Determinants of outcome prior to and after total hip and knee arthroplasty
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Chapter II

Preoperative radiographic osteoarthritis severity modifies the effect of preoperative pain on pain/function after total knee arthroplasty. Results at 1 and 2 years postoperatively.

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Abstract

Background: Osteoarthritis (OA) severity as demonstrated by preoperative radiographs and preoperative pain play an important role in the indication for total knee arthroplasty (TKA). We investigated whether preoperative radiographic evidence of OA severity modified the effect of preoperative self-reported pain on postoperative pain and function 1 and 2 years after TKA for OA.

Methods: Data from the Longitudinal Leiden Orthopaedics Outcomes of Osteoarthritis Study (LOAS), a multicenter cohort study on outcomes after TKA were used. OA severity was assessed radiographically with the Kellgren and Lawrence (KL) score (range, 0 to 4). Pain and function were evaluated with the Knee Injury and Osteoarthritis Outcome Score (KOOS). After adjustment for body mass index (BMI), age, sex, and Mental Component Summary Scores from the Short Form-12, multivariate linear regression analyses with an interaction term between the preoperative KL score and preoperative pain were performed.

Results: The study included 559 patients. The preoperative KL score was independently associated with 1-year postoperative pain (β = 5.4, 95% confidence interval [CI] = 1.4 to 9.4, and β = 7.7, 95% CI = 3.2 to 12.2, while preoperative pain was associated only with postoperative pain (β = 0.3, 95% CI = 0.1 to 0.6) and not with postoperative function (β = 0.2, 95% CI = -0.2 to 0.5). Comparable associations were found between 2-year postoperative pain and KL score (β = 8.0, 95% CI = 3.2 to 12.7) and preoperative pain (β = 0.5, 95% CI = 0.1 to 0.8) and between 2-year postoperative function and KL score (β = 7.7, 95% CI = 3.2 to 12.2. The study showed a trend toward the KL score modifying the effect of preoperative pain on 1-year postoperative pain (β = -0.1, 95% CI = -0.1 to 0.0) and 2-year postoperative pain (β = -0.1, 95% CI = -0.2 to 0.0) and on 1 and 2-year function (β = -0.1, 95% CI -0.2 to 0.0 for both), with the effect of preoperative pain on postoperative pain and function seeming to become less important when there was radiographic evidence of greater preoperative OA severity.

Conclusions: Patients with less pain and higher KL grades preoperatively had better function and pain outcomes 1 and 2 years after TKA. However, the effect of preoperative pain on the postoperative outcomes seems to become less important when the patient has radiographic evidence of more severe OA. We believe that analysis of the severity of preoperative pain is an important proxy for optimal postoperative patient outcome.

Level of Evidence: Prognostic Level II.

Introduction

Total knee arthroplasty (TKA), performed to treat end-stage symptomatic knee osteoarthritis (OA), results in improved physical function (1-7) and long-term pain alleviation in the majority of patients (8-10). Yet, approximately 20% of patients who have undergone TKA experience persisting pain and overall dissatisfaction (10) or are undecided or dissatisfied concerning their improvement in physical function (9). Therefore, efforts have been made to preoperatively define the subgroup of patients who will experience postoperative pain and/or impaired joint function (7, 8, 11-25).

Since OA severity seen on preoperative radiographs (7, 12-19) and self-reported pain (11, 14, 19-25) are important determinants of whether orthopaedic surgeons will perform TKA (26-28), several studies focused on the predictive value of these factors. In these studies, patients with radiographic evidence of severe OA preoperatively had greater improvements in physical function and greater relief of pain postoperatively (7, 13, 15-17). Furthermore, greater preoperative pain was associated with more improvement but also with more postoperative pain (12). However, none of these studies investigated the combined effect of OA severity seen on preoperative radiographs and preoperative pain on postoperative outcomes.

Preoperatively, a discordance is observed between OA severity seen radiographically and preoperative pain – i.e., more severe OA on radiographs is poorly associated with more preoperative pain. This illustrates that the experience of preoperative pain cannot be explained only by the structural damage of the knee in all patients with OA (12, 29, 30). Pain symptoms may originate from other sources such as central pain sensitization, peripheral knee lesions, or psychological factors (12, 31). Therefore, TKA outcomes in patients with relatively moderate damage seen on radiographs may differ between those with moderate pain and those with severe pain simply because all of the underlying causes for the severe pain may not be resolved by TKA.

