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SYNOVITIS AND THE RISK OF KNEE OSTEOARTHRITIS: THE MOST STUDY

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Abstract

Objective—To identify the independent relation of synovitis with incident radiographic knee osteoarthritis (OA) after adjusting for other structural factors known to cause synovitis.

Design—We examined MRIs from knees that developed incident radiographic OA from the Multicenter Osteoarthritis Study (MOST) and compared these case knees with controls that did not develop OA. We examined baseline MRIs for knees developing OA at any time up to 84 months follow-up. We scored lesions in cartilage, meniscus, bone marrow and synovitis. Synovitis scores were summed (0-9) across 3 regions, suprapatellar, infrapatellar and intercondylar region, each of which was scored 0-3. After bivariate analyses examining each factor's association with incidence, we carried out multivariable regression analyses adjusting for age, sex, BMI, alignment and cartilage and meniscal damage.

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AUTHOR CONTRIBUTIONS

Conception and Design: DTF, TN, MCN
Analysis and Interpretation: JN, FR, AG, JT, CEL
Drafting of article: DTF, TN, JN
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Provision of Study materials or patients: JG, FR, JT, CEL, AG

COMPETING INTEREST STATEMENT

There are no competing interests for any of the authors.

Results—We studied 239 case and 731 control knees. In bivariate analyses, cartilage lesions, meniscal damage, synovitis and bone marrow lesions were all risk factors for OA. After multivariable analyses, synovitis was associated with incident OA. A higher synovitis score increased the risk of incident OA (adjusted OR per unit increase 1.1; (95% CI 1.0, 1.2, p=.02), but increased risk was associated only with synovitis scores of >=3 (adjusted OR 1.6; 95% CI 1.2, 2.1, p = .003)

Conclusions—Synovitis, especially when there is a substantial volume within the knee, is an independent cause of OA.

Keywords

knee osteoarthritis; magnetic resonance imaging; cohort studies; incidence

INTRODUCTION

Osteoarthritis (OA) of the knee is the most common cause of knee pain in middle-aged and older persons[1] and its prevalence is increasing[2].

Persons with symptomatic knee OA have much intra-articular structural pathology including cartilage loss, meniscal damage, bone marrow lesions and synovitis. Unfortunately, little treatment is available that could reverse most of these pathological joint features. And, to make it worse, in those with knee OA, these features often coexist[3]. Furthermore, the abnormal joint mechanics that develop as part of OA, resulting in excessive focal loads across the knee play a major role in disease progression[4, 5]. These pathomechanics may be extremely difficult to treat or reverse, putting affected knees beyond the reach of structure modifying therapy.

Given the constellation of findings that often coexist in knees with extant disease, it makes sense to move prevention and treatment efforts in OA to an earlier stage of disease. At an earlier stage, it is more likely that focal loads across the knee joint would not be excessive, and that tissue pathology within the joint would be limited. Even though we may not yet be able to treat abnormalities within a single tissue, it would inform efforts at prevention to determine which pathologic lesions trigger the onset of disease. While cartilage loss and meniscal damage are not yet clearly treatable, especially in the face of mechanopathology, treatments targeting inflammation within the joint are available.

The effect of synovitis, inflammation of the synovial lining of the joint on incident OA is not known. Evidence on its contribution to progressive structural disease in knees that already have disease has been inconsistent and has suggested that only severe forms of synovitis increase risk[6, 7] or that it plays no role[8]. In general, studies examining synovitis and its relation to OA have not adjusted for the structural pathology known to cause synovitis. Synovitis can be caused by release of cartilage fragments that activate synovial lining cells[9] and can be caused by meniscal damage[10]. Thus, in theory, any effect of synovitis on disease occurrence could be confounded by other known causes of disease: cartilage and meniscal damage. In one recent report[11], synovitis was found to increase risk of incident OA, but these findings were not adjusted for the co-occurrence of cartilage and meniscal damage,

and there was no association of synovitis at baseline before disease incidence, suggesting that it arose secondary to damage. In another recent report, Wang et al[12] reported that, among persons without OA, synovitis increased the risk of worsening cartilage defects but did not increase risk of quantitative cartilage loss. To our knowledge, there have been no studies examining synovitis and its relation to incident radiographic OA after adjustment for structural pathology known to cause synovitis. This issue is critical because, if there is no independent effect of synovitis on OA, then treating synovitis will have no structural benefit. Also, reports have suggested that only synovitis which appears advanced or severe on MRI[10] or arthroscopy[6] is associated with structural worsening and that there is not a 'dose response' relation of synovitis to OA.

The acquisition of baseline MRIs in large numbers of subjects in the Multicenter Osteoarthritis Study (MOST) who were subsequently followed for the development of OA created the opportunity to examine which structural pathology triggers disease development. Many subjects did not have OA at baseline but were at high risk of disease, and developed disease during follow-up, enabling investigators to examine MRI findings prior to disease occurrence. We took advantage of these opportunities to ask three questions: ***1.*** Which structural features increased the risk of disease? ***2.*** Was synovitis related to disease onset after adjusting for other risk factors thought to cause synovitis? and ***3.*** Was more synovitis associated linearly with risk of disease or rather, was there a threshold of synovitis above which risk of disease increased?

METHODS

MOST Study

The MOST cohort includes persons with or at high risk of symptomatic knee OA recruited from Birmingham, Alabama and Iowa City, Iowa. The goal of the study was to evaluate risk factors for incidence and progression of knee OA. 3,026 subjects aged 50-79 at baseline were recruited at baseline with follow-up clinic visits at 30, 60 and 84 months. For those without symptomatic OA, eligibility criteria included those who were overweight or obese, with knee pain or with a history of knee injury or operation. At each visit, weight and height were measured and PA weight bearing radiographs obtained. Long limb radiographs were acquired in all MOST subjects at the baseline visit[13]. Mechanical alignment (also known as HKA) was measured at study baseline to the nearest 0.1° on these x-rays with high inter-reader reproducibility (ICC = 0.98)[14].

MRI's of the knee were acquired in MOST subjects at each visit using a 1.0 T magnet (OrthOne, ONI Inc., Wilmington, MA, USA) and circumferential extremity coil. The protocol included fat-suppressed (FS) fast spin-echo intermediate-weighted (IW) sequences in two planes, sagittal (TR = 4800 ms, TE = 35 ms, 3 mm slice thickness, 32 slices, 288 × 192 matrix, 2 excitations (NEX), 140 × 140 mm field of view (FOV), echo train length (ETL) = 8) and axial (TR = 4680 ms, TE = 13 ms, 3 mm slice thickness, 20 slices, 288 × 192 matrix, 2 NEX, 140 × 140 mm FOV, ETL = 8), and a short tau inversion-recovery (STIR) sequence in the coronal plane (TR = 6650 ms, TE = 15 ms, TI = 100 ms, 3 mm slice thickness, 28 slices, 256 × 192 matrix, 2 NEX, 140 mm^2 FOV, ETL = 8). All images were

acquired without contrast and the images provided information for semiquantitative assessments.

Definition of Incident OA

In MOST, at each clinic visit subjects obtained posteroanterior and lateral weight bearing knee radiographs using a Synaflexer frame[15, 16]. X-ray readings were carried out centrally at Boston University by a team of three readers. For each subject, all x-rays were read paired. Each of two readers read all x-rays. If there was a disagreement as to whether a knee had radiographic OA (Kellgren & Lawrence >= Grade 2), the reading was adjudicated by a panel of three readers including the two who read the films and one other (DTF). A consensus reading was arrived at when at least two of three readers agreed. Agreement was high when the same knee films were read repeatedly (for Kellgren and Lawrence (KL) grade, weighted kappa = 0.75, p<.0001 and for joint space narrowing grade (scored 0-3) weighted kappa = 0.86, p <.0001).

Incident OA was defined as present when a knee with KL grade 0 or 1 developed grade 2 which was defined as joint space narrowing and definite osteophytosis[17] .

MRI Reading

MRIs from MOST were read by experienced musculoskeletal radiologists using the WORMS scale. We have shown[18, 19] that BLOKS and WORMS provide nearly identical assessments of all features of OA. Synovitis, cartilage defects, meniscal tears and extrusion and bone marrow lesions were scored in all MRIs at baseline for cases and controls. MRIs were read by two experienced musculoskeletal radiologists (FR and AG). We have previously reported on their interobserver agreement for each of these features[18]. Mechanical alignment measures (at baseline) were available in subjects in MOST and were included in analyses.

Synovitis was scored 0-3 in three separate regions of the knee, two within the Hoffa's fat pad (infrapatellar and intercondylar), and in the suprapatellar pouch (the latter region is often labelled effusion/synovitis) (see Figure 1 for examples of scores for infrapatellar Hoffa's fat pad and suprapatellar pouch). We treated these regions as the same qualitatively given recent evidence[11] that their association with OA is similar, although we also examined the association of synovitis in each location with later OA. To create a sum of the amount of synovitis, we added scores from all 3 regions, creating a 0-9 score. We note that in non-contrast images, synovium and synovial fluid are indistinguishable so that our measurements combine these two parameters.

We read MRIs of knees that developed radiographic incidence at any time point after baseline (cases) and knees that did not develop incidence by radiograph by 84 months (controls). Those with x-ray OA at baseline were excluded. For knees with x-ray incidence at any time point, we examined whether baseline MRIs were acquired and if they were readable for all features. Non-cases were all persons in MOST who did not have x-ray OA at baseline or follow-up and who had one knee MRI read. For those coming to 60 and 84 month visits, we read MRIs for all non-cases.

Analysis Plan

We focused analyses on identifying MRI risk factors for incident radiographic OA, testing cartilage, meniscal, bone marrow and synovial abnormalities. We studied the tibiofemoral compartments and excluded the patellofemoral joint because the lateral joint films provided insufficient radiographic incidence data for the latter joint. Long limb films to measure mechanical alignment, a known risk factor for OA [20] were assessed.

We studied one knee per person. To examine risk factors for incident disease, we used a logistic regression with incidence/no incidence as the dependent variable. For each structure (e.g. cartilage), we used a referent group with a score of 0 and tested whether specific structural abnormality scores increased incidence risk after adjusting for age, sex, body mass index, and alignment. To evaluate the specific association of synovitis with incidence, we additionally adjusted for the knee's maximal cartilage score and maximal meniscal tear and extrusion score. We carried out secondary analyses in which we examined specific sites of synovitis and their relation to incident OA and in which we limited eligible knees to those with Kellgren and Lawrence grade 0 at baseline.

RESULTS

Of subjects in MOST, some were ineligible for MRI (see Figure 2), others had radiographic OA at baseline and were ineligible for this analysis of incident OA and yet others did not come for follow-up. There were 239 incident cases and 731 controls with baseline MRI data (see Table 1 and Figure 2). Baseline body mass index and female gender were increased in cases. Risk of incident OA was increased in knees with baseline KL grade 1 as opposed to grade 0 findings.

In MOST, hyaline cartilage lesions increased risk of disease. However, small lesions extending to bone (grade 2.5) conferred a substantially higher risk of disease than small lesions that did not reach bone (grade 2) (Table 2). Bone marrow lesions also conferred an increased risk of OA. Meniscal tears increased risk of disease as did meniscal extrusion. When tested as a single measure unadjusted for the co-occurrence of other MRI findings, synovitis conferred a modest increased risk of later disease (OR = 1.2 per unit increase of synovitis, 95% CI 1.1, 1.3, p<.001). The odds ratios associated with incidence did not change appreciably when we adjusted for mechanical axis.

When we then adjusted for cartilage defects, meniscal tears and extrusion using the WORMS scores for these findings, we found that synovitis was still associated with incident OA. For the synovitis score as a continuous measure, a one unit increase in the score was associated with an odds or 1.1 of OA (95% CI 1.0, 1.2, p =.02) (see Table 3). However, increasing synovitis score on a continuum was not necessarily associated with an increase in OA risk. Rather scores of 3 or more were associated with a substantial increased risk (adjusted OR 1.6, p =.003) whereas scores of 1 or 2 did not confer a significantly increased risk. Increased risk of OA was seen both for knees with synovitis in the suprapatellar pouch and for knees with synovitis in the Hoffa's fat pad.

Of knees with baseline synovitis scores of 3 or greater, 149/195 (76.4%) had at least one subregion synovitis score of at least 2, whereas that was uncommon for knees with total synovitis scores of 2 (35/214; 16.4%). Of knees with baseline synovitis scores at Hoffa's fat pad of 3 or greater, all had at least one subregion synovitis score of at least 2, whereas that was uncommon for knees with summary scores of 2 (37/113; 32.7%).

When we restricted our analyses to knees with baseline Kellgren and Lawrence scores of 0, our results were similar. For the synovitis score as a continuous measure, a one unit increase was associated with an odds or 1.1 of OA (95% CI 1.0, 1.2, p =.04). A synovitis score of 1 was not associated with an increase in OA risk compared with a synovitis score of 0 (adjusted OR = 0.9, 95% CI 0.7, 1.3), but synovitis scores of 2 or greater were associated with an increased risk of OA after adjustment.

DISCUSSION

Our findings strongly suggest that synovitis is an independent risk factor for new onset knee OA even after adjusting for other structural pathology that has been linked causally to synovitis. Our findings suggest further that small increases in synovitis confer little if any risk, but that risk is limited to knees with substantial increases in synovial volume.

The etiology of OA is complex. Synovitis is triggered by other pathology in the joint including not only cartilage and meniscal damage but by crystal deposition and also by ligamentous damage[21]. Bivariate analyses examining the relation of synovitis with OA could show an association even if the relation of synovitis with OA were completely confounded by factors that cause both synovitis and disease, and strong evidence already exists that cartilage and meniscal damage cause synovitis. Even so, our analysis suggests that synovitis is an independent cause of disease. While bivariate analyses suggested that even small increases in synovitis score increased risk (as shown in Table 2), the multivariable analyses (Table 3) did not confirm this; only when synovitis volume, as assessed by MRI, was increased substantially was OA risk increased.

While the relation of synovitis with OA is confounded by cartilage and meniscal damage, the same approach cannot be used to examine independent effects of cartilage and meniscal damage with incident OA. The causal path tying each these two structures with OA has both an independent line to OA and a line mediated through synovitis and therefore, the relation of cartilage and meniscal damage to OA is not 'confounded' by synovitis. It could be argued that synovitis could cause OA through its own effects on cartilage and that the causal model is more complex than the one we tested. However, we regard the cartilage loss effect as a proxy for incident OA, the outcome we tested.

Other studies have also suggested that more than mild synovitis is required for there to be a deleterious effect on disease progression. For example, in a longitudinal arthroscopy-based study, Ayral[6] reported that reactive synovium (a proliferation of synovial villi of normal morphology) did not confer an increased risk of later cartilage loss whereas 'inflammatory' synovium (hypervascularization seen on arthroscopy) markedly increased risk. In an MRI based study from MOST without adjustment for confounding factors and focusing on

change in cartilage score, Roemer et al[7] reported that only synovitis scores of 2 or greater were associated with cartilage loss. It could be argued that we should not have tested synovitis as a ordinal measure if a threshold of synovitis was required to cause disease, but our results for mild synovitis are equivocal, with small increases in risk that may have reached significance with a bigger sample, so that our approach of testing synovitis as an ordinal measure is justifiable.

The degree of synovial thickening on MRI has been correlated especially with both macroscopic and microscopic evidence of inflammation in the synovium[9, 22]. While non-contrast enhanced MRIs have been validated for the assessment of synovitis[9], we are not sure how an increased score for synovitis on these images translates into enhanced pathology in the synovium. Without contrast enhancement, nodularity within the synovium which might reflect subsynovial infiltration of inflammatory cells cannot be assessed. Increased synovitis scores within the Hoffa's fat pad represent increased signal alterations in an otherwise fatty tissue.

While our work and that of others suggests that synovitis has deleterious effects on knee structure, it is well known that synovitis increases the frequency[9, 23] and severity[8] of pain in persons with knee OA. This evidence, along with the current evidence on structure, suggests that synovitis constitutes an excellent target for treatment. Observational studies, even with adjustment for confounders, do not prove causal associations and trials of treatments abrogating the synovial response in OA may be necessary to prove that synovitis causes disease. Further, we note that the effect of synovitis on incidence disease, as assessed by the associated odds ratios were less for synovitis than for meniscal tears or bone marrow lesions, pointing to the complexity of OA causation and the critical element of mechanopathogenesis in disease causation.

One of the main limitations of our study was the use of non-contrast enhanced MRIs. While the optimal imaging approach would be contrast enhanced images, it was impractical and possibly unethical to perform contrast enhanced images on such a large number of subjects unaffected at the time by osteoarthritis. Further, studies[24] have shown a high correlation between findings on contrast enhanced and non-contrast enhanced images.

In summary, synovitis is an independent cause of incident knee OA, especially synovitis of sufficient severity to increase synovial thickness or increase signal intensity in affected areas of the knee.

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REFERENCES

1. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann.Rheum.Dis. 2001; 60:91–97. [PubMed: 11156538]
2. Nguyen US, Zhang Y, Zhu Y, Niu J, Zhang B, Felson DT. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. Ann.Intern.Med. 2011; 155:725–32. [PubMed: 22147711]
3. Hernandez-Molina G, Neogi T, Hunter DJ, Niu J, Guermazi A, Roemer FW, et al. The association of bone attrition with knee pain and other MRI features of osteoarthritis. Ann.Rheum.Dis. 2008; 67:43–47. [PubMed: 19623678]
4. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA. 2001; 286:188–95. [PubMed: 11448282]
5. Felson DT, McLaughlin S, Goggins J, Lavalley MP, Gale ME, Totterman S, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann.Intern.Med. 2003; 139:330–36. [PubMed: 12965941]
6. Ayral X, Pickering EH, Woodworth TG, Mackillop N, Dougados M. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis -- results of a 1 year longitudinal arthroscopic study in 422 patients. Osteoarthritis.Cartilage. 2005; 13:361–67. [PubMed: 15882559]
7. Roemer FW, Guermazi A, Felson DT, Niu J, Nevitt MC, Crema MD, et al. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. Ann Rheum Dis. 2011; 70:1804–09. [PubMed: 21791448]
8. Hill CL, Hunter DJ, Niu J, Clancy M, Guermazi A, Genant H, et al. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. Ann.Rheum.Dis. 2007; 66:1599–603. [PubMed: 17491096]
9. Fernandez-Madrid F, Karvonen RL, Teitge RA, Miller PR, An T, Negendank WG. Synovial thickening detected by MR imaging in osteoarthritis of the knee confirmed by biopsy as synovitis. Magn Reson.Imaging. 1995; 13:177–83. [PubMed: 7739358]
10. Roemer FW, Felson DT, Yang T, Niu J, Crema MD, Englund M, et al. The association between meniscal damage of the posterior horns and localized posterior synovitis detected on T1-weighted contrast-enhanced MRI--the MOST study. Semin.Arthritis Rheum. 2013; 42:573–81. [PubMed: 23270763]
11. Atukorala I, Kwoh CK, Guermazi A, Roemer FW, Boudreau RM, Hannon MJ, et al. Synovitis in knee osteoarthritis: a precursor of disease? Ann.Rheum Dis. 2014
12. Wang X, Blizzard L, Halliday A, Han W, Jin X, Cicuttini F, et al. Association between MRI-detected knee joint regional effusion-synovitis and structural changes in older adults: a cohort study. Ann.Rheum Dis. 2014
13. Sharma L, Song J, Dunlop D, Felson D, Lewis CE, Segal N, et al. Varus and valgus alignment and incident and progressive knee osteoarthritis. Ann.Rheum.Dis. 2010; 69:1940–45. [PubMed: 20511608]
14. Sled EA, Sheehy LM, Felson DT, Costigan PA, Lam M, Cooke TD. Reliability of lower limb alignment measures using an established landmark-based method with a customized computer software program. Rheumatol Int. 2011; 31:71–77. [PubMed: 19882339]
15. Nevitt MC, Peterfy C, Guermazi A, Felson DT, Duryea J, Woodworth T, et al. Longitudinal performance evaluation and validation of fixed-flexion radiography of the knee for detection of joint space loss. Arthritis Rheum. 2007; 56:1512–20. [PubMed: 17469126]
16. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis.Cartilage. 2004; 12:177–90. [PubMed: 14972335]

17. Felson DT, Niu J, Guermazi A, Sack B, Aliabadi P. Defining radiographic incidence and progression of knee osteoarthritis: suggested modifications of the Kellgren and Lawrence scale. Ann Rheum Dis. 2011; 70:1884–86. [PubMed: 21908453]

18. Lynch JA, Roemer FW, Nevitt MC, Felson DT, Niu J, Eaton CB, et al. Comparison of BLOKS and WORMS scoring systems part I. Cross sectional comparison of methods to assess cartilage morphology, meniscal damage and bone marrow lesions on knee MRI: data from the osteoarthritis initiative. Osteoarthritis Cartilage. 2010; 18:1393–401. [PubMed: 20816979]

19. Felson DT, Lynch J, Guermazi A, Roemer FW, Niu J, McAlindon T, et al. Comparison of BLOKS and WORMS scoring systems part II. Longitudinal assessment of knee MRIs for osteoarthritis and suggested approach based on their performance: data from the Osteoarthritis Initiative. Osteoarthritis.Cartilage. 2010; 18:1402–07. [PubMed: 20851202]

20. Sharma L, Chmiel JS, Almagor O, Felson D, Guermazi A, Roemer F, et al. The role of varus and valgus alignment in the initial development of knee cartilage damage by MRI: the MOST study. Ann.Rheum.Dis. 2013; 72:235–40. [PubMed: 22550314]

21. Benjamin M, McGonagle D. Histopathologic changes at “synovio-entheseal complexes” suggesting a novel mechanism for synovitis in osteoarthritis and spondylarthritis. Arthritis Rheum. 2007; 56:3601–09. [PubMed: 17968880]

22. Loeuille D, Chary-Valckenaere I, Champigneulle J, Rat AC, Toussaint F, Pinzano-Watrin A, et al. Macroscopic and microscopic features of synovial membrane inflammation in the osteoarthritic knee: correlating magnetic resonance imaging findings with disease severity. Arthritis Rheum. 2005; 52:3492–501. [PubMed: 16255041]

23. Baker K, Grainger A, Niu J, Clancy M, Guermazi A, Crema M, et al. Relation of synovitis to knee pain using contrast-enhanced MRIs. Ann.Rheum.Dis. 2010; 69:1779–83. [PubMed: 20472593]

24. Krasnokutsky S, Belitskaya-Levy I, Bencardino J, Samuels J, Attur M, Regatte R, et al. Quantitative magnetic resonance imaging evidence of synovial proliferation is associated with radiographic severity of knee osteoarthritis. Arthritis Rheum. 2011; 63:2983–91. [PubMed: 21647860]

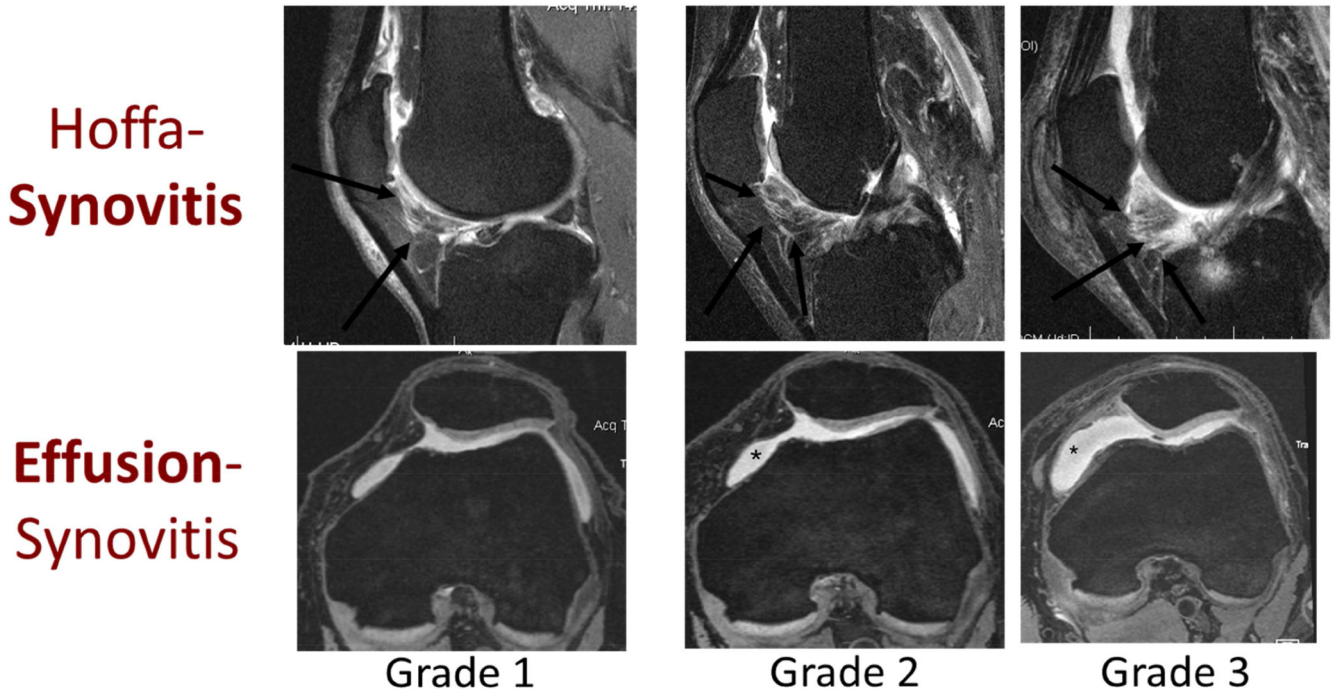

Figure 1. Examples of Synovitis Scoring From MOST MRIs

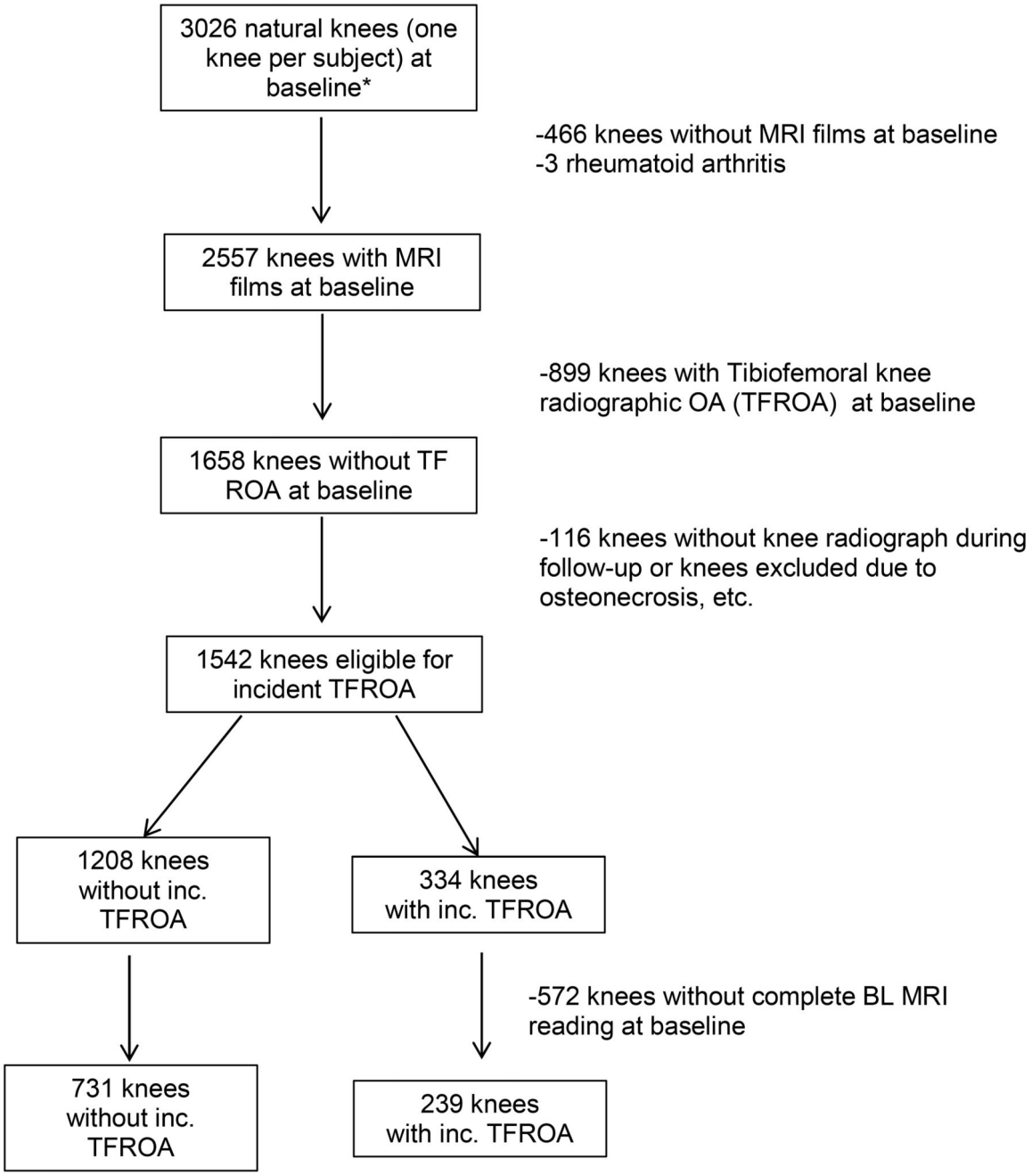

Figure 2. Flow Chart

TABLE 1
Characteristics of Incident Radiographic OA (ROA) Cases and Controls in MOST

	ROA cases (N=239)	Non ROA controls (N=731)
Baseline		
Baseline age, year, mean (SD)	61.6 (7.7)	60.3 (7.4)
Baseline BMI, kg/m^{2}mean (SD)	30.8 (5.3)	28.8 (4.6)
Baseline physical activity scale for the elderly (PASE), mean (SD)	186.1 (89.9)	184.1 (85.5)
Women, N(%)	162 (67.8%)	417 (57.0%)
Whites, N(%)	203 (84.9%)	634 (86.7%)
Baseline history of knee injury, N(%)	54 (22.6%)	144 (19.8%)
Baseline KL grade 1, N(%)	135 (56.5%)	142 (19.4%)
Baseline HKA, degree, mean (SD)		
Varus (<179)	84 (35.9%)	295 (40.5%)
Neutral (179-181)	109 (46.6%)	307 (42.1%)
Valgus (>181)	41 (17.5%)	127 (17.4%)

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TABLE 2

MOST Study - Baseline MRI features and incident TFOA

		Non ROA knees (N=731)	Inc ROA knees (N=239)	Crude model		Adjusted model 1[1]		Adjusted model 2[2]	
MRI feature at baseline	**level**	**n (%) of MRI feature**	**n (%) of MRI feature**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Cartilage Lesion*	0:none	293 (84.9)	52 (15.1)	1		1		1	
	2	124 (82.7)	26 (17.3)	1.2(0.9,1.6)	0.3111	1.3(0.9,1.8)	0.11	1.3(1.0,1.8)	0.08
	3-4	119 (61.3)	75 (38.7)	2.5(2.0,3.1)	<.0001	2.6(2.1,3.4)	<.0001	2.7(2.1,3.4)	<.0001
	5-6,2.5	195 (69.4)	86 (30.6)	3.4(2.6,4.3)	<.0001	4.1(3.1,5.2)	<.0001	4.2(3.2,5.4)	<.0001
Bone marrow lesion [3], Maximum of 10 subregions	0:none	566 (78.5)	155 (21.5)	1		1		1	
	1	133 (69.6)	58 (30.4)	1.5(1.3,1.9)	<.0001	1.7(1.4,2.1)	<.0001	1.7(1.4,2.2)	<.0001
	2-3	32 (55.2)	26 (44.8)	2.7(2.0,3.8)	<.0001	3.1(2.2,4.3)	<.0001	3.0(2.1,4.2)	<.0001
Meniscal tear, Maximum of 6 subregions	0:none	582 (82.3)	125 (17.7)	1		1		1	
	1	40 (59.7)	27 (40.3)	2.9(2.1,3.9)	<.0001	3.9(2.8,5.4)	<.0001	3.9(2.8,5.5)	<.0001
	2	82 (59.0)	57 (41.0)	2.9(2.3,3.6)	<.0001	3.9(3.0,5.0)	<.0001	3.7(2.9,4.8)	<.0001
	3	27 (47.4)	30 (52.6)	5.3(3.8,7.3)	<.0001	8.0(5.6,11.4)	<.0001	7.4(5.2,10.6)	<.0001
Meniscal extrusion, Maximum of 2 subregions	0:none	532 (80.6)	128 (19.4)	1		1		1	
	1	180 (64.8)	98 (35.3)	1.4(1.2,1.7)	0.0002	1.5(1.2,1.8)	<.0001	1.6(1.3,1.9)	<.0001
	2	19 (59.4)	13 (40.6)	1.6(1.2,2.1)	0.0005	1.6(1.2,2.2)	0.0005	1.6(1.2,2.2)	0.0007
Summary score of synovitis (2 subregions) and effusion (1 subregion), continuous				1.2(1.1,1.3)	<.0001	1.2 (1.1,1.3)	<.0001	1.2(1.1,1.3)	<.0001
Summary score of synovitis (2 subregions) and effusion (1 subregion)	0:none	207 (81.8)	46 (18.2)	1		1		1	

		Non ROA knees (N=731)	Inc ROA knees (N=239)	Crude model		Adjusted model 1[1]		Adjusted model 2[2]	
MRI feature at baseline	**level**	**n (%) of MRI feature**	**n (%) of MRI feature**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
	1	240 (77.9)	68 (22.1)	1.3(1.0,1.7)	0.0369	1.2(0.9,1.5)	0.25	1.2(0.9,1.5)	0.24
	2	159 (74.3)	55 (25.7)	1.6(1.2,2.1)	0.0004	1.5(1.1,1.9)	0.004	1.5(1.1,2.0)	0.005
	3+	125 (64.1)	70 (35.9)	2.3(1.8,3.0)	<.0001	2.1(1.6,2.8)	<.0001	2.2(1.7,2.9)	<.0001
Summary score of synovitis at Hoffa's fat pad (2 subregions), continuous				1.1(1.0,1.2)	0.003	1.1(1.1,1.2)	0.0007	1.2 (1.1,1.2)	0.0005
Summary score of Hoffa's fat pad (2 subregions)	0:none	353 (79.3)	92 (20.7)	1		1		1	
	1	242 (72.2)	93 (27.8)	1.5(1.2,1.8)	<.0001	1.6(1.3,1.9)	<.0001	1.6(1.3,2.0)	<.0001
	2	84 (74.3)	29 (25.7)	1.2(0.9,1.6)	0.1628	1.3(1.0,1.8)	0.05	1.3(1.0,1.8)	0.07
	3+	52 (67.5)	25 (32.5)	1.7(1.3,2.4)	0.0006	1.7(1.2,2.4)	0.0010	1.8(1.3,2.5)	0.0005
Synovitis / Effusion (1 subregion)	0:none	366 (81.3)	84 (18.7)	1		1		1	
	1	306 (72.7)	115 (27.3)	1.7(1.5,1.9)	<.0001	1.5(1.3,1.7)	<.0001	1.5(1.3,1.7)	<.0001
	2-3	59 (59.6)	40 (40.4)	2.8(2.3,3.3)	<.0001	2.4(2.0,2.9)	<.0001	2.5(2.1,3.0)	<.0001

[1] Adjusted model 1: adjusting for baseline age, sex, race, BMI, PASE, history of knee injury

[2] Adjusted model 2: adjusting for baseline age, sex, race, BMI, PASE, history of knee injury, malalignment

* cartilage lesion scores of 2.5, 5 or 6 constitute lesions extending to bone.

TABLE 3

Association of synovitis with incident OA in 970 MOST knees after adjustment for cartilage defects, meniscal tears and extrusion

		Adjusted model[1]		Adjusted model[2]	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Summary score of synovitis (2 subregions) and effusion (1 subregion)	0:none	1		1	
	1	1.1(0.8,1.4)	0.72	1.1(0.8,1.4)	0.71
	2	1.1(0.9,1.5)	0.37	1.1(0.8,1.5)	0.43
	3+	1.5(1.1,2.1)	0.004	1.6 (1.2,2.1)	0.003
Summary score of synovitis (2 subregions) and effusion (1 subregion), continuous		1.1(1.0,1.1)	0.03	1.1(1.0,1.2)	0.02

[1] Adjusted model 1: adjusting for baseline age, sex, race, BMI, PASE, history of knee injury, WORMS cartilage score, meniscal tears and meniscal extrusion

[2] Adjusted model 2: adjusting for baseline age, sex, race, BMI, PASE, history of knee injury, WORMS cartilage score, meniscal tears and meniscal extrusion and malalignment