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Osteophytes and Cartilage Damage in Knees with Incident OA

Title:

MRI-defined Osteophyte Presence and Concomitant Cartilage Damage in Knees with Incident Tibiofemoral Osteoarthritis: Data From The Pivotal Osteoarthritis Initiative Magnetic Resonance Imaging Analyses (POMA) Study

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ABSTRACT

Objective

To describe compartmental frequencies of MRI-defined osteophytes and co-localized cartilage damage and evaluate the associations of osteophyte (OP) size with any ipsicompartmental cartilage damage in knees with incident tibiofemoral radiographic knee osteoarthritis (ROA).

Methods

We evaluated knees from the Osteoarthritis Initiative without ROA at baseline that developed ROA during a 4-year interval. Semi-quantitative MRI scoring of osteophytes and cartilage damage was performed at the time point when ROA was diagnosed, defined as Kellgren-Lawrence grade ≥ 2, using the MOAKS instrument. The frequencies of maximum osteophyte size and maximum grade of ipsicompartmental (i.e., patellofemoral, medial tibiofemoral, lateral tibiofemoral, posterior femur) cartilage damage were assessed. Generalized estimating equations were used to determine the association of MRI-defined maximum osteophyte size with presence of any (excluding focal superficial defects) ipsicompartmental cartilage damage.

Results

296 knees that did not have tibiofemoral ROA at the baseline visit but developed ROA during the 48- month observational period were included. In the patellofemoral, medial tibiofemoral and lateral tibiofemoral compartments, the most frequent OP grade was 1 (67.6%, 59.1% and 51.7%, respectively), and in the posterior femur it was 0 (51.7%). For all compartments except the posterior femur, a linear trend was found between increasing maximum OP size and the presence of any concomitant cartilage damage.

Conclusions

In this sample of knees with incident tibiofemoral ROA, the patellofemoral joint showed more severe cartilage damage than other compartments regardless of concomitant osteophyte size. In the posterior femur, cartilage damage was rare despite the presence or size of concomitant osteophytes.

SIGNIFICANCE AND INNOVATION

- Prior studies have evaluated the presence of osteophytes and any cartilage damage in the same knee, but whether this relationship is compartment-specific or not was not known.
- Here we show that the presence of MRI-defined osteophytes is, in general, associated with cartilage damage in the same compartment in knees with incident radiographic osteoarthritis.
- The patellofemoral joint commonly demonstrated high grade cartilage damage regardless of concomitant osteophyte presence or size.
- In the posterior femur, cartilage damage was rare despite the presence or size of concomitant osteophytes.

INTRODUCTION

Radiographic diagnosis of knee osteoarthritis (OA) is determined by the presence of a definite osteophyte, equivalent to grade 2 on the Kellgren-Lawrence (KL) scale. However, the validity of this definition remains uncertain, as radiography cannot directly visualize many intra-articular tissue changes characteristic of OA. OA is now recognized as a disease of the whole joint (1), including cartilage damage and other bone and soft tissue pathology that is common in pre-radiographic OA (2). While the KL scale is based on a composite measure of presence or absence of osteophytes and joint space narrowing without differentiating which knee compartment is involved, the OARSI atlas grading system takes into account the compartmental location of both osteophytes and joint space narrowing (3). However, the OARSI system cannot differentiate whether joint space narrowing is based on cartilage loss, meniscal damage/extrusion, or both (4). Radiographic presence of a definite osteophyte, particularly when there is no joint space narrowing (i.e., KL2), does not allow extrapolation on whether concomitant ipsicompartmental cartilage damage is present or not. It has previously been demonstrated that on a whole knee basis, osteophytes detected by radiography and magnetic resonance imaging (MRI) are associated with cartilage damage (detected by MRI) and that osteophyte size correlates with degree of cartilage damage in most cases for all KL grades (5,6). However, the compartmental relationship between osteophytes and cartilage damage has not previously been characterized, which makes it difficult to understand whether the presence of an osteophyte can be regarded as a reliable surrogate of cartilage damage in the same compartment. This may also have implications for interventional approaches targeting early OA. Given the known high prevalence of MRI-detected tissue alterations in pre-radiographic OA, our hypothesis is that MRI-detected osteophytes are an indicator of ipsicompartmental cartilage damage in knees with incident radiographic tibiofemoral OA (ROA).

Therefore, the purpose of this study was to 1.)describe cross-sectionally MRI-defined maximum osteophyte size and maximum grade of co-localized cartilage damage by compartment, and 2.)analyze the association of maximum osteophyte size with concomitant presence of any cartilage damage in the same compartment on MRI for knees that had recently developed radiographic tibiofemoral ROA.

METHODS

Participants

Participants were drawn from the Osteoarthritis Initiative (OAI), a prospective cohort study of 4976 adults with or at risk of developing knee OA. The OAI was approved by the Institutional Review Boards of the University of California, San Francisco and the four OAI clinical centers. Informed consent was given by all participants. We included knees from the POMA (Pivotal OAI MRI Analyses) substudy (7). Participants in POMA had at least one knee which did not have ROA at baseline but developed ROA prior to or at the 48-month OAI visit. The time point of incident ROA was defined as the first visit with a radiographic KL grade of ≥ 2 (P0). Our sample was limited to knees within the POMA study who had MRI available for grading at P0 and the year prior.

Image acquisition

OAI knee radiograph acquisition has been described in detail(8). Radiographs were acquired on an annual basis using a posteroanterior fixed-flexion weight-bearing protocol with a Plexiglas positioning frame (SynaFlexer; BioClinica, Newark, CA). KL grades were determined by central readings of the fixed-flexion knee radiographs.

MRI examination of both knees was performed on identical 3T magnets (Siemens Magnetom Trio, Erlangen, Germany) at the four OAI clinical sites according to the OAI MRI acquisition protocol. The full MRI protocol has been described in detail(9). In brief, MRIs included 2D coronal intermediate-weighted (IW) turbo spin echo (TSE), 2D sagittal IW fat-suppressed (FS) TSE and 3D sagittal dual echo in steady-state (DESS) sequences with axial and coronal reformats.

Image analysis

Two musculoskeletal radiologists (FWR and AG, with 12 and 14 years of experience in semi-quantitative assessment of knee MRI at time of analysis) read the MRIs at P0 according to the validated MRI Osteoarthritis Knee Score (MOAKS) system(1). Osteophytes were scored at 12 locations: six patellofemoral locations (superior and inferior, medial and lateral patella, medial and lateral anterior femur), two medial tibiofemoral (central medial femur and central medial tibia), two lateral tibiofemoral (central lateral femur and central lateral tibia) and two posterior femoral locations (posterior medial femur and posterior lateral femur). Osteophytes were graded on a 4-

point ordinal scale based on size (0=none, 1=small, 2=medium, 3=large). Locations of osteophyte assessment are shown in **Figure 1**.

Corresponding subregions for cartilage damage were patella (medial and lateral patella) and anterior femur (medial and lateral), medial tibiofemoral (anterior, central, posterior medial tibia, central medial femur), lateral tibiofemoral (anterior, medial, posterior lateral tibia, central lateral femur) and posterior femur (posterior medial and posterior lateral femur). MOAKS cartilage grading is performed in a two-digit manner taking into account 1)the percentage of area in each subregion affected by any cartilage damage and 2)the percentage of area of each subregion affected by full thickness cartilage damage (both scored from 0 to 3; 0=none, 1=<10%, 2=10-75%, 3=>75%). Intra- and interobserver reliability results for these readers in this cohort have previously been reported, with all MOAKS features demonstrating substantial or almost perfect agreement(7).

Statistical analysis

We performed a cross-sectional analysis at the time point when ROA was diagnosed (P0). We used descriptive statistics to describe the frequencies of maximum osteophyte size and maximum grade of co-localized cartilage damage by compartment. Due to the focus on matching osteophyte presence/size with ipsicompartmental cartilage damage/severity, we defined 'compartments' as follows: 1.patellofemoral (6 osteophyte locations, 4 cartilage locations), 2.medial tibiofemoral (2 osteophyte locations, 4 cartilage locations), 3.lateral tibiofemoral (2 osteophyte locations, 4 cartilage locations), and 4.posterior femur (2 osteophyte locations, 2 cartilage locations). For grading of cartilage damage, we grouped area and full thickness assessments into four categories: 0 (none), 1.0/1.1 (focal superficial or full-thickness defects), 2.0/2.1/2.2 (medium to large superficial or full thickness damage) or >2.2 (extensive full thickness cartilage damage). We used generalized estimating equations (GEE) adjusted for the correlation of two knees within an individual to determine the association between MRI-defined maximum osteophyte size (independent variable) in a given compartment with the presence of any ipsicompartmental cartilage damage (dependent variable, defined as grade 1.0 or higher). For the GEE analyses, we present the results for crude (unadjusted) models and adjusted for potential confounders (i.e., age, gender, body mass index, race and contralateral knee KL status). Due to low numbers of compartments with large osteophytes, we grouped knees with maximum osteophyte size of 2 and 3 together. All

statistical calculations were performed with SAS software (version 9.4 for Windows; SAS Institute, Cary, North Carolina, USA).

RESULTS

We included 296 knees from 273 OAI participants that developed ROA during the 48-month observational period. Participants were on average 60.4 years old (SD ± 8.5), predominantly female (67.4%) and overweight (mean BMI 28.8 SD ± 4.4). The radiographic status for knees in the cohort and contralateral knees at baseline was KL 0/0 for 57 (19.3%), KL 0/1 for 59 (19.9%), KL 1/1 for 67 (22.6%), KL 0/≥2 for 56 (18.9%) and KL 1/≥2 for 57 (19.3%) knees. At timepoint P0, ROA status was KL 2 for 237 (80.1%), KL 3 for 57 (19.3%), and KL 4 for 2 (0.7%) knees. The case-defining visit of radiographic OA incidence was 12 months for 119 knees (33.5%), 24 months for 83 knees (23.4%), 36 months for 103 knees (29.0%), and 48 months for 50 knees (14.1%). As shown in detail in **Table 1**, 45/200/51 knees demonstrated grade 0/1/2-3 osteophytes respectively in the patellofemoral compartment, compared with 93/175/28 knees in the medial compartment, 78/153/65 knees in the lateral compartment and 153/121/22 knees in the posterior femur. In the patellofemoral compartment, 40/33/210/13 knees demonstrated grade 0/1.0-1.1/2.0-2.2/>2.2 cartilage defects, compared with 108/45/140/3 knees in the medial compartment, 148/23/98/5 knees in the lateral compartment and 217/23/56/0 knees in the posterior femur. Only 21 knees (7.1%) showed extensive full thickness cartilage loss (>2.2) in any compartment.

A linear trend was observed for all compartments for increased odds of any cartilage damage with increasing osteophyte grade, except for the posterior femur. For the patellofemoral compartment, compared to those with no osteophytes, the adjusted odds ratio (aOR) for any cartilage damage and a maximum osteophyte grade of 1 was 1.50 (95% CI 0.62, 3.63), and for osteophyte grades 2 and 3 combined it was 11.36 (95% CI 1.46, 88.22), p for trend 0.004. In the medial tibiofemoral compartment, the aOR for concomitant presence of any cartilage damage was 2.60 (95% CI 1.45, 4.66) for a maximum osteophyte grade of 1, and 4.46 (95% CI 1.55, 12.85) for a maximum osteophyte size of grade 2/3 osteophytes, with p for trend <0.001. For the lateral tibiofemoral compartment, compared to those with no osteophytes, the aOR for co-

locational presence of any cartilage damage for a maximum osteophyte grade of 1 was 3.39 (95% CI 1.89, 6.08), and for grade 2/3 it was 5.27 (95% CI 2.44, 11.37), p for trend <0.001. No statistically significant associations between cartilage damage categories and osteophyte grade were observed for the posterior femur. Full results of GEE analyses are provided in **Table 2**.

DISCUSSION

In this study of knees that had recently developed tibiofemoral ROA, we found a strong association between the maximum grade of osteophyte within a compartment and the presence of ipsicompartmental cartilage damage, with the exception of the posterior femur. In general, the odds for ipsicompartmental cartilage damage increased with increasing size of osteophytes. In the patellofemoral compartment, higher grade cartilage loss was common regardless of osteophyte grade, and in the posterior femur higher grade cartilage loss was rare regardless of osteophyte size and less than 50% of knees demonstrated any osteophytes in this region.

The radiography-based KL scale is based on the assumption that osteophytes and cartilage loss appear in a sequential fashion, i.e., cartilage damage follows osteophytes. However, taking into account previous studies on prevalence of cartilage damage in knees that do not exhibit radiographic osteophytes, it must be assumed that cartilage damage is also highly prevalent in early ROA knees (i.e., KL 2) despite the fact that no joint space narrowing is observed(2).

Interpreting our findings in the context of interventional approaches focusing on cartilage restoration or anti-catabolic effects on cartilage, knees with incident ROA as analysed in our study commonly exhibit superficial and full thickness cartilage damage, with highest prevalence in the patella and medial tibiofemoral compartment. Extensive wide-spread full thickness damage, was rare, however, making these knees potentially ideal targets for cartilage preservation or restoration approaches, assuming that wide-spread full thickness damage is less amenable to such approaches(10). However, it should be acknowledged that there was a high prevalence of contralateral knee ROA in our sample which may preclude eligibility for therapies targeting a single symptomatic joint.

Katsuragi and colleagues compared a small subgroup from the OAI that developed ROA (KL grade ≥ 2) with a larger non-OA control using the WORMS MRI-based scoring system focusing on osteophytes. They analysed the baseline visit and found that “mild”-size osteophytes (grade 2 of 7 on the WORMS scale) are more frequently observed at the medial femur, medial tibia, the tibial spines, patella and intercondylar notch in knees that will develop ROA as compared to those that do not(11). The authors conclude that knees with intercondylar osteophytes are at increased risk for ROA development. Longitudinal prediction based on osteophyte location or size is not possible using our

data, which is a limitation. While we could show that the posterior femur (the intercondylar region in Katsuragi's study) shows osteophytes in about half of the cases, moderate or severe cartilage damage seems to be less common than in other locations. It is possible that the lack of association seen in the posterior femur region reflects the difference between weight bearing and non-weight bearing regions (although this would not explain the strong associations seen in the patellofemoral region) or the fact that the drivers of osteophyte development and cartilage damage differentially affect different compartments.

Our findings agree with the results of multiple prior studies demonstrating a close relationship between bone and cartilage pathology in OA(12). We have shown previously using MRI data that knees with moderate to large osteophytes exhibit markedly increased odds for severe cartilage damage, with increasing likelihood of having severe cartilage damage with increasing osteophyte size(6). In the current study the odds of any cartilage damage increased with osteophyte grade consistently across all compartments (with the exception of the posterior femur), suggesting that osteophyte size is a marker of concomitant or co-locational cartilage damage in these KL2 knees. We observed the greatest magnitude of association between osteophyte size and ipsicompartmental cartilage damage in the lateral tibiofemoral compartment, complementing the findings of a previous study which found that isolated lateral tibiofemoral OA was associated with a greater severity of MRI lesions, including osteophytes and cartilage damage(13). We did not assess the role of osteophytes for longitudinal progression, but previous longitudinal studies have demonstrated associations between the presence of osteophytes at baseline with both prevalent and incident cartilage damage and radiographic progression(14).

Our sample included only knees that had recently developed tibiofemoral ROA (i.e., knees with KL grade ≥ 2) due to the relative homogeneity of this sample and the availability of MOAKS grades in this group. However, this limits the wider interpretation of our results in other OA populations and the entire spectrum of radiographic OA severity. In addition, it should be acknowledged that contralateral knee tibiofemoral ROA was common at baseline in this sample, making this a cohort biased towards individuals at high risk of progression. An additional limitation of our study is the absence of information on symptomatic OA. We do not know if subjects who developed radiographic OA also

developed symptoms or if subjects developed symptoms prior to the diagnosis of OA. Inclusion of these clinical parameters would have gone beyond the scope of this study, although they are highly important and need to be explored further. For example, given the variable previously reported associations between osteophytes and pain, it would be interesting to evaluate whether the strengths of compartmental association between osteophytes and cartilage damage differed between symptomatic and asymptomatic subjects. Finally, we used an uncommon definition for 'compartments' in our study. Commonly the patellofemoral, the medial and lateral tibiofemoral compartments are differentiated in imaging research. As our focus was on co-localization of osteophytes and cartilage damage, we matched these as much as possible. The posterior femur is assessed for both osteophytes and cartilage but does not contribute to the features commonly assessed on posterior-anterior radiography and, thus, was considered a separate 'compartment'.

In conclusion, in this sample of knees with early radiographic tibiofemoral OA, the patellofemoral joint more frequently demonstrated severe cartilage damage regardless of concomitant osteophyte size than other compartments, while in the posterior femur cartilage damage was rare despite concomitant osteophyte presence and size. An increased risk for concomitant cartilage damage was observed with increase in osteophyte size for all locations except the posterior femur. This suggests that in early TF ROA osteophytes are a marker of co-locational cartilage damage, and the presence of larger osteophytes increases odds for concomitant ipsicompartmental cartilage damage.

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Table 1. Frequencies of osteophytes and ipsicompartmental cartilage damage on MRI.

[1]Compartment	Maximum osteophyte grade		Maximum cartilage damage grade n (%)			
	Grade	n (%)	0	1.0/1.1	2.0/2.1/2.2	>2.2
Patellofemoral	0	45 (15.2%)*	10 (22.2)**	3 (6.7)	31 (68.9)	1 (2.2)
	1	200 (67.6%)	29 (14.5)	26 (13.0)	142 (71.0)	3 (1.5)
	2 and 3	51 (17.2%)	1 (2.0)	4 (7.8)	37 (72.6)	9 (17.7)
Medial tibiofemoral	0	93 (31.4%)	49 (52.7)	13 (14.0)	30 (32.3)	1 (1.1)
	1	175 (59.1%)	53 (30.3)	27 (15.4)	93 (53.1)	2 (1.1)
	2 and 3	28 (9.5%)	6 (21.4)	5 (17.9)	17 (60.7)	0
Lateral tibiofemoral	0	78 (26.4%)	57 (73.1)	8 (10.3)	13 (16.7)	0
	1	153 (51.7%)	69 (45.1)	24 (15.7)	56 (36.6)	4 (2.6)
	2 and 3	65 (22.0%)	22 (33.9)	13 (20.0)	29 (44.6)	1 (1.5)
Posterior femoral	0	153 (51.7%)	115 (75.2)	9 (5.9)	29 (19.0)	0
	1	121 (40.9%)	89 (73.6)	11 (9.1)	21 (17.4)	0
	2 and 3	22 (7.4%)	13 (59.1)	3 (13.6)	6 (27.3)	0

[1]Definitions of compartments: Patellofemoral: 4 subregions for cartilage (medial and lateral patella, medial and lateral anterior femur), 6 locations for osteophytes (superior, inferior, medial, lateral patella, medial and lateral anterior femur); Medial tibio-femoral: 4 subregions for cartilage (anterior, central, posterior medial tibia, central medial femur), 2 locations for osteophytes (central medial femur, central medial tibia); Lateral tibio-femoral: 4 subregions for cartilage (anterior, central, posterior lateral tibia, central medial femur), 2 locations for osteophytes (central lateral femur, central lateral tibia); Posterior femur: 2 subregions for cartilage (medial and lateral posterior femur), 2 locations for osteophytes (medial and lateral posterior femur).

*column %

**row %

Table 2. Association of maximum osteophyte grade and odds of ipsicompartmental cartilage damage.

Patella			
Maximum osteophyte grade in the PFJ (6 locations)	Any (≥ 1.0) cartilage damage in 4 patellofemoral subregions n/N (%)	Crude model Odds ratio (95% CI)	Adjusted model* Odds ratio (95% CI)
0 (ref)	35/45 (77.8%)	1.0(reference)	1.0 (reference)
1	171/200 (85.5%)	1.68 (0.77, 3.67)	1.50 (0.62, 3.63)
2 and 3	50/51 (98.0%)	14.29 (1.75, 116.46)	11.36 (1.46, 88.22)
p-value for linear trend		0.0008	0.0042
Medial tibiofemoral joint (TFJ)			
Maximum osteophyte grade in medial TFJ (2 locations)	Any (≥ 1.0) cartilage damage in 4 medial TFJ subregions n/N (%)	Crude model Odds ratio (95% CI)	Adjusted model* Odds ratio (95% CI)
0 (ref)	44/93 (47.3%)	1.0 (reference)	1.0 (reference)
1	122/175 (69.7%)	2.57 (1.53, 4.32)	2.60 (1.45, 4.66)
2 and 3	22/28 (78.5%)	4.09 (1.52, 11.01)	4.46 (1.55, 12.85)
p-value for linear trend		0.0002	0.0007
Lateral tibiofemoral joint (TFJ)			
Maximum osteophyte grade in lateral TFJ (2 locations)	Any (≥ 1.0) cartilage damage in 4 lateral TFJ subregions n/N (%)	Crude model Odds ratio (95% CI)	Adjusted model* Odds ratio (95% CI)
0 (ref)	21/78 (26.9%)	1.0 (reference)	1.0 (reference)
1	84/153 (54.9%)	2.61 (1.59, 4.28)	3.39 (1.89, 6.08)
2 and 3	43/65 (66.2%)	4.89 (2.50, 9.57)	5.27 (2.44, 11.37)
p-value for linear trend		<0.0001	<0.0001
Posterior femur			

Maximum osteophyte grade in PF (2 locations)	Any (≥ 1.0) cartilage damage in 2 PF subregions n/N (%)	Crude model Odds ratio (95% CI)	Adjusted model* Odds ratio (95% CI)
0 (ref)	38/153 (24.8%)	1.0 (reference)	1.0 (reference)
1	32/121 (26.4%)	1.08 (0.64, 1.82)	1.06 (0.64, 1.76)
2 and 3	9/22 (40.9%)	2.03 (0.77, 5.34)	1.55 (0.44, 5.49)
p-value for linear trend		0.2375	0.4849

*Model adjusted for age, gender, body mass index, race, contralateral knee KL (Kellgren-Lawrence) status

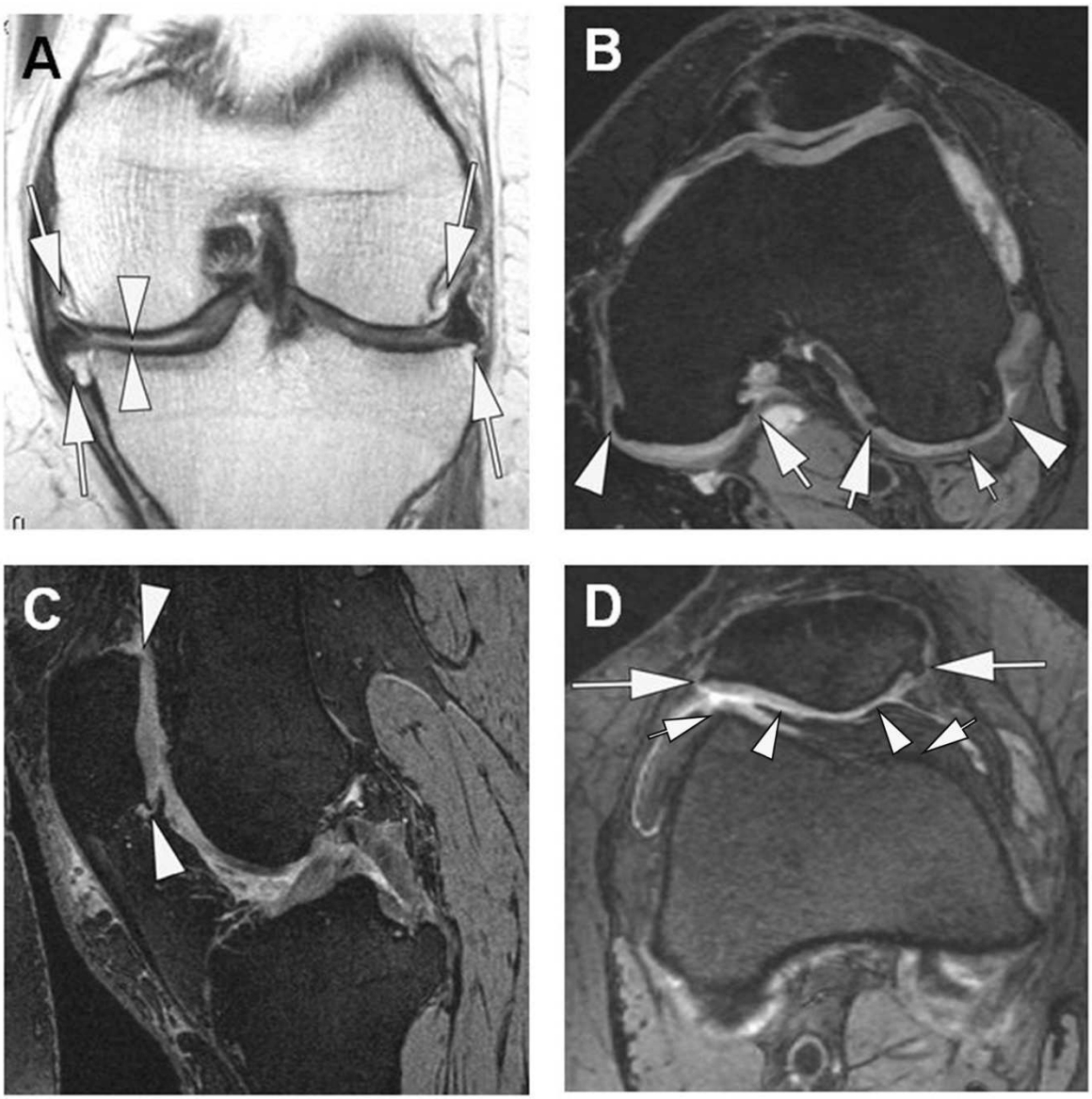

Figure 1. Locations for osteophyte assessment in the current study according to the MOAKS scoring system. **A**. The MRI locations best reflecting the Kellgren-Lawrence radiographic approach but without the projectional issues of radiography are the medial and lateral femoral and tibial locations (arrows). Note in addition there is diffuse superficial cartilage damage at the medial femur and tibia. **B**. Axial reformatted image of the sagittal DESS sequence shows the posterior femoral locations for osteophyte scoring. Osteophyte are scored medially and laterally either at the intercondylar location (large arrows) or at the more marginal locations medially and laterally (arrowheads). The larger of the two sites are considered as the MOAKS grade for the posterior femur. Note in addition there is superficial cartilage damage at the lateral posterior femur (small arrow). **C**. Sagittal DESS image depicts the two osteophyte locations at the superior and inferior patella (arrowheads). **D**. Axial DESS image shows the medial and lateral patellar locations for osteophyte assessment (arrows). Osteophytes are also assessed at the medial and lateral anterior femur (short arrows). In addition, there is superficial medial and lateral cartilage thinning (arrowheads).