The aim of the current study was to investigate whether OA severity seen on preoperative radiographs modified the effect of preoperative pain on postoperative pain and function 1 and 2 years after TKA for OA. We hypothesized that patients with less OA severity on preoperative radiographs and more preoperative pain would report poorer postoperative outcomes regarding pain and function. We believe that additional insight into the effects of radiographic evidence of OA severity and preoperative pain on postoperative pain and function will lead to a better understanding of the mechanisms influencing postoperative outcomes and to a better prediction of outcomes.

Materials and methods

Setting

This study is part of the Longitudinal Leiden Orthopaedics Outcomes of Osteoarthritis Study (LOAS; Trial ID NTR3348), an ongoing multicenter (7 hospital), longitudinal, prospective cohort study started in June 2012 that was designed to investigate long-term outcomes of total hip arthroplasty (THA) and TKA (32, 33). Ethical approval for the LOAS was granted by the Medical Ethics Committee of the Leiden University Medical Centre (LUMC; P12.047). All patients included in the LOAS provided written informed consent according to the Declaration of Helsinki.

General inclusion criteria for the LOAS included a diagnosis of OA, an age of 18 years or older, being listed for primary or revision THA or TKA, and sufficient Dutch language skills to complete the questionnaires. Included patients received questionnaires preoperatively; at 6, 12, 24 months postoperatively; and every consecutive 2 years until 10 years postoperatively. For the current study, we selected a subgroup of the LOAS cohort namely, all patients treated with primary TKA who had been included from June 2012 until June 2015 from the hospitals with, at the time of analysis, accessible radiographic images (LUMC Leiden, Alrijne Hospital Leiderdorp, LangeLand Hospital Zoetermeer, and Groene Hart Hospital Gouda) (n = 863). Patients with 12 months of postoperative data were eligible (n = 649). Excluded from the analysis were patients who had had a previous THA or TKA (either ipsilaterally or contralaterally), those who were treated with a hemiprosthesis and those for whom the severity of knee OA could not be determined properly from radiographs because of logistic or technical errors, for example. In total, 559 patients were included for this analysis (Fig. 1)

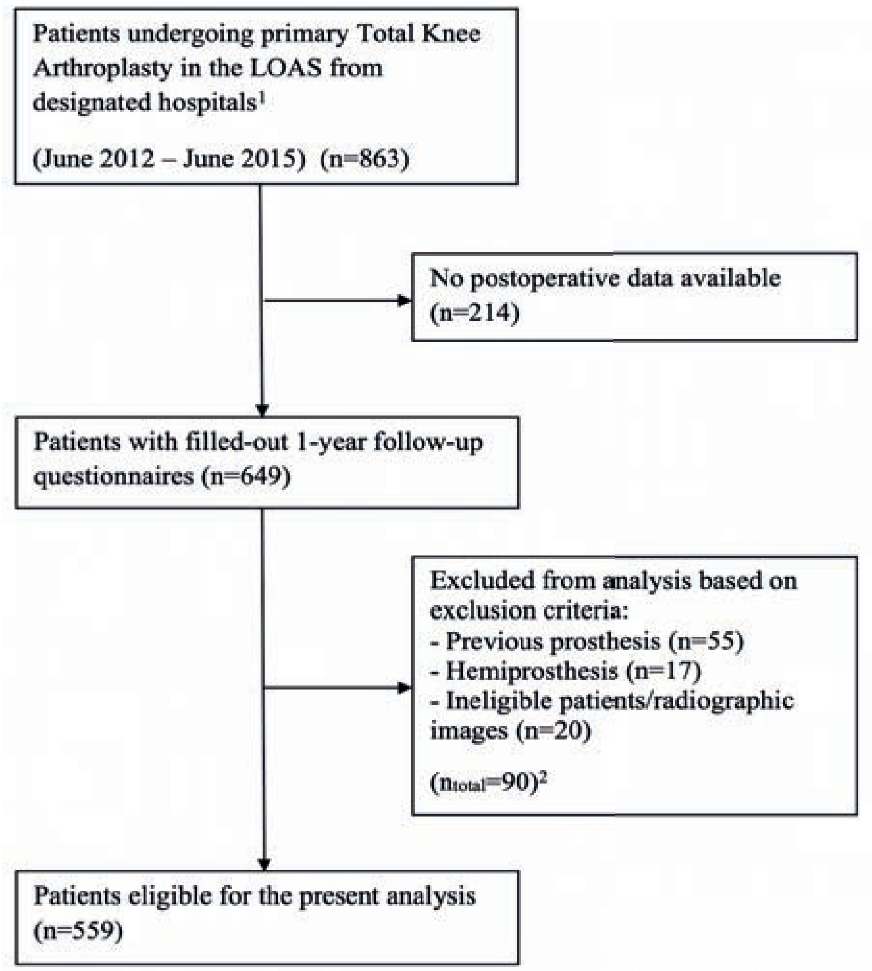


Figure 1. Flowchart of inclusion and exclusion of patients in the study.

[1]These hospitals included the LUMC, Alrijne Hospital Leiderdorp, LangeLand Hospital and Groene Hart Hospital. [2]The number of excluded patients per exclusion criterion does not add up to the total number of excluded patients due to patients complying with multiple exclusion criteria.'

Measurements

Patients' Baseline Characteristics

Sex, age at primary TKA, and height and weight to calculate the body mass index (BMI) were assessed at baseline. In addition, self-reported comorbidities were analyzed using the list of the Dutch Central Bureau of Statistics (34) and divided into 2 categories (33); non-musculoskeletal (chronic lung, cardiac or coronary disease; arteriosclerosis; hypertension; stroke; severe bowel disorder; diabetes mellitus; migraine; psoriasis; chronic eczema; cancer; incontinence; hearing or vision impairments; and dizziness in combination with falling) and musculoskeletal (severe elbow, wrist, hand or back pain and other rheumatic diseases).

Mental health was assessed with the Mental Component Summary Scale (MCS) on the Short Form-12 (SF-12) questionnaire. This questionnaire consists of 12 questions covering 8 different dimensions (General Health, Physical Functioning, Role Physical, Role Emotional, Bodily Pain, Vitality, Social Functioning and Mental Health). The MCS score ranges between 0 (lowest mental health) and 100 (highest mental health). Scores were standardized based on the basis of the average for the population of the United States at a mean of 50 and a standard deviation of 10.

Lastly, preoperative usage of medications was assessed. These included; paracetamol (paracetamol alone, Panadol, Finimal and Sinaspril), glucosamines, nonsteroidal anti-inflammatory drugs (NSAIDs; ibuprofen, diclofenac, diclofenac sodium/misoprostol, celecoxib and naproxen), tramadol (alone and tramadol hydrochloride/paracetamol), supplements (vitamin D, calcium, and bisphosphonates) and others (oxycontin; OxyNorm [oxycodone hydrochloride], MS Contin [morphine sulfate extended-release tablets], and buprenorphine).

Pain and Function

Pain was assessed preoperatively and at 12 and 24 months postoperatively using the validated Dutch version of the Knee Injury and Osteoarthritis Outcome Score (KOOS) (35). The KOOS consists of 42 items subdivided into 5 subscales, including the pain subscale (9 items), which ranges from 0 (severe pain) to 100 (no pain). Preoperative and 12 and 24 month postoperative function was assessed with the KOOS functioning in daily living subscale (activities of daily living; 17 items). Function scores were determined on a scale from 0 (severe impairments in function) to 100 (no impairments in function).

OA Severity Seen on Preoperative Radiographs

Weight-bearing anteroposterior radiographs were obtained prior to surgery as part of routine care. Subsequently, the OA severity was assessed on these radiographs according to the Kellgren and Lawrence (KL) grading system by an experienced musculoskeletal radiologist (H.M.K.). Patients whose KL score was either 0 or 1 were analysed as a single group because the difference in severity between these scores was deemed negligible. As such, the patients were divided into groups ranging from ‘’no visible OA’’ (grade 0 or 1) to ‘’severe OA’’ (grade 4) (36). In addition, 10% of the images were randomly reclassified to assess intraobserver reliability, which was found to be 98% (95% confidence interval [CI] = 97% to 99%).

Statistical Analysis

To assess selection bias, baseline characteristics of the patients with knee OA who were included in the study were compared with those of the patients who were lost to follow-up (those with no 1-year postoperative data). The group that was lost to follow-up was also subjected to the set exclusion criteria prior to comparative analysis.

To correctly address partial or missing responses, multiple data imputation was performed on the data of patients who did not complete all items of the LOAS questionnaire or did not return the 2-year postoperative questionnaire. Predictive mean matching was used with the default SPSS (IBM) settings. Per individual, age, sex, BMI, SF-12 MCS score, and preoperative as well as 1- and 2-year postoperative pain and function were used to impute the missing values. Comparison of the original values (see Supplementary Tables 1 through 4) and the imputed values showed minimal differences.

To determine variances between the groups, 2-sample Student t-tests were used for continuous variables and Pearson chi-square test were used for categorical variables. Also, the baseline patient characteristics of the OA-severity groups were compared with each other using analysis of variance (ANOVA) for continuous data and Pearson chi-square test for discrete data. Five regression models were built to analyze the effects of the radiographic OA severity score (KL score) and preoperative pain on postoperative pain and function. In model 1, the effect of the KL score on postoperative pain and function was assessed with univariate linear regression analysis. Moreover, all regression models on postoperative function were adjusted for preoperative function. In model 2, the effect of preoperative pain on postoperative pain and function was evaluated. Model 3 included both KL score and preoperative pain. In model 4, the interaction between the KL score and preoperative pain was added to analyze whether effect modification was present in the unadjusted setting. Lastly, model 5 was generated to adjust model 4 for possible confounding factors—namely, BMI, age at primary TKA, sex and SF-12 MCS score. Analyses were free from normality assumptions because of sufficiently large sample sizes (37). In addition, figures were created to illustrate the effects of preoperative KL and pain on postoperative pain and function using Qplot (R, version R 3.2.3). The figures were based on the raw (non-imputed) dataset, and geom_smooth (lm) was used to estimate the colored lines. Significance was assumed at a p value of ≤0.05. All analyses were done using SPSS version 23.0.

Results

Study population

No significant differences were observed between the group in the study and the group lost to follow-up with the exception of the mean SF-12 MCS score, which was better for the study population (see Supplementary Table 5). Of the included patients, 66 had a KL score of 0 or 1; 85, a KL score of 2; 335, a KL score of 3; and 73, a KL score of 4 (Table 1). In all groups, the majority of patients were female; patients were on average 67 years of age at the time of surgery. The KL groups did not differ with regard to the mean preoperative KOOS pain (p = 0.681) or function (p = 0.171) score. In addition, no differences were found between BMI, self-reported comorbidities, usage of preoperative pain medication, or SF-12 MCS score (p > 0.05; Table 1).

Table 1: Baseline characteristics of patients with different KL grades.

	KL 0 or 1 (n=66)	KL 2 (n=85)	KL 3 (n=335)	KL 4 (n=73)	Total (n=559)	P value
Female (no (%))	52 (79)	56 (66)	216 (65)	54 (74)	378 (68)	0.081
Age at inclusion Mean* (yr)						0.059
No. (%)	64 ±10	67 ±9	67 ±8	67 ±10	67 ±9	
<50 yr						0.107
50-59 yr	6 (9)	1 (1)	11 (3)	3 (4)	21 (4)	
60-69 yr	13 (20)	14 (17)	47 (14)	14 (19)	88 (16)	
>70 yr	31 (47)	34 (40)	146 (44)	25 (34)	236 (42)	
	66 (24)	85 (42)	131 (39)	31 (43)	214 (38)	
BMI* (kg/m^2)	29 ±4	29 ±4	29 ±5	29 ±5	29 ±5	0.915
Comorbidities# (no (%))						
Musculoskeletal	19/38 (50)	29/50 (58)	99/199 (50)	22/46 (48)	169/333 (51)	0.730
Non-musculoskeletal	33/56 (59)	47/68 (69)	213/281 (76)	44/59 (75)	337/464 (73)	0.065
Preoperative pain medication use (no. (%))	61/65 (94)	71/82 (87)	293/319 (92)	67/72 (93)	492/538 (91)	0.353
Preoperative HOOS score (0-100)*						
Pain						
	38 ±18	37 ±19	40 ±17	39 ±19	39 ±18	0.681
Function	43 ±18	43 ±20	46 ±17	46 ±16	45 ±18	0.171
Preoperative SF-12 MCS score (0-100)*	56 ±9	57 ±8	56 ±9	56 ±10	56 ±9	0.849

BMI: Body-mass Index

KL: Kellgren & Lawrence

MCS: mental component summary scale

SF-12: Short Form 12

*The values are given as the mean and standard deviation. #The values to the right of the slash indicate the number of patients who answered the specific question.

Effects of Preoperative Pain and KL Score on Postoperative Pain

A positive association was found between the preoperative KL score and 1-year postoperative pain score (model 1) (β = 3.5, 95% CI = 1.7 to 5.2), suggesting better 1-year postoperative pain outcomes in patients with more severe OA seen on preoperative radiographs (Table 2).

Table 2: Preoperative prediction of 1-year postoperative pain*

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.5	1.7	5.2
Model 2	Preoperative pain	0.2	0.2	0.3
Model 3	KL score	3.3	1.6	5.0
	Preoperative pain	0.2	0.1	0.3
Model 4	KL score	5.5	1.6	9.5
	Preoperative pain	0.4	0.1	0.7
	KL score x preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	5.4	1.4	9.4
	Preoperative pain	0.3	0.1	0.6
	KL score x preoperative pain	-0.1	-0.1	0.0

*Multivariate linear regression models on the imputed dataset consisted of the following.
Model 1: KOOS pain outcome = β0 + β1*(KL score) + ε

Model 2: KOOS pain outcome = β0 + β1*(KOOS preoperative pain) + ε

Model 3: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + ε

Model 4: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + β3*(KL score*KOOS preoperative pain) + ε

Model 5: Model 4 adjusted for BMI, age, gender and SF-12 MCS

Preoperative pain was also positively associated with 1-year postoperative pain (model 2) (β = 0.2, 95% CI = 0.2 to 0.3). This indicates that patients with higher preoperative pain levels can be expected to experience more pain after TKA. After combining models 1 and 2 (that is, including the KL score and pain [model 3]), the effects of the preoperative KL score and preoperative pain showed little change compared with the previous models (β = 3.3, 95% CI = 1.6 to 5.0 and β = 0.2, 95% CI = 0.1 to 0.3, respectively). Moreover, the interaction term between the KL score and preoperative pain showed a negative trend in model 4 (β = -0.1, 95% CI = 0.2 to 0.0) and in model 5 (after correction for confounding factors) (β = -0.1, 95% CI = -0.1 to 0.0). Comparable results were found for the association with 2-year postoperative pain outcomes (table 3).

Table 3: Preoperative prediction of 2-year postoperative pain*

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	4.3	2.2	6.5
Model 2	Preoperative pain	0.2	0.1	0.3
Model 3	KL score	4.2	2.0	6.3
	Preoperative pain	0.2	0.1	0.3
Model 4	KL score	8.1	3.3	12.8
	Preoperative pain	0.5	0.2	0.8
	KL score x preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	8.0	3.2	12.7
	Preoperative pain	0.5	0.1	0.8
	KL score x preoperative pain	-0.1	-0.2	0.0

*Multivariate linear regression models on imputed dataset consisted of the following.
Model 1: KOOS pain outcome = $\beta0 + \beta1$*(KL score) + ε

Model 2: KOOS pain outcome = $\beta0 + \beta1$*(KOOS preoperative pain) + ε

Model 3: KOOS pain outcome = $\beta0 + \beta1$*(KL score) + $\beta2$*(KOOS preoperative pain) + ε

Model 4: KOOS pain outcome = $\beta0 + \beta1$*(KL score) + $\beta2$*(KOOS preoperative pain) + $\beta3$*(KL score*KOOS preoperative pain) + ε

Model 5: Model 4 adjusted for BMI, age, gender and SF-12 MCS

Effect of Preoperative Pain and KL Score on Postoperative Function

The preoperative radiographic KL score was found to have a positive association with 1 and 2-year postoperative function (Tables 4 and 5), suggesting that radiographic evidence of more severe damage is associated with better postoperative function (that is, higher KOOS scores). There was no association between preoperative pain and 1 and 2-year postoperative function. The interaction term between the KL score and preoperative pain again displayed a negative trend toward effect modification ($\beta = -0.1$, 95% CI = -0.2 to 0.0, for both 1 and 2-year postoperative function).

Table 4: Preoperative prediction of 1-year postoperative function*

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.6	1.9	5.2
Model 2	Preoperative pain	-0.1	-0.2	0.0
Model 3	KL score	3.2	1.2	5.2
	Preoperative pain	-0.2	-0.3	0.0
Model 4	KL score	7.3	2.8	11.8
	Preoperative pain	0.1	-0.2	0.5
	KL score x preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	7.7	3.2	12.2
	Preoperative pain	0.2	-0.2	0.5
	KL score x preoperative pain	-0.1	-0.2	0.0

*Multivariate linear regression models on imputed dataset consisted of the following.
All models were adjusted for preoperative function.
Model 1: KOOS function outcome = $\beta0 + \beta1*(\text{KL score}) + \varepsilon$

Model 2: KOOS function outcome = $\beta0 + \beta1*(\text{KOOS preoperative pain}) + \varepsilon$

Model 3: KOOS function outcome = $\beta0 + \beta1*(\text{KL score}) + \beta2*(\text{KOOS preoperative pain}) + \varepsilon$

Model 4: KOOS function outcome = $\beta0 + \beta1*(\text{KL score}) + \beta2*(\text{KOOS preoperative pain}) + \beta3*(\text{KL score*KOOS preoperative pain}) + \varepsilon$

Model 5: Model 4 adjusted for preoperative function, BMI, age, gender and SF-12 MCS

Table 5: Preoperative prediction of 2-year postoperative function*

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.3	1.2	5.3
Model 2	Preoperative pain	-0.2	-0.4	0.0
Model 3	KL score	3.2	1.2	5.2
	Preoperative pain	-0.2	-0.3	0.0
Model 4	KL score	7.3	2.8	11.8
	Preoperative pain	0.1	-0.2	0.5
	KL score x preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	7.7	3.2	12.2
	Preoperative pain	0.2	-0.2	0.5
	KL score x preoperative pain	-0.1	-0.2	0.0

*Multivariate linear regression models on imputed dataset consisted of the following.
All models were adjusted for preoperative function
Model 1: KOOS function outcome = $\beta0 + \beta1*(\text{KL score}) + \varepsilon$

Model 2: KOOS function outcome = $\beta0 + \beta1*(\text{KOOS preoperative pain}) + \varepsilon$

Model 3: KOOS function outcome = $\beta0 + \beta1*(\text{KL score}) + \beta2*(\text{KOOS preoperative pain}) + \varepsilon$

Model 4: KOOS function outcome = $\beta0 + \beta1*(\text{KL score}) + \beta2*(\text{KOOS preoperative pain}) + \beta3*(\text{KL score*KOOS preoperative pain}) + \varepsilon$

Model 5: Model 4 adjusted for preoperative function, BMI, age, gender and SF-12 MCS

Illustration of Effects of KL Score and Preoperative Pain on Postoperative Pain and Function

The associations of preoperative radiographic OA severity score and pain with 1 and 2-year postoperative pain and function levels in the raw (non-imputed) dataset are illustrated by figure 2-A through 2-D. Each figure consists of a graph with 4 lines illustrating the association between preoperative pain and 1 or 2-year postoperative pain or function in the different KL score subgroups. Patients with more severe OA seen on preoperative radiographs (higher KL grades) and less preoperative pain are expected to have good outcomes in terms of pain (Figs. 2-A and 2-C) and function (Figs. 2-B and 2-D) 1 and 2 years after TKA. The effect of preoperative pain on postoperative pain (that is, the steepness of the slope) seems smaller in patients with greater OA severity (that is, higher KL score) seen on preoperative radiographs than in patients with less severe OA seen on preoperative radiographs. This effect seems less evident with respect to postoperative function.

Fig. 2-A

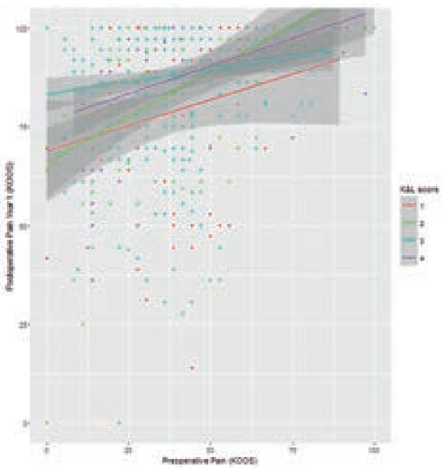


Fig. 2-B

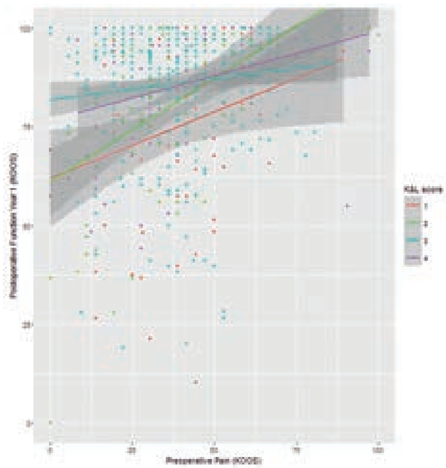


Fig. 2-C

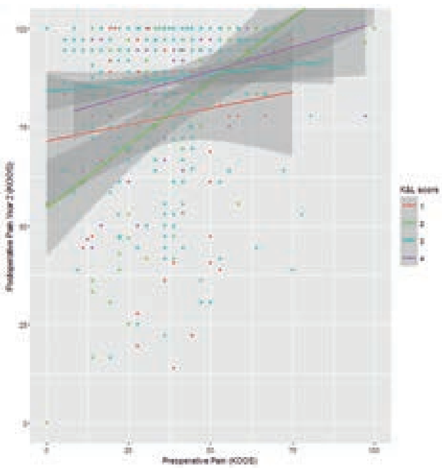
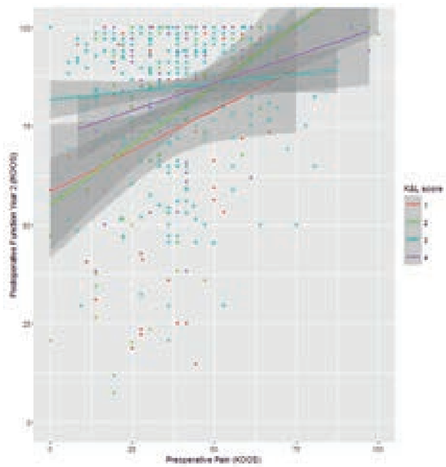


Fig. 2-D



Figures. 2-A through 2-D Graphs displaying the association between preoperative pain and postoperative outcomes in each KL group. The lines are plotted in the raw, non-imputed data. The associations are displayed divided by the KL score. **Fig. 2-A** Associations between preoperative pain (x axis) and 1-year postoperative pain (y axis). **Fig. 2-B** Fig. 2-B Associations between preoperative pain (x axis) and 1-year postoperative function (y axis). **Fig. 2-C** Fig. 2-C Associations between preoperative pain (x axis) and 2-year postoperative pain (y axis). **Fig. 2-D** Fig. 2-D Associations between preoperative pain (x axis) and 2-year postoperative function (y axis).'

Discussion

This is the first study of which we are aware that investigated the effect modification of radiographic evidence of OA severity on pain experienced by the patient preoperatively and their association with postoperative pain and knee function 1 and 2 years after TKA. Low OA severity seen on preoperative radiographs resulted in poorer scores for postoperative pain and function after TKA, whereas greater preoperative pain resulted in poorer postoperative pain scores (but not function). The reverse was also true; high OA severity seen on preoperative radiographs resulted in better postoperative pain and function levels, whereas low preoperative pain solely resulted in better postoperative pain (but not function). Furthermore, the effect of the preoperative pain level on postoperative outcomes seemed to become less important when more severe OA seen on preoperative radiographs was present.

Our finding that severe OA seen on preoperative radiographs was associated with better postoperative KOOS pain and function outcomes is in accordance with previous literature (7, 17, 38). However, some previous studies did not demonstrate these associations between OA severity and improvements in postoperative outcomes (39, 40). These divergent results may be due to variability in follow-up time, smaller study populations and variability in methods to assess pain and function in patients. Also, our finding that patients with more preoperative pain experienced more postoperative pain following TKA has been reported previously (12, 41-43). Nevertheless, none of these previous studies investigated whether radiographically demonstrated OA severity modified the effect of preoperative pain on postoperative pain and function after TKA. The effect of the interaction between widespread hyperalgesia (a reduced pain threshold at body sites distant to the painful joint) and the radiographic OA severity score on preoperative and postoperative pain was previously studied (44). The authors of that study found that patients with greater widespread hyperalgesia and limited OA severity seen on preoperative radiographs tended to have less improvement in pain after TKA than patients with less widespread hyperalgesia(44). That study included only patients with KL grades 3 and 4, limiting the variability in

OA severity. We expect that the effect modification of the radiographic grade of OA severity on widespread hyperalgesia would have been more pronounced if patients with KL grades lower than 3 had been included.

Our findings show that patients with lower radiographic OA severity scores are more likely to be managed with surgery because of pain rather than OA severity. This is underscored by the fact that the baseline pain levels were similar among all 4 different KL groups. The true source of pain that cannot be explained by structural damage of the knee joint remains a matter of debate. A possible explanation is central pain sensitization. In a study by Finan *et al.* (12) patients with low KL grades and high pain levels showed heightened central pain sensitization. When pain sensitization is apparent, the central nervous system is altered in such a way that patients experience higher levels of pain with less provocation. Consequently, patients with low KL grades and high pain levels derive less improvement from TKA compared with patients with high KL grades and high pain levels, as the true source of the pain is not from structural damage of the knee. This is also in accordance with the fact that preoperative anxiety and depression heighten preoperative pain and have adverse effects on postoperative outcomes (41). Comorbidities other than psychosocial conditions might have similar effects on the association between the preoperative and postoperative variables and may further explain the observed association. To our knowledge, however, no one has previously investigated these different possible underlying mechanisms in a single study. More research is necessary.

Our study had some strengths and limitations. Strengths included the large sample size, the multicenter longitudinal study design, and the consistent grading with the KL system as reflected by the high intra-rater reliability. One of the limitations was that we assessed pain and function with the KOOS questionnaire, which has been showed to be sensitive to ceiling effects (35, 45). In our cohort, 31.4% and 14.9% of the patients reported the maximum postoperative pain and function scores, respectively. The KOOS was chosen over other commonly used questionnaires such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire, as its ceiling effects are known to be less prevalent (45). Also, some selection bias may have occurred in our study, as the patients who were loss to follow-up showed lower SF-12 MCS scores than our study group (see Supplementary Table 5). However, the mean difference was only 2 points on the 100 point scale, which we interpret as not clinically relevant (46-52).

Conclusion

We observed a trend that OA severity seen on preoperative radiographs modified the effect of preoperative pain on pain and function 1 and 2 years following TKA. As such, the effect of preoperative pain on postoperative pain and function seems to become less important when more severe OA is demonstrated by radiographs. We believe that the effect modification of the radiographic OA severity grade on the association of preoperative pain with postoperative outcomes after TKA should be taken into account when new prognostic models for outcomes after TKA are developed.

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Supplementary table 1: Preoperative prediction of 1-year postoperative pain; outcomes of original, not-imputed data

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.5	1.7	5.2
Model 2	Preoperative pain	0.2	0.2	0.3
Model 3	KL score	3.3	1.6	5.0
	Preoperative pain	0.2	0.1	0.3
Model 4	KL score	5.5	1.6	9.5
	Preoperative pain	0.4	0.1	0.7
	KL score * preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	6.1	1.7	10.5
	Preoperative pain	0.4	0.1	0.7
	KL score * preoperative pain	-0.1	-0.2	0.0

Multivariate linear regression models
Model 1: KOOS pain outcome = β0 + β1*(KL score) + ε

Model 2: KOOS pain outcome = β0 + β1*(KOOS preoperative pain) + ε

Model 3: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + ε

Model 4: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + β3*(KL score*KOOS preoperative pain) + ε

Model 5: Model 4 adjusted for BMI, age, gender and SF12 MCS

Supplementary table 2: Preoperative prediction of 1-year postoperative function; outcomes of original, not-imputed data.

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.6	1.9	5.2
Model 2	Preoperative pain	-0.1	-0.2	0.0
Model 3	KL score	3.5	1.9	5.2
	Preoperative pