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Severe radiographic knee osteoarthritis – does Kellgren and Lawrence grade 4 represent end stage disease? – the MOST Study

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Abstract

Objective—To determine what MRI-detectable osteoarthritis features that are not visualized on radiography demonstrate progression longitudinally in Kellgren and Lawrence (KL) grade 4knees.

Methods—We studied subjects from the Multicenter Osteoarthritis Study who had KL grade 4 knees at baseline and had baseline and 30-month MRI. Cartilage damage, bone marrow lesions (BMLs), meniscal damage, synovitis (signal changes in Hoffa fat pad), and effusion (fluid

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- **(c)** Final approval of the version to be published: All authors
- **(d)** Literature search: AG, DH, FWR
- **(e)** Statistical expertise: DTF, KW, MN
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equivalent signal in the joint cavity) were semiquantitatively scored using the WORMS system in 5 subregions of the medial and lateral tibiofemoral (TF) compartments. Analysis was performed for the compartment showing bone-on-bone appearance ("index") on radiograph and also for the other TF compartment of the same knee. Synovitis and effusion were assessed for the whole knee. Changes in scores at follow-up were noted for each feature. For cartilage and BML, within-grade changes were also recorded.

Results—140 subjects (164 knees) were included (50% women, mean age 66.0±8.6 years, mean BMI 30.4±5.1 kg/m^2). Longitudinally, 51 index compartments (34%) showed an increase in the sum of cartilage scores from all subregions. In the other compartment, 25% showed an increase in the sum score for cartilage damage. For BMLs in the index compartment, 50 knees (33%) showed an increase in maximum score and 32 (21%) showed a decrease. Meniscal status mostly remained stable. Effusion worsened in 36 knees (25%) and improved in 13 knees (9%). Synovitis worsened in 14 knees (10%) and improved in 6 knees (4%).

Conclusion—In KL grade 4 knees, MRI-detected cartilage loss and fluctuation of BMLs, effusion, and synovitis occurred frequently over a 30-month period.

Keywords

end-stage; osteoarthritis; MRI; knee; radiography

Introduction

In Kellgren and Lawrence scoring system [1], grade 4 (KL4) is the highest grade that can be assigned and once a knee is assigned to be KL4 with bone-on-bone contact at the tibiofemoral joint the severity of radiographic osteoarthritis (OA) based on KL system cannot progress any further even if there is further structural progression. However, since radiography is unable to directly depict cartilage damage [2], cartilage loss over time in a KL4 knee can be missed if follow-up is only assessed by radiography in a longitudinal study. Furthermore, bone marrow lesions are an important feature of OA not visualized by radiography. Bone marrow lesions are associated with pain [3] and thus can potentially become a target for clinical trials. Additionally, a recent study showed that meniscal pathology on MRI increases the risk for both incident and enlarging subchondral bone marrow lesions of the knee [4]. Lastly, synovitis and effusion can be seen in knee OA and it has been demonstrated that synovitis is associated with pain in OA [5,6].

MRI is able to reveal cartilage damage, bone marrow lesions, meniscal pathology or the presence of synovitis which cannot be appreciated by radiography. To date, there is paucity of evidence to demonstrate if KL4 knees represent true 'end-stage' OA, i.e. it is unclear if MRI shows progression or worsening of OA features in KL4 knees in a longitudinal study.

Nowadays there is a trend that OA researchers focus on early disease detection, which is certainly appropriate given the fact prevention of a disease or early intervention is better than trying to treat far advanced disease. On the other hand, it is unclear if excluding patients with KL4 knees from OA studies and clinical trials is actually an appropriate thing to do just because they 'already have end-stage radiographic knee OA'. Indeed, a study

based on the Osteoarthritis Initiative data showed KL4 knees had high rates of MRI-detected quantitative cartilage thickness loss and concluded that, from the perspective of sensitivity to change, KL4 knees need not be excluded from longitudinal studies using MRI cartilage morphology as an end point [7].

While there are several OA grading systems based on radiography [1, 8–11], and thus "radiographic end-stage OA" can potentially be defined by more than one ways, KL grading is a system that is most widely used for screening purposes of patients being enrolled onto OA research studies and clinical trials. Other scoring system such as the Cooke grading may be better suited to address the question at hand, but as KL grading is the only one available in MOST, our study needed to focus on KL4 knees.

The aim of our study was to determine if five major features of knee OA only detectable by MRI, i.e. cartilage damage, bone marrow lesions, meniscal damage, Hoffa-synovitis, and effusion-synovitis, demonstrate longitudinal progression in KL4 knees.

Methods

Study design and subjects

The Multicenter Osteoarthritis (MOST) Study is a prospective cohort study of 3026 individuals aged 50–79 years with or at high risk of knee OA. Those considered at high risk included persons who were overweight or obese, those with knee pain, aching or stiffness on most of the last 30 days, a history of knee injury that made it difficult to walk for at least 1 week, or previous knee surgery. Subjects were recruited from two US communities, Birmingham, Alabama and Iowa City, Iowa. The study protocol was approved by the Institutional Review Boards at the University of Iowa, University of Alabama, Birmingham, University of California, San Francisco and Boston University Medical Campus.

Subjects were excluded from MOST if they screened positive for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, had renal insufficiency that required hemo- or peritoneal dialysis, a history of cancer (except for non-melanoma skin cancer), had or planned to have bilateral knee replacement surgery, were unable to walk without assistance, or were planning to move out of the area in the next 3 years. Assessments at the baseline and 30-month follow-up were performed using the same protocol, and each included a telephone interview and clinic visit.

Our study sample included all subjects who had at least one KL 4 knee with 'bone-on-bone' appearance in the medial and/or lateral tibiofemoral compartment on radiography, and had MRI examination at baseline and at 30-month follow-up visit.

Radiography

At baseline, all subjects underwent weight-bearing postero-anterior fixed flexion view knee radiographs using the SynaFlexer positioning frame (Synarc, San Francisco, CA)[12]. A musculoskeletal radiologist and a rheumatologist (who are not co-authors) with over 10 years experience each in reading study films and over 30 years of clinical experience graded all baseline postero-anterior films independently according to KL grading, blinded to

clinical and MRI data. For subjects who had both baseline and follow-up radiographs, disagreements in radiographic reading among the readers were adjudicated by a panel of three readers (DTF and the other two readers). The weighted kappa coefficient of interobserver reliability for the KL grade readings was 0.79.

MRI acquisition

At baseline and follow-up, MRI scans were obtained with a 1.0 T MR system (OrthOne, ONI Medical Systems, Wilmington, MA) with a circumferential transmit-receive extremity coil using a fat-suppressed (FS) fast spin echo (FSE) proton density-weighted (PD-w) sequence in two planes: sagittal, repetition time (TR) = 4800 ms, echo time (TE) = 35 ms, 3 mm slice thickness, 0 mm interslice gap, 30 slices, 288 × 192 matrix, number of excitations (NEX) = 2, 140 × 140 mm field of view (FOV), echo train length (ETL) = 6; and axial (TR = 4680 ms, TE = 13 ms, 3 mm slice thickness, 0 mm interslice gap, 26 slices, 288 × 192 matrix, NEX = 2, 140 × 140 mm FOV, ETL = 10). Also, a short-tau inversion recovery (STIR) sequence in the coronal plane was obtained (TR = 8448 ms, TE = 17 ms, TI = 100 ms, 3 mm slice thickness, 0 mm interslice gap, 34 slices, 256 × 192 matrix, two NEX, 140 × 140 mm FOV, ETL = 8).

MRI interpretation

MRI findings of knee OA were semiquantitatively assessed with the Whole Organ MRI Score (WORMS) method by two musculoskeletal radiologists (AG, FWR) who were experts of standardized semiquantitative MRI assessment of knee OA with 14 and 11 years of experience, respectively. Readers were blinded to clinical and radiographic data including the alignment status, and unaware of the study hypothesis, and read the paired images separately with knowledge of time sequence [13].

Cartilage was scored on a 0–6 scale at baseline and at 30-month follow-up in five tibiofemoral subregions (anterior, central and posterior tibial, and central and posterior femoral) of the medial and lateral compartments using WORMS [14] as follows: Grade 0 = normal thickness and signal; 1=normal thickness but increased signal on T2-weighted images; 2.0=partial-thickness focal defect <1 cm in greatest width; 2.5=full-thickness focal defect <1 cm in greatest width; 3=multiple areas of partial-thickness (Grade 2.0) defects intermixed with areas of normal thickness, or a Grade 2.0 defect wider than 1 cm but <75% of the region; 4=diffuse (≥75% of the region) partial-thickness loss; 5=multiple areas of full-thickness loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but <75% of the region; 6=diffuse (≥75% of the region) full-thickness loss. Cartilage scores from all five subregions were summed up to create the summary cartilage score (0–30) for each compartment. Also, a maximum subregional score within a compartment was recorded. For cartilage, we recorded increase in cartilage score (i.e. worsening cartilage damage) between baseline and follow-up. Within-grade scoring for recording longitudinal change was also deployed, including those knees with baseline cartilage score of 6 [15]. The use of within-grade scoring enabled us to detect any potential progression of grade 6 cartilage damage by assigning a grade of 6.5 where appropriate, i.e. we did not consider grade 6 cartilage damage as a ceiling score that could not progress further. WORMS defines a grade 6 lesion for

cartilage as a subregion with more than 75% of full thickness damage, which still leaves room for progression until 100% of full thickness loss is observed in a given subregion.

Subchondral bone marrow lesions were scored on a 0–3 scale (0 = none; 1 = <25% of the subregion; 2 = 25–50%; 3 = >50%) at baseline and at 30-month follow-up in five tibiofemoral subregions (same as above) of the medial and lateral compartments, using WORMS as follows: A maximum subregional score within a compartment was recorded. Within-grade scoring for recording longitudinal change was also deployed, including those knees with baseline score of 3 [15]. We did not assess the summary bone marrow lesion score for each compartment, since bone marrow lesions can both progress and regress over time within each subregion, unlike cartilage damage which can only worsen over time, and interpretation of summary score is difficult (e.g. summary score may be the same at baseline and follow-up, but the unchanged summary score at follow-up may mask a possible scenario in which the same degree of increase and decrease in scores in different subregions within the same compartment cancelled out overall. In such a case, it is difficult to judge if this compartment demonstrates interval progression, improvement, or unchanged status.)

Meniscal damage was scored on a 0–4 scale at baseline and at 30-month follow-up in the anterior horn, body and posterior horn of the medial or lateral meniscus (0=intact; 1=minor radial tear or parrot beak tear; 2=non-displaced tear or prior surgical repair; 3=displaced tear or partial resection; 4=complete maceration/destruction or complete resection). Then, the following scheme was used to determine total scores for the medial or lateral meniscus (category 0 = score zero in all subregions; category 1 = at least one 1, but no>1; category 2 = 2 in only one subregion; category 3 = 2 in more than one subregion; category 4 = 3 in one or more subregion; category 5 = 4 in only one subregion; category 6= 4 in more than one subregion). Only the meniscus belonging to the compartment in which bone-on-bone appearance was observed on radiography was taken into account. There was no subject who had bone-on-bone appearance in both medial and lateral compartments.

Signal changes within the Hoffa fat pad, a surrogate marker for synovitis on non-contrast MRI, was scored on a 0–3 scale at infrapatellar and intercondylar sites (0=none; 1=mild; 2=moderate; 3=severe) and the maximum grade at either site was recorded. Hoffa fat pad is an intracapsular but extrasynovial structure that is lined by synovial tissue and includes fat, vessels and synovium. Increased signal in this tissue is a possible surrogate for synovitis. In this manuscript, we will refer to this feature as “Hoffa synovitis” to differentiate it from the other measure for synovitis on non-contrast MRI, as described below.

Joint effusion (high T2 signal filling the joint cavity) was scored on a 0–3 scale (0=none; 1= <33% of maximum potential distension of the synovial cavity; 2= ≥33% and ≤66% of maximum potential distension; 3= >66% maximum potential distension). On non-contrast MRI, it is not possible to discriminate between synovial fluid (true effusion) and the synovial lining of the distended and fluid-filled joint cavity, hence “effusion” is actually a composite measure of fluid and thickened synovium (synovitis). For this reason, in this manuscript, we call this feature “effusion-synovitis” to reflect the composite nature of this imaging finding on fluid sensitive sequences.

The weighted kappa coefficients of interobserver reliability for the MRI semiquantitative readings were 0.78 for cartilage morphology, 0.62 for bone marrow lesions, 0.80 for meniscal tears, 0.65 for effusion-synovitis, and 0.65 for Hoffa-synovitis.

Statistical analysis

This was a descriptive study to show the proportion of subjects who demonstrated changes in MRI-detected OA features between baseline and 30-month follow-up. We stratified the data according to sex, age group (<60, ≥60), and BMI group (<25, ≥25), and used Cochran-Mantel-Haenszel Statistics to assess the presence of statistically significant differences between men and women, and among different age and BMI groups. Age 60 was chosen because roughly half of our sample was above and below this threshold. This was not true of a BMI of 25, however. We chose that threshold because we were interested in whether overweight and obesity (BMI ≥25) drove continued disease progression in those with advanced disease or whether progression was present even in those considered non-overweight. For cartilage damage, bone marrow lesions, and meniscal damage, results were stratified according to the index compartment (the one with bone-on-bone appearance) and the non-index compartment of the tibiofemoral joint. As mentioned before, there was no subject who had bone-on-bone appearance in both medial and lateral compartments. All statistical analyses were performed with SAS for Windows, version 9.1. Results were considered to be significant when a two tailed $P<0.05$.

Results

140 subjects (164 knees) were included (50% women, 83% White, mean age 66.0±8.6 years, mean BMI 30.4±5.1 kg/m^2). For analysis of cartilage damage, bone marrow lesions, meniscal damage and Hoffa-synovitis, no statistically significant differences were noted among different sex, BMI and age groups. At baseline, in the index TF compartment (medial compartment in 127 knees, lateral compartment in 37 knees), all knees showed severe cartilage damage (Table 1). Subregional analysis demonstrated that the central femoral and central tibial subregions (i.e. subregions that are the first points of contact on weight-bearing) showed grade 5 or 6 cartilage damage in almost all knees within the index compartment (Table 1). Other subregions in the index compartment showed variable degrees of cartilage damage at baseline. In contrast, in the non-index compartment, most knees showed none to mild cartilage damage in all subregions (Table 1). Longitudinally, 51 index compartments (34%) showed an increase in the sum of cartilage scores from all subregions, and 7 (5%) showed an increase in the maximum cartilage score (Table 1). Weight-bearing subregions within the index tibiofemoral compartment (central femoral and tibial subregions) mostly did not show progression of cartilage damage at follow-up. However, 21.6%of knees showed progression of cartilage damage in the posterior femoral subregion. In the non-index compartment, 40 knees (26%) showed an increase in the sum score for cartilage damage, while 28 knees (18%) showed an increase in maximum subregional score (Table 1).

For bone marrow lesions, 129 knees (81%) showed moderate to large lesions (maximal WORMS score 2 or 3) (Table 2) in the index compartment. Longitudinally, in the index

compartment, 50 knees (33%) showed an increase in maximum score and 32 (21%) showed a decrease (Table 2).

Changes of bone marrow lesion scores were also seen in the non-index compartment, but to a lesser extent.

In the index compartment, 157 knees (95.1%) had severe meniscal damage (i.e. displaced tear or maceration) (Table 3), while in the non-index compartment 123 knees (92%) had no meniscal damage. Meniscus status mostly remained the same in the index and non-index compartments (Table 3).

At baseline, 91 knees (56%) had moderate to severe effusion-synovitis and 135 knees (84%) had mild or moderate Hoffa-synovitis. Effusion-synovitis worsened in 36 knees (25%) and improved in 13 knees (9%), with score increase seen more frequently in women (39.4%, 28/71) than in men (8/71, 11.3%, p=0.0006). There were no statistically significant differences between different BMI and age groups. Hoffa-synovitis worsened in 14 knees (10%) and improved in 6 knees (4%).

Discussion

Our study demonstrated that, in KL grade 4 knees, progression of MRI-detected cartilage loss and fluctuation of bone marrow lesions, effusion-synovitis, Hoffa-synovitis occurred frequently over a 30-month period (Figure 1). Meniscal status remained essentially stable. Overall, it appears that OA disease process is still ‘active’ and the term ‘end-stage’ no longer seems to be appropriate when MRI is used to image KL grade 4 knees.

We observed all KL grade 4 knees had MRI-confirmed severe cartilage damage in the index tibiofemoral compartment (bone-on-bone appearance on radiography). In this regard, it can be said that KL grading based on radiography is a highly sensitive for detection of severe cartilage loss in the form of bone-on-bone appearance, using MRI as the reference. On the other hand, such sensitivity is confined to the most weight-bearing subregion of the tibiofemoral joint, i.e. central femoral and central tibial subregions, and KL grading based on radiography is unable to accurately assess the integrity of cartilage in other subregions (posterior femoral, anterior tibial and posterior tibial) in the absence of bone-on-bone appearance. This finding is in line with data from a population based study that showed various severity of MRI-detected cartilage damage exists in knees without radiographic OA [2,16]. The highest frequency of cartilage damage progression at follow-up was seen in the posterior femoral subregion in the index compartment. On radiography, it is not possible to assess the status of articular cartilage in the posterior femur because there is no opposing tibia with which to create the ‘joint space’ when the knee is extended or slightly flexed. A recent observational study showed cartilage damage in the posterior femoral subregion is much lower than that seen in central weight-bearing subregions [2,17,18]. This is likely due to the fact that this portion of cartilage does not bear weight when the patient is standing, and thus is not subjected to as much mechanical load as central weight-bearing subregions, leading to relative sparing of cartilage at baseline and giving rise to potential for progression

of damage at follow-up (while the central weight-bearing subregions have already been damage to such a severe extent that they cannot progress any further).

It was not surprising that only less than 5% of knees showed interval increase in the maximal subregional cartilage score in the index compartment. Perhaps, this rate of progression is somewhat lower than expected, given the evidence from a study by Eckstein et al that showed KL4 knees had the highest rate of quantitative cartilage thickness loss compared to KL0-3 knees [7]. However, that study did not separate 'index' and 'non-index' compartments and therefore their analytic approach may not be directly comparable to our study. In our study, 18.1% of knees showed increase in the maximal subregional cartilage score in the non-index compartment. Interestingly, in the non-index compartment, highest frequency of cartilage damage progression was seen in the central femoral and the central tibial subregions. This implies that once cartilage damage becomes so severe in the index compartment that it cannot progress any further (bone-on-bone), then the most weight-bearing subregions (central femoral and central tibial) of the nonindex compartment will primarily start losing cartilage. Knees that are KL grade 4 at baseline are expected to be the same KL grade at follow-up, since it cannot progress beyond grade 4, provided the same and appropriate imaging acquisition technique is deployed at baseline and follow-up [19]. However, both index (33.5%) and non-index (25.8%) compartments showed progression in cumulative cartilage damage in each compartment in the form of increase in the summed score from all subregions – again demonstrating the limitation of radiography-based KL grading. Also, this finding highlights the importance of deploying within-grade scoring for longitudinal studies when semiquantitative MRI reading is used as an outcome measure, e.g. WORMS grade 6 cartilage damage can still progress to grade 6+ at follow-up.

Despite the fact that very little cartilage damage progression occurred in the index compartment, a large proportion of bone marrow lesions showed either increase or decrease in severity, irrespective of the subject's sex, BMI or age. Exact pathogenesis of bone marrow lesions and their role in the knee osteoarthritis disease pathway is still under investigation. Previous epidemiological studies have reported MRI-detected bone marrow lesions can be present in knees without radiographic knee osteoarthritis [16,20] and fluctuation in lesion size/severity over time occurs in persons with or without knee osteoarthritis [21,22]. Our study demonstrated bone marrow lesions can still fluctuate in size/severity even when the cartilage damage has become so severe that is it not progressing any more in the index compartment. Our finding, together with available literature evidence, suggests bone marrow lesions have a mechanism for size fluctuation independent of the cartilage status in the same compartment.

Over 80% of KL4 knees had mild to moderate (grade 1 and 2) effusion-synovitis and Hoffa-synovitis. 25.4% of effusion-synovitis progressed at follow-up, while 9.2% regressed. 10% of Hoffa-synovitis progressed, while 4.3% regressed. Presence of histologically proven synovitis in 'end-stage' knee osteoarthritis requiring total knee replacement has been reported [23]. However, such fluctuation of effusion-synovitis and Hoffa-synovitis has not been reported in KL4 knees. Presence of synovitis indicates active 'inflammatory' disease process and implies that it is incorrect to call all KL4 knees as 'end-stage' osteoarthritis. A recent observational study based on MOST study [5] showed a linear increasing trend for

severity of synovitis with higher KL grade. Furthermore, it is known that synovitis is a risk factor for progression of knee structural damages in osteoarthritis [24–27], thus as long as synovitis is present the osteoarthritis disease process likely continues to progress even in KL4 knees.

The current trend in the osteoarthritis research community is to focus on early osteoarthritis [28], however our study demonstrated KL 4 knees can still provide useful information in regard to knee osteoarthritis disease mechanism and thus should not be forgotten. Specifically, KL4 knees should not be automatically excluded from osteoarthritis clinical trials, since lesions fluctuating with pain, i.e. fluctuating bone marrow lesions and synovitis, can be observed in such knees and high rates of cartilage loss are observed in KL4 knees. These fluctuating lesions can potentially be targeted for medical therapy to provide symptomatic relief.

Limitations of our study include a lack of arthroscopic evaluation of cartilage and meniscal damage as well as histologic confirmation of synovitis in the knee joint. However, these are only possible in patients who undergo arthroscopy and such invasive examination is outside the scope of the MOST study, which is an epidemiologic observational study. For assessment of synovitis, use of contrast-enhanced MRI would have been ideal, however longitudinal data for synovitis based on contrast-enhanced MRI is not available and thus could not be incorporated into our longitudinal study. Nevertheless, the use of effusion-synovitis and Hoffa-synovitis as an imaging marker for synovitis in knee osteoarthritis is a commonly deployed method based on non-contrast enhanced MRI. An additional potential limitation is a lack of data regarding specific activity immediately prior to MRI scan, which could have affected the severity of effusion-synovitis and Hoffa-synovitis. The use of semiquantitative grading including within-grade scoring is nowadays commonly deployed method when using MRI-derived data. However, we do note that the WORMS system is only one of several standardized MRI grading scales available to assess the degree of joint degeneration on MRI and that there is limited validation of the grades of Hoffa-synovitis and effusion-synovitis, as well as the use of within-grade scoring in semiquantitative MRI analysis.

Conclusion

Our study focused on KL 4 knees, which are generally considered to have ‘end-stage’ knee osteoarthritis. We demonstrated progression of cartilage damage can frequently occur especially in the non-index tibiofemoral compartment. Fluctuation of bone marrow lesions and effusion-synovitis and Hoffa-synovitis also frequently occurs in KL 4 knees. While KL 4 knees cannot progress any further on the basis of radiographic findings, disease progression that could be only detected by MRI occurred often, highlighting the limitation of radiographic KL grading system both for screening purposes and for longitudinal studies of disease progression in knee osteoarthritis.

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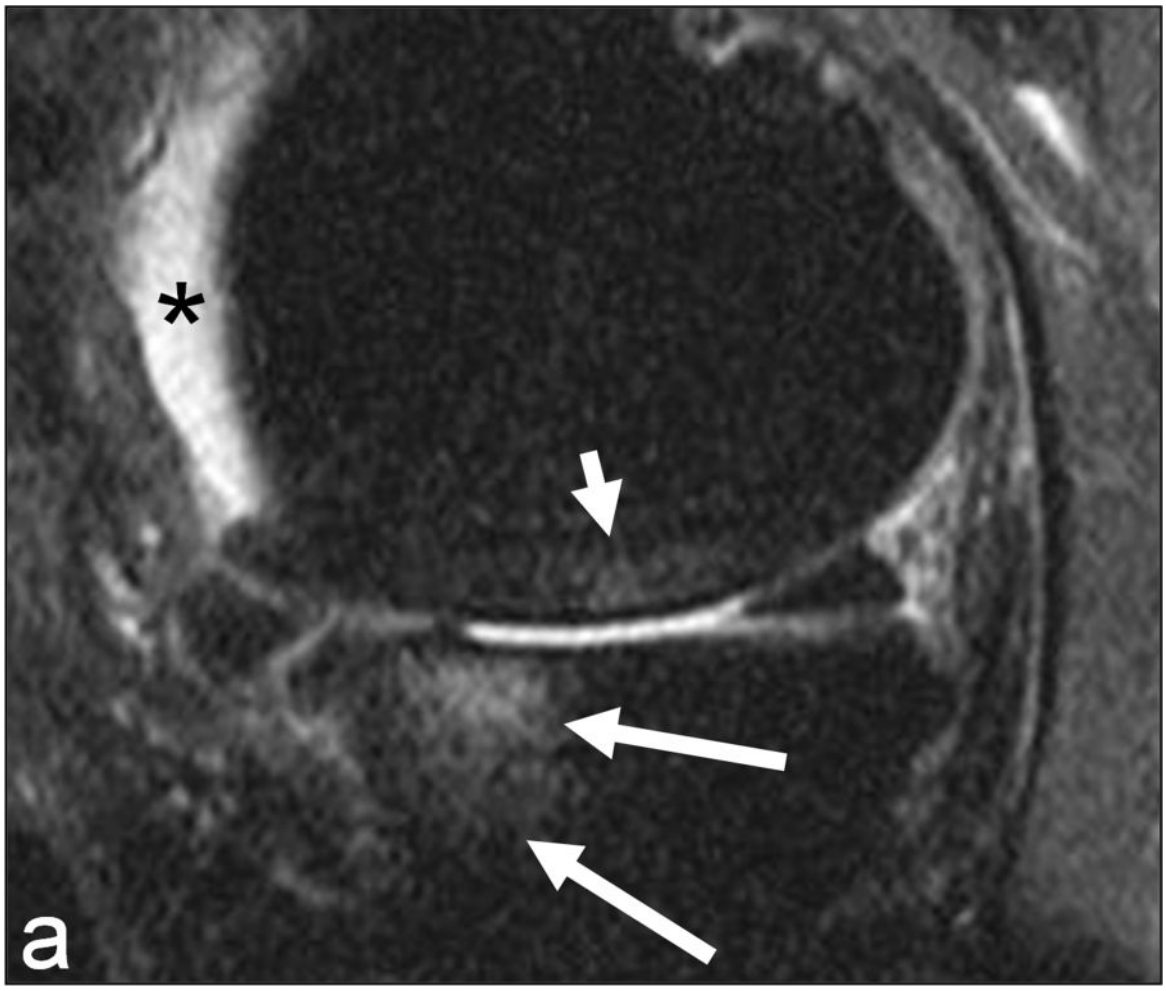

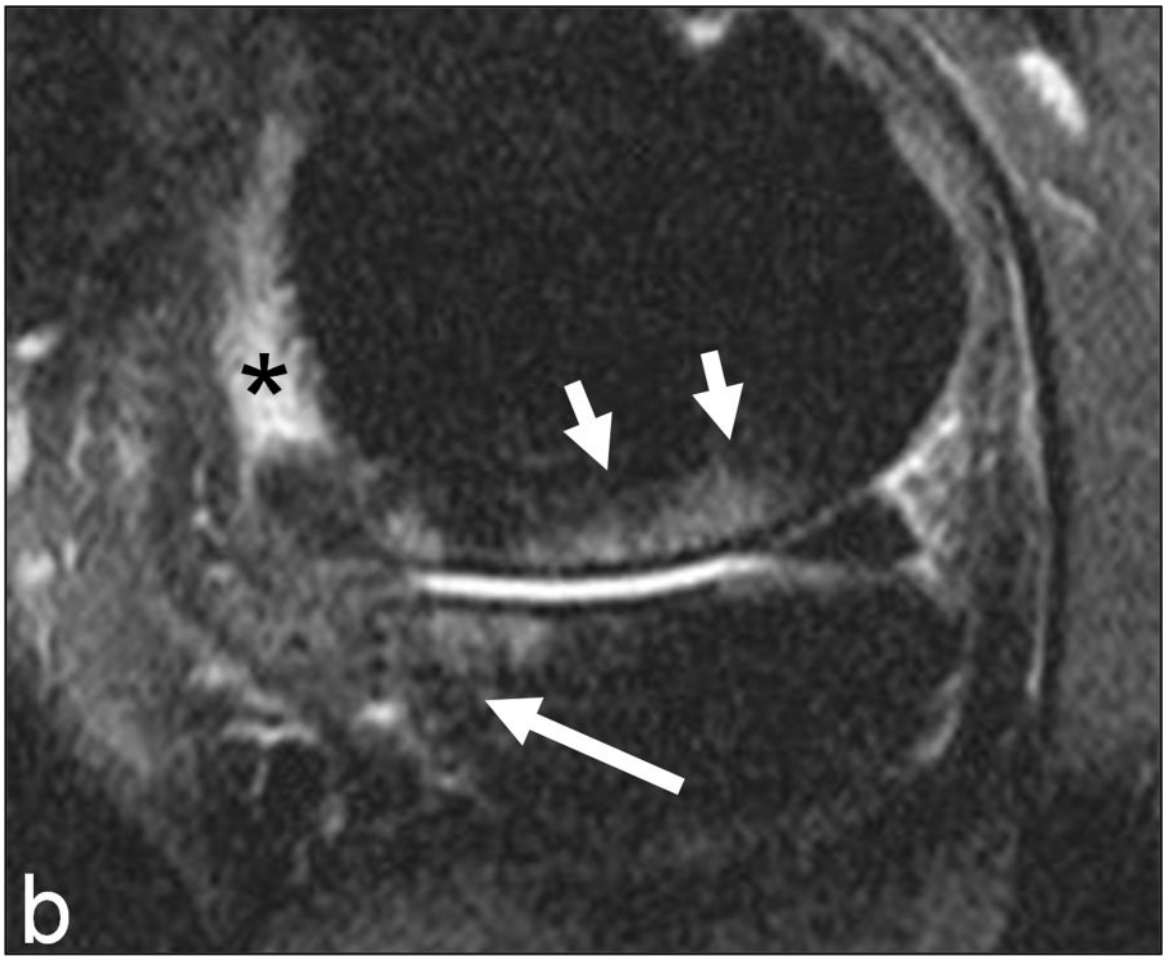

Figure 1.

a. Sagittal Fs PDw baseline MRI shows tibiofemoral cartilage loss and subchondral bone marrow lesions in the femur (short arrow) and the tibia (long arrows).

b. Sagittal Fs PDw 30-month follow-up MRI shows worsening of the tibiofemoral cartilage loss, increase in size of the femoral bone marrow lesion (short arrows) and decrease in size of the tibial subchondral bone lesion (long arrow). Effusion-synovitis appears less severe (*).

Table 1

Baseline WORMS cartilage score of each subregion and max subregional score within the index compartment in Kellgren and Lawrence grade 4 knees.

	Central femoral	Posterior femoral	Anterior tibial	Central tibial	Posterior tibial	Max subregional score from all subregions
WORMS score	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Index compartment (“bone-on-bone” appearance on radiograph)						
0–2.5	1 (0.6)	5 (3.1)	15 (9.3)	1 (0.6)	23 (14.2)	**0**
3	0	51 (3.5)	56 (34.5)	0	58 (35.8)	**0**
4	0	3 (1.9)	1 (0.6)	0	3 (1.9)	**0**
5	20 (12.4)	88 (54.3)	56 (34.5)	22 (13.7)	43 (26.5)	**10 (6.2)**
6	140 (87.0)	15 (9.3)	33 (20.5)	138 (85.7)	36 (22.2)	**151 (93.8)**
No score increase	144 (94.1)	120 (78.4)	139 (90.8)	146 (95.4)	145 (94.2)	**145 (95.4)**
Score increase	9 (5.9)	33 (21.6)	14 (9.2)	7 (4.6)	9 (5.8)	**7 (4.6)**
Non-Index compartment						
0–2.5	97 (59.8)	131 (80.9)	156 (96.3)	110 (67.9)	129 (79.6)	**80 (49.4)**
3	56 (34.6)	28 (17.3)	3 (1.8)	39 (24.1)	28(17.3)	**64 (39.5)**
4	0	0	0	0	0	**0**
5	9 (5.6)	3 (1.8)	3 (1.8)	11 (6.8)	4 (2.5)	**16 (9.9)**
6	0	0	0	2 (1.2)	1 (0.6)	**2 (1.2)**
No score increase	131 (84.5)	146 (94.2)	155 (100)	139 (89.7)	145 (93.6)	**127 (81.9)**
Score increase	24 (15.5)	9 (5.8)	0	16 (10.3)	10 (6.4)	**28 (18.1)**

Table 2

Baseline bone marrow lesion scores and longitudinal score changes for the index and non-index compartments in KL4 knees.

	Index compartment N (%)	Non-index compartment N (%)
Baseline WORMS max subregional score		
0	2 (1.3)	107 (66.9)
1	29 (18.1)	36 (22.5)
2	56 (35.0)	14 (8.8)
3	73 (45.6)	3 (1.9)
Score change over time		
No change in the max subregional score	69 (45.7)	108 (70.1)
Increase in the max subregional score	50 (33.1)	29 (18.8)
Decrease in the max subregional score	32 (21.2)	17 (11.0)

Table 3

Baseline meniscus categories and longitudinal category changes for the index and nonindex compartments in KL4 knees.

	Index compartment N (%)	Non-index compartment N (%)
Baseline meniscus status category		
0	2 (1.2)	123 (91.8)
1	0	1 (0.8)
2	3 (1.9)	8 (6.0)
3	3 (1.9)	2 (1.5)
4	138 (85.2)	0
5	13 (8.0)	0
6	3 (1.9)	0
Category change over time		
No change	146 (96.0)	123 (95.4)
Worsening	6 (4.0)	6 (4.6)