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From early radiographic knee osteoarthritis to joint arthroplasty: Determinants of structural progression and symptoms

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Abstract

Objective—Aims were to assess (1) structural progression in knees with no/mild radiographic osteoarthritis (ROA) (i.e. Kellgren-Lawrence (K-L) grades 0 to 2) that will undergo knee replacement (KR) during a 5-year period; (2) differences in structural damage on MRI between knees with no/mild ROA vs. those with severe ROA (i.e. K-L 3 and 4) at baseline; and (3) differences in pain levels between those groups.

Methods—All participants who underwent KR from baseline (BL) to 60 months were drawn from the Osteoarthritis Initiative. MRIs were assessed for bone marrow lesions (BMLs), Hoffa- and effusion-synovitis (i.e. hyperintensity signal changes in the fat pad and abnormal amount of capsular distension due to intraaticular joint fluid and/or synovial thickening) at BL and the time point before KR (T0). The measures of WOMAC and KOOS pain were used for pain characterization. WOMAC Activity of Daily Life (ADL) and KOOS Quality of Life (QoL) were applied to characterize functional status of the included participants. Logistic regression was used to assess the association of no/mild ROA with these MRI features and pain.

Results—Based on inclusion criteria 181 knees were selected. Participants were predominantly female (57.8%) with a mean age of 64.4 years. 51 (28.2%) knees had no/mild ROA at BL. Of these, 51.0% progressed to severe ROA. No/mild ROA knees showed higher odds of BMLs in the patellofemoral joint (PFJ) at BL (OR 7.92 95%CI [3.45,18.16]) and T0 (OR 9.44 95%CI [4.00, 22.28]) compared to severe ROA knees. In addition, no/mild ROA knees were associated with change from “no pain” to “pain” from BL to T0 (aOR 5.48, 95%CI [1.25, 24.00]).

Conclusion—Over half of the knees with no/mild ROA before KR progressed to severe ROA over 4 years of follow-up. BMLs in the PFJ were more often seen among knees that had no/mild ROA. Worsening pain status may contribute to KR in knees with no/mild ROA.

Keywords

Arthroplasty; Magnetic Resonance Imaging; Osteoarthritis; X-ray; Fast progression

Introduction

Osteoarthritis (OA) is a complex, heterogeneous condition, and the most common cause of disability in the ageing population[1]. Progression of radiographic OA (ROA) is typically slow, although a subtype with more rapid structural progression has been described[2,3]. Structural hallmarks of the pathophysiology of OA include the breakdown of cartilage and associated changes in adjacent soft tissue and subchondral bone that can lead to debilitating

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joint symptoms such as pain and disability accompanied by structural deformity[1]. Identifying the prognosis of disease progression on an individual level is challenging. While MRI has increased the understanding of the multiple pathologies contributing to the OA phenotype, it is not clear how it should be used in routine clinical care. As the role of imaging in clinical practice for OA diagnosis, management and follow-up has not been clearly defined, a recent consensus statement by EULAR has emphasized that imaging is recommended if there is unexpected rapid progression of symptoms or change in clinical characteristics[4].

Rates of knee replacement (KR) have more than doubled in the United States from 1999 to 2008[5]. In the absence of disease modifying OA drugs, further increases in knee replacement volume are projected to continue into the future due to an ageing population, the obesity epidemic, the growing prevalence of sports-related knee injuries, and other factors[6,7]. Joint arthroplasty is commonly considered the therapy of choice for advanced symptomatic ROA[7]. However, despite low-grade ROA being uncommon before joint replacement compared to knees with severe structural ROA[8], we recently observed that the proportion of knees in the Osteoarthritis Initiative (OAI) undergoing knee replacement within a 5-year period with no or only mild radiographic disease (Kellgren-Lawrence [K-L] grades 0–2) at baseline was surprisingly high, i.e. 28%[9]. There are several potential explanations, including: 1.) Knees with no/mild tibiofemoral ROA at baseline may have had rapid radiographic progression over the follow-up period, resulting in advanced structural disease prior to the time point of knee replacement; 2.) Knees may have had worsening symptoms that were associated with MRI features but not radiographic disease worsening; and/or 3.) Differences in pain and function levels close to the time point of knee replacement or in pain trajectories over time may be present between those with no/mild ROA at baseline compared to those with severe ROA at baseline.

To examine these hypotheses further, we aimed to assess whether knees with no/mild tibiofemoral ROA at baseline progressed to higher grade structural disease during an observation period of 4 years of follow-up and whether structural damage commonly considered to be associated with pain (i.e. bone marrow lesions [BMLs], Hoffa- synovitis and effusion-synovitis)[10] not visible on radiographs but seen on MRI differed at baseline and at the time point immediately prior to reported knee replacement (i.e. time point “T0”). In addition, we evaluated whether pain and function levels at T0 differed between the two groups, and also whether the change in pain levels from baseline to the time point before knee replacement (T0) differed between the two groups.

Methods

The Osteoarthritis Initiative (OAI)

The OAI is a longitudinal cohort study designed to identify biomarkers of the onset and/or progression of knee OA. Both knees of 4,796 participants were studied using MRI and radiography at baseline, and annually over five years of follow-up[11]. OAI participants were 45 to 79-years-old at baseline, with or at risk of developing symptomatic knee OA in at least one knee. General exclusion criteria were the presence of prior bilateral KR, rheumatoid or other inflammatory arthritis, bilateral end-stage knee OA, inability to walk without aids, and

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MRI contraindications. Participants were recruited at four clinical sites in the United States. The Institutional Review Boards at each of the sites approved the study, and all participants gave informed consent.

The current study is a secondary analysis nested within the OAI and based on the POMA (Pivotal OAI MRI Analyses; NIH/NHLBI Contract No. HHSN2682010000 21C) sample.

Knee Selection and Clinical Assessment

OAI participants were interviewed yearly and asked about knee replacement in the preceding 12 months. For the current analysis, we selected all knees for which:

- **a.** a knee replacement was reported after baseline and up to the five-year follow-up visit, which was confirmed by radiography and/or review of medical records;
- **b.** central radiographic readings were available; and
- **c.** MRI measurements were available at the baseline and the time point before the visit of reported knee replacement.

The K-L grade was determined by central readings (OAI Dataset Release 0.4) of serial posterior-anterior (PA) fixed-flexion knee radiographs at each annual visit. Lateral or Merchant's view X-rays for assessment of the patello-femoral joint were not available. Clinical symptoms were assessed with the Western Ontario and McMaster Universities Arthritis (WOMAC) and Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaires at baseline and at the time point before the visit of reported knee *replacement* acknowledging that questions asked to assess pain in these instruments are similar[12,13]. The measures of WOMAC and KOOS pain were used for pain characterization. WOMAC Activity of Daily Life (ADL) and KOOS Quality of life (QoL) were applied to characterize functional status of the included participants. Both WOMAC and KOOS have demonstrated adequate content validity, internal consistency, test-retest reliability, construct validity and responsiveness[14–16]. Participants could contribute one or two knees to the analyses.

MRI Acquisition

MRI of both knees was performed on identical 3 T systems (Siemens Trio, Erlangen, Germany). The MRI pulse sequence protocol included a coronal two-dimensional intermediate-weighted (IW) turbo spin-echo (TSE), sagittal three-dimensional (3D) dual-echo at steady-state (DESS), coronal and axial multiplanar reformations of the 3D DESS, and sagittal IW fat saturated (fs) TSE sequences. Additional parameters of the full OAI pulse sequence protocol and sequence parameters have been published in detail elsewhere[11]. MRIs were acquired without the administration of intra-venous contrast agents.

MRI Assessment

Two musculoskeletal radiologists with 13 (F.W.R.) and 15 (A.G.) years' experience in semi-quantitative assessment of knee OA, blinded to clinical data and radiographic scores and later outcomes (KR or not), read the MRIs according to the MRI Osteoarthritis Knee Score (MOAKS), a validated scoring system for whole joint MRI OA assessment[17]. Data on validity and responsiveness of MOAKS has been published[18–20]. Each reader scored half of

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the cases that were randomly assigned. For our study, subchondral BMLs, Hoffa-synovitis and effusion-synovitis were considered, as these represent features commonly associated with the presence or development of OA symptoms[10].

BMLs were assessed in 14 articular subregions taking into account percentage of a subregion that is affected by BML (from 0 to 3). Signal alterations in the intercondylar region of Hoffa's fat pad were scored from 0 to 3 as a surrogate for synovial thickening termed Hoffa-synovitis. Joint effusion (also called effusion-synovitis, as it is not possible to discern joint fluid from synovial thickening on MRI without intravenous contrast) was graded from 0 to 3 regarding the estimated maximal distention of the synovial cavity[17].

One radiologist (F.W.R.) re-scored 20 randomly chosen MRIs in random order for the same features after a 4-week interval to determine intra-reader reliability. Inter-observer reliability between the two readers was assessed using the same 20 cases. Summarizing the intra- and inter-observer reliability results, all of the measures showed substantial (0.61–0.80) or reached almost perfect agreement (0.81–1.0). Appendix 1 gives a detailed overview of the reliability results of the MRI readings.

Statistical Analysis

Weighted kappa statistics were applied to determine inter- and intra-observer reliability for the MRI assessments. Logistic regression adjusted for the correlation of knees in an individual using generalized estimating equations (GEE) was used to assess the association of mild ROA, defined as knees with a baseline K-L grade of 0, 1, or 2, with the number of subregions affected by any BMLs per compartment (medial tibio-femoral, lateral tibio-femoral, patello-femoral) and presence of any Hoffa-synovitis and effusion-synovitis at baseline and T0. Logistic regression was applied to assess the association of no/mild ROA with the presence of pain at baseline and T0, and with change in pain from baseline to T0 using the parameters WOMAC and KOOS pain and functioning using the severe OA group (i.e. knees with a baseline K-L grade of 3 or 4) as the referent. In models, the KOOS scores were reversed so that higher scores indicated more pain/lower quality of life in order to be able to interpret odds ratios in the same direction as the other pain measures. Models for change in pain/functioning were adjusted for baseline pain/functioning age, sex, baseline body mass index (BMI), baseline reported previous knee injury and baseline reported knee surgery.

We considered a two-tailed p-value of less than 0.05 as statistically significant. All statistical calculations were performed using SAS 9.4 for Windows (SAS Institute, Cary, NC).

Results

Sample characteristics

A total of 181 knees from 161 participants with radiographic, MRI and pain assessments available underwent knee replacement during the 5 years of observation. Only ten of the knees in this study did not undergo total KR. Of the partial KRs, 8 were medial and only one each were lateral or a PFJ replacement. At baseline, subjects were on average 64.4 years old (SD ± 8.5), predominantly female (57.8%) and overweight (mean BMI 29.7 SD ± 4.6). Of

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these, 125 participants contributed knees to the severe ROA group (baseline K-L 3 and 4, 55.2% female, aged 64.5 +/− 8.8 years, BMI 29.6 +/− 4.7) and 46 to the no/mild ROA group (baseline K-L 0–2; 65.2% female, aged 64.7 +/− 7.8 years, BMI 29.8 +/− 7.2). The mean time interval from baseline to T0 was 863 +/− 495 days for the total sample, with the median being 767 days and the 25th and 75th percentiles at 403 and 1424 days. In regard to time from baseline to T0 the two subgroups differed significantly (p=0.015) with a longer interval for the no/mild ROA group (992 +/− 451 vs. 812 +/− 504 days, median 1089 vs. 753 days and the 25th and 75th percentiles at 716 vs. 367 and 1453 vs. 1168 days). There was a considerable time lag between T0 and KR for some knees. The mean number of days was 178 (SD = 102.6) and the median was 167.5 days. While the minimum number of days was 1, 75% of the knees had 98 days or more between T0 and KR. There was no difference between the two study groups (t-test, p = 0.91).

Distribution of radiographic disease severity

Knee replacement was reported for 20 (11.0%) knees at 12-month follow-up, for 32 (17.7%) at 24 months, for 46 (25.4%) at 36 months, for 38 (21.0%) at 48 months, and for 45 knees (24.9%) at 60 months (Table 1). Of the 181 knees included, 130 (71.8%) knees had severe ROA at baseline while 51 (28.2%) knees had no/mild ROA at baseline. Of the no/mild ROA knees, 19 (37.3%) progressed to K-L grade 3, and 7 (13.7%) knees to K-L grade 4 at the time point T0. Of the 26 knees that went from no or mild OA (K-L 0,1 or 2) at baseline to severe OA at T0 (K-L 3 or 4), just over half (n = 14) were progressing from K-L 2 to K-L 3. Only three knees with baseline K-L 2 increased to K-L 4 at T0, but nine knees had larger increases in K-L grades starting at either K-L 0 or 1.

BML load by compartment and BML associations

Of the 25 knees that did not progress to severe ROA, 17 knees had a BML in two or more subregions of the patello-femoral joint (PFJ) at baseline and 20 knees at the time point T0 (Table 2). Compared to knees with severe ROA at baseline, no/mildOA knees that later underwent knee replacement were more strongly associated with two or more subregions in the PFJ having BMLs (OR 7.92, 95% CI [3.45,18.16]) at the baseline visit. 67% of the mild ROA knees had ≥ 2 subregions with BMLs in the PFJ at baseline vs. only 24% in severe ROA knees. Similar findings were observed for T0, with no/mildROA being associated with two or more subregions with BMLs in the PFJ (OR 9.44 95% CI [4.00, 22.28]) but decreased odds for medial (OR 0.21 95%CI [0.10,0.47]) and lateral (OR 0.39 95%CI [0.17,0.92]) TFJ BML subregion counts.

Associations with inflammatory MRI markers

Over two-thirds of mild ROA knees had none or minimal effusion-synovitis at baseline, whereas over half of severe ROA knees had moderate or large effusion-synovitis (Table 3). No/mild ROA knees were less likely to be associated with the presence of effusion-synovitis and Hoffa-synovitis at baseline (OR 0.32, 95% CI [0.16,0.65]) and 0.35, 95% CI [0.17,0.73], respectively), while at T0 there were no differences between knees with no/mild ROA compared to those with severe ROA.

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Associations with pain measures

The no/mild ROA knees had better WOMAC and KOOS scores at baseline (3.80 vs. 5.58 and 64.95 vs. 76.01), but at T0 there were no differences with regard to any of the pain measures between the two groups (Table 4).

Trajectory of pain measures

No associations of increased odds were seen for change in either WOMAC or KOOS pain scores. This agrees with the finding that the adjusted mean changes in pain levels between the no/mild and severe OA groups were not statistically significant using those two measures. Nevertheless, based on WOMAC or KOOS pain scores, both the no/mild OA and the severe OA groups did have statistically significant increases in pain from baseline to the clinic visit just prior to KR (all $p<0.0001$) (Table 5).

Discussion

The determinants of progression from low-grade structural knee OA to knee replacement are poorly understood. Among OAI participants who received a knee replacement within the first 5 years of follow-up, we observed during four years of follow-up that over half of the knees with no/mild tibio-femoral ROA at baseline progressed to severe ROA at the annual OAI visit before knee replacement, indicating a more rapid progression of disease than commonly observed in such a period[21]. As the indication for knee replacement is based on both patients' symptoms and structural parameters, we compared differences in both structural features and symptoms for the pre-defined subgroups that exhibited no/mild, or severe tibio-femoral ROA at the baseline visit. The PFJ is not part of the K-L grading scheme and is only visualized on skyline or lateral radiographs, yet based on our findings, it seems to play a relevant contributory role regarding structural damage that contributes to knees undergoing replacement. In this sample of knees that went on to knee replacement, BMLs in the PFJ at baseline and T0 were more often observed among knees that had mild ROA at baseline, while the opposite was true for those with medial and lateral TFJ disease. The importance of structural damage in the PFJ was also reflected by the high numbers of knees without rapid tibio-femoral radiographic progression that exhibited BMLs in the PFJ in the year prior to knee replacement. While inflammatory MRI markers were less prevalent in the no/mild ROA group at baseline, at the visit prior to knee replacement (T0) there were no differences between groups, indicating development of an inflammatory component in the no/mild ROA group over the time period since baseline. Knees with severe ROA at baseline reported pain more frequently and at higher levels at baseline compared to the mild ROA group, while at the visit prior to knee replacement no differences between these two groups were observed. Worsening pain status over the follow-up period was also observed in knees with no/mild ROA at baseline that subsequently underwent knee replacement, confirming previous work on the relevance of clinical symptom progression in the decision process for knee replacement[22]. This contrasts with severe OA knees at baseline, which predominantly tended to have persistent pain at both visits, baseline and T0. The clinical implications of these findings need to be further elucidated; particularly the role of PFJ symptoms and structural damage needs to be better understood in the context of indications for KR.

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This study was nested within the large OAI cohort, in which participants were examined on an annual basis over a 60-month period. Multiple clinical and structural assessment metrics were gathered in the OAI, offering the unique opportunity to follow structural and symptomatic progression with frequent assessments over time. The discordance between symptoms and structural damage in OA has long remained enigmatic, although more recent data has shown that there seems to be a stronger association than previously thought, a conclusion also reflected by our data, in which more than half of the subjects progressed structurally and symptomatically[23,24].

Pain and the severity of ROA are considered important variables in the decision to perform knee replacement surgery[25–27]. A recently published survey of Dutch orthopedic surgeons reported that age and severe structural ROA were variables that are considered to be important in the decision to perform knee replacement, while pain symptoms of moderate or severe pain were unequivocal[8].

Our hypothesis that knees with mild ROA at baseline progressed quickly to higher grades of structural (radiographic) OA was supported for approximately half of the knees with K-L grades 0 to 2 at baseline. Although half of the knees remained low grade according to the K-L scale, this was based on the TF joint only and disregards structural damage and progression in PFJ. The finding that particularly patello-femoral BMLs, which are commonly considered to be associated with symptoms, were more prevalent in the no/mild ROA knees at the time point before knee replacement supports the premise that the PFJ seems to play a relevant role in the decision process for knee replacement[28,29]. Other markers of active disease that are commonly associated with measures of pain are the MRI findings of Hoffa synovitis and effusion-synovitis, which are surrogates for whole joint inflammation[10]. While at baseline these markers were markedly less frequently observed in the mild ROA group compared to the severe ROA group, at the time point before knee replacement no differences were seen between the two groups, indicating the development of active disease in mild ROA group[30]. Whether aggressive treatment of inflammation might reduce the risk for knee replacement remains to be examined in future randomized studies.

We have also recently used a nested, matched case-control design within the OAI cohort to demonstrate that multiple features of MRI tissue pathology were related to clinical prognosis and predicted knee replacement in the following year[9]. The time point closest to surgery seems to be most relevant in regards to both structural disease manifestations and clinical symptoms. In addition, our findings are in line with knee OA being considered a disease following the principles of inertia as suggested by Felson and colleagues[21]. Our results suggest that the knees that appeared to have mild ROA at baseline, but progressed to knee replacement over the follow-up period were already in a rapidly progressive state at the baseline visit. We encourage further characterization of these knees, given that knees at risk of fast progression are of high relevance to potential treatment and prevention efforts. On the other hand it was surprising to observe that six knees with mild or no OA at baseline still exhibited K-L grades 0 or 1 at the time point T0 and went on to knee replacement between T0 and the next annual visit, i.e. underwent surgery without severe radiographic changes. The reasons for this remain enigmatic but underlines that the decision making process is complex and based on individual decisions between patient and treating physician.

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The MOAKS scoring system that has been applied in our study is the latest whole organ assessment tool for MRI-based knee OA evaluation and has emerged from experiences with other systems such as WORMS or BLOKS[31,32]. Reliability data has been published and responsiveness has been shown recently for the FNIH sample showing the predictive value of MOAKS for clinical and structural joint progression[20]. Measures of agreement for MRI assessment were not perfect but in the range commonly reported for experienced readers applying semi-quantitative MRI scoring systems for knee OA evaluation[31,32].

There are limitations to our study that warrant mention. The OAI does not include X-rays of the patello-femoral joint (PFJ) and, thus, radiographic changes from baseline to T0 in this joint could not be assessed. We focused only on certain structural measures that are considered particularly relevant for clinical disease manifestations, i.e. BMLs and markers of inflammation[10,17]. To assess the degree of joint inflammation, we used a surrogate of signal alterations in Hoffa's fat pad and separately evaluated effusion-synovitis in the joint. We did not have histological confirmation of those MRI findings, nor contrast-enhanced MRI, which is considered the gold standard for synovitis assessment in knee OA[33].

There was a considerable time lag between T0 and KR for some knees which may explain why some knees without relevant levels of pain at T0 had reported KR at the next annual visit. An increase in pain after the T0 visit is likely but unfortunately this remains speculative. In addition, fluctuation of MRI features between time points may explain additional discrepancies between symptoms at T0 and the time point of reported KR.

The moderate precision for some of the estimates, particularly for the BML PFJ models and the change in pain models needs to be acknowledged, and thus, these findings should be interpreted cautiously given the observed variability around the point estimates. Additionally, because of the limited numbers of knees with some features, statistical power was often only sufficient to reliably find large effects and small effects may be present.

In summary, our study showed that about half of the knees with no/mild tibio-femoral ROA at baseline that underwent knee replacement during the observational period progressed to higher-grade tibiofemoral ROA closer to the time point of surgery. However, the other half of these knees did not progress to severe tibio-femoral ROA, but had evidence of patello-femoral BMLs, which seemed to play a role in structural disease that ultimately led to knee replacement. Also, joint inflammation developed over time as active disease in the year prior to knee replacement was observed in a majority of knees. Finally, while pain levels differed markedly at baseline, no differences were observed between no/mild and severe ROA knees at the time point before knee replacement, indicating marked progression of symptoms over time.

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Appendix 1

Intra- and inter-observer·reliability

		Intra-observer agreement				Inter-observer agreement			
		Weighted Kappa	Standard Error	95% confidence interval		Weighted Kappa	Standard Error	95% confidence interval	
				Lower	Upper			Lower	Upper
BML size (0–3)	PFJ	0.85	0.101	0.65	1.00	0.92	0.100	0.73	1.00
	Whole knee	0.87	0.050	0.77	0.97	0.90	0.050	0.80	1.00
	Medial TFJ	0.84	0.081	0.68	1.00	0.90	0.082	0.74	1.00
	Lateral TFJ	0.90	0.087	0.73	1.00	0.90	0.086	0.73	1.00
Hoffa-Synovitis (0–3)		0.68	0.157	0.38	0.99	0.68	0.157	0.38	0.99
Effusion-synovitis (0–3)		0.95	0.174	0.61	1.00	0.91	0.171	0.57	1.00

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Significant and/or Innovative Findings

- A substantial proportion of knees (28.2%) undergoing knee replacement within a five year period in the Osteoarthritis Initiative study did not have severe radiographic OA (Kellgren Lawrence grades 3 and 4) at the baseline visit.
- Of these knees with no or only mild radiographic OA (Kellgren Lawrence grade 0–2), 37.3% progressed to K-L grade 3, and 13.7% knees to K-L grade 4.
- MRI-defined joint inflammation defined as effusion- or Hoffa-synovitis, reflecting whole joint inflammation, developed over time in a majority of knees, indicating the presence of active disease at time points close to knee replacement
- Patello-femoral bone marrow lesions were more likely to be observed in no/mild ROA knees compared to severe ROA knees, emphasizing the role of the patello-femoral joint in the decision for knee replacement.
- While pain levels differed markedly between knees with no/mild ROA and severe ROA at baseline, no differences were observed between no/mildand severe ROA knees at the time point before knee replacement, indicating marked clinical symptomatic progression over time.

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Table 1

Sample Description

Baseline Demographics			
	All Participants (N = 161 †)	**Baseline no/mild OA Participants * (N = 46)**	**Baseline severe OA Participants * (N = 125)**
Female, N (%)	93 (57.8)	30 (65.2)	69 (55.2)
Age in years, Mean (SD)	64.4 (8.5)	64.7 (7.8)	64.5 (8.8)
BMI, Mean (SD)	29.7 (4.7)	29.8 (4.2)	29.6 (4.7)
Radiographic OA severity in the two subgroups at baseline and T0			
	All knees (%) (N = 181)	**Baseline no/mild OA (%) * (N = 51)**	**Baseline severe OA (%) * (N = 130)**
Time point of T0			
12 Month	20 (11.0)	3 (5.9)	17 (13.1)
24 Month	32 (17.7)	6 (11.8)	26 (20.0)
36 Month	46 (25.4)	15 (29.4)	31 (23.9)
48 Month	38 (21.0)	11 (21.6)	27 (20.8)
60 Month	45 (24.9)	16 (31.4)	29 (22.3)
Kellgren-Lawrence grade at Baseline			
0	7 (3.9)	7 (13.7)	0 (0.0)
1	8 (4.4)	8 (15.7)	0 (0.0)
2	36 (19.9)	36 (70.6)	0 (0.0)
3	66 (36.5)	0 (0.0)	66 (50.8)
4	64 (35.4)	0 (0.0)	64 (49.2)
Kellgren-Lawrence grade at T0			
0	2 (1.1)	2 (3.9)	0 (0.0)
1	4 (2.2)	4 (7.8)	0 (0.0)
2	19 (10.5)	19 (37.3)	0 (0.0)
3	56 (30.9)	19 (37.3)	37 (28.5)
4	100 (55.3)	7 (13.7)	93 (71.5)

† Note that ten individuals contributed one knee each to both groups.

* No/Mild OA: Kellgren –Lawrence grades 0–2; Severe OA: Kellgren–Lawrence grades 3 and 4

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Table 2

Compartmental presence of bone marrow lesions (BMLs) at baseline and T0

BML load in compartment (Predictor)	Severe OA (n=130) N (%)	No/Mild OA (n=51) N (%)	Odds of being a no/mild OA knee (Outcome) Crude odds ratio (95% confidence intervals)
BL - BML medial TFJ (number of subregions affected)			
0	26 (20.0)	37 (72.6)	Reference
1	16 (12.3)	8 (15.7)	0.35 (0.13,0.94) *
≥ 2	88 (67.7)	6 (11.7)	0.05 (0.02,0.13) *
BL -BML lateral TFJ (number of subregions affected)			
0	69 (53.5)	39 (76.5)	Reference
1	26 (20.2)	9 (17.7)	0.61 (0.26,1.44)
≥ 2	34 (26.3)	3 (5.9)	0.16 (0.05, 0.54) *
BL - BML PFJ (number of subregions affected)			
0	65 (50.0)	9 (17.7)	Reference
1	34 (26.2)	8 (15.7)	1.70 (0.60,4.80)
≥ 2	31 (23.8)	34 (66.6)	7.92 (3.39,18.53) *
T0 - BML medial TFJ (number of subregions affected)			
0	24 (18.5)	20 (40.0)	Reference
1	10 (7.7)	13 (26.0)	1.56 (0.57,4.31)
≥ 2	96 (73.8)	17 (34.0)	0.21 (0.10,0.47) *
T0 - BML lateral TFJ (number of subregions affected)			
0	62 (48.1)	34 (68.0)	Reference
1	30 (23.3)	8 (16.0)	0.49 (0.20,1.18)
≥ 2	37 (28.6)	8 (16.0)	0.39 (0.17,0.94) *
T0 - BML PFJ (number of subregions affected)			
0	65 (50.0)	8 (16.0)	Reference
1	34 (26.2)	6 (12.0)	1.43 (0.46,4.47)
≥ 2	31 (23.8)	36 (72.0)	9.44 (3.92,22.69) *

BML – bone marrow lesion; TFJ – tibio-femoral joint; PFJ – patello-femoral joint, OA – osteoarthritis, T0 – OAI visit prior knee replacement

*Statistically significant at $p < 0.05$

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Table 3

Inflammatory MRI markers at baseline and T0

Inflammatory MRI marker (Predictor)	Severe OA (n=130) N (%)	No/Mild OA (n=51) N (%)	Odds of being a no/mild OA knee (Outcome) Crude odds ratio (95% confidence intervals)
BL – Effusion-synovitis			
0	21 (16.2)	19 (37.3)	Reference
1	41 (31.5)	16 (31.4)	
2	47 (36.2)	10 (19.6)	0.32 (0.16,0.65) [1*]
3	21 (16.2)	6 (11.8)	
BL – Hoffa-synovitis			
0	21 (16.2)	18 (35.3)	Reference
1	66 (50.8)	24 (47.1)	
2	42 (32.3)	9 (17.6)	0.35 (0.17,0.73) [1*]
3	1 (0.8)	0 (0.0)	
T0 – Effusion-synovitis			
0	13 (10.0)	8 (15.7)	Reference
1	32 (24.6)	9 (17.7)	
2	47 (36.2)	23 (45.1)	0.60 (0.24,1.48) [1]
3	38 (29.2)	11 (21.6)	
T0 – Hoffa-synovitis			
0	17 (13.1)	10 (19.6)	Reference
1	62 (47.7)	26 (51.0)	
2	48 (36.9)	14 (27.5)	0.62 (0.26,1.47) [1]
3	3 (2.3)	1 (2.0)	

[1] odds ratio presented for any grade ≥1 combined

[*] statistically significant at $p < 0.05$

OA – osteoarthritis, BL – baseline visit, T0 – OAI visit directly prior knee replacement

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Table 4

Cross sectional pain measures for mild and severe OA knees

Pain measure	Severe OA (n=130)	No/Mild OA (n=51)	Odds of being a no/mild OA knee (Outcome) Crude odds ratio (95% confidence intervals)
BL – WOMAC and KOOS Pain			
WOMAC, mean (SD)	5.58 (3.48)	3.80 (4.10)	0.86 (0.76, 0.98) *
KOOS, mean (SD)	64.95 (17.51)	76.01 (21.22)	0.97 (0.94, 0.99) *
BL – WOMAC and KOOS Functioning			
WOMAC ADL, mean (SD)	17.98 (11.49)	14.30 (13.31)	0.97 (0.94, 1.01)
KOOS QoL, mean (SD)	46.97 (18.47)	50.37 (25.01)	0.99 (0.97, 1.01)
T0 – WOMAC and KOOS Pain			Odds ratio per one unit increase
WOMAC, mean (SD)	7.49 (3.89)	7.00 (4.06)	0.97 (0.89,1.05)
KOOS, mean (SD)	57.05 (18.38)	58.04 (19.80)	1.00 (0.98,1.02)
T0 – WOMAC and KOOS Functioning			
WOMAC ADL, mean (SD)	23.56 (12.85)	23.26 (11.81)	1.00 (0.97,1.02)
KOOS QoL, mean (SD)	40.72 (17.60)	36.76 (19.79)	1.01 (0.99,1.03)

* statistically significant at $p<0.05$

In models, the KOOS pain score was reversed so that higher scores indicated more pain in order to be able to interpret odds ratios in the same direction as the other pain measures.

WOMAC – Western Ontario and McMaster Universities Arthritis Index; KOOS – Knee Injury and Osteoarthritis Outcome Score; SD – standard deviation; OA – osteoarthritis, BL – baseline, T0 – OAI visit directly prior knee replacement

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Table 5

Change in pain from baseline to T0[#]

Change in pain (Predictor)	Severe OA (n=130) N (%)	No/Mild OA (n=51) N (%)	Odds of being a no/mild OA knee (Outcome) adjusted Odds Ratio[1] (95% confidence intervals)
Change in WOMAC and KOOS Pain			Odds ratio per one unit increase[2]
WOMAC pain	+1.91 (3.78)	+3.20 (4.19)	1.00 (0.90,1.11)
KOOS pain	−7.89 (19.31)	−17.71 (21.86)	1.01 (0.98,1.03)
Change in WOMAC and KOOS Functioning			
WOMAC ADL	+5.56 (11.57)	+8.78 (13.44)	1.00 (0.96,1.03)
KOOS QoL	−6.25 (17.26)	−13.60 (20.03)	1.02 (1.00,1.05)

[1] adjusted for age, sex, baseline BMI, baseline reported previous knee injury, baseline reported knee surgery

[2] adjusted for the same as above plus the baseline value for that scale.

[*] statistically significant at $p<0.05$

[#] days from baseline to T0 (days): mean 222, SD ± 495, median 767, IQR 403 – 1424, maximum 1560