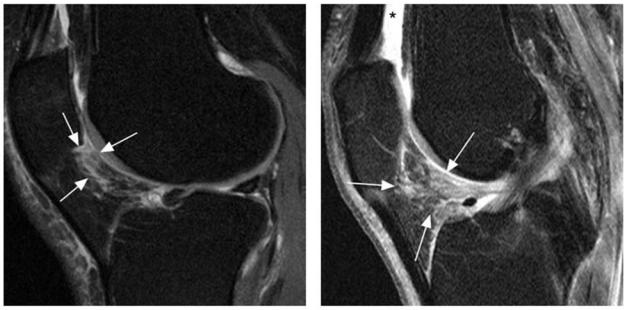

Figure B. Hoffa-synovitis. A. Sagittal intermediate-weighted fat suppressed image shows infrapatellar areas of hyperintensity within Hoffa's fat pad representing a surrogate of synovitis on non enhanced MRI. In this case grade 2 Hoffa-synovitis is shown (arrows). B. Another knee exhibits marked signal alterations within Hoffa's fat pad representing grade 3 Hoffa-synovitis (arrows). Note effusion-synovitis in addition (asterisk).

Figure 1.

Effusion- synovitis and Hoffa synovitis on Magnetic resonance imaging

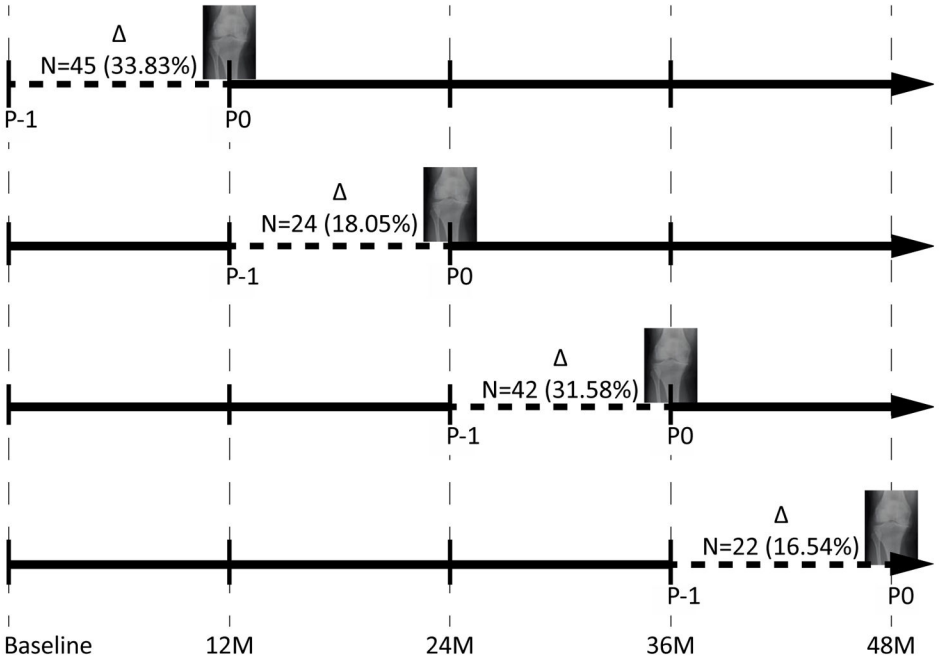

Figure 2.

Schema detailing the timing of onset of ROA (radiographic KOA) with number of subjects who developing ROA at each time point. P0 =time of onset of ROA), P-1=1 year prior to P0, and BL=Baseline. N=Number (%). Red line – 1 year prior to the onset ROA

Table 1

Baseline characteristics of the cases and controls in the study population

	Cases (N= 133) N (%)	Controls (N=133) N (%)	P value
Gender			
Male	50 (37.59)	50 (37.59)	NA
Female	83 (62.41)	83(62.41)	
Age (mean +SD)	60.44±8.95	60.30±8.95	NA
BMI (mean +SD)	29.01±4.96	27.33±4.35	
Number of knee bending activities	2.36 (1.37)	1.95 (1.39)	.0229
Knee Pain			
No pain	50 (37.59)	52 (39.01)	.2264
Infrequent pain	43 (32.33)	53(39.85)	
Frequent pain	40 (30.08)	28(21.05)	
Previous Knee Injury	27 (20.30)	17(12.78)	.1230
Previous Knee Surgery	5 (3.76)	4 (3.01)	.7394
Prevalence of Hoffa-synovitis at baseline	50 (37.59)	40 (30.08)	.0194
Prevalence of effusion-synovitis at baseline	61 (46.21)	41(30.08)	.1436
Contralateral knee Kellgren Lawrence Grade			
0	63(47.37)	63(47.37)	NA
1	11 (8.27)	11(8.27)	
2+	59 (44.36)	59 (44.36)	

Note: Group difference tests by GEE method accounting for case-control pairs and correlation of knees in individuals with bilateral OA. Criteria used for matching could not be tested.

Table 2

Conditional logistic regression analysis for occurrence of effusion-synovitis and Hoffa-synovitis in the study population including the model adjusted for injury/surgery at baseline. P1- one year prior to occurrence of ROA; P0- point of occurrence of ROA

	Total	Cases N (%)	Controls N (%)	Odds ratios* (95% Confidence Interval)	Adjusted Odds Ratio** (95% confidence Interval)
Baseline effusion-synovitis					
Present	90	50 (37.59)	40 (30.08)	1.56 (0.86–2.81)	1.41 (.77 – 2.58)
P-1 effusion-synovitis					
Present	103	66 (52.80)	37 (29.60)	3.23 (1.72–6.06)	2.63 (1.35 – 5.13)
P0 effusion-synovitis					
Present	127	82 (65.60)	45 (36.00)	4.70 (2.35–9.40)	5.00 (2.42 – 10.35)
Baseline Hoffa-synovitis					
Present	102	61 (46.21)	41 (30.83)	1.80 (1.10–2.95)	2.06 (1.21 – 3.50)
P1 Hoffa-synovitis					
Present	104	66 (53.23)	38 (30.40)	2.47 (1.45–4.23)	3.05 (1.72 – 5.44)
P0 Hoffa-synovitis					
Present	110	69 (55.65)	41 (33.06)	2.40 (1.43–4.04)	2.66 (1.57–4.51)

*GEE method with a robust sandwich estimator was used to account for the correlation of two knees within an individual.

**Adjusted for self-reported knee injury, knee surgery at baseline, BMI, and knee bending activities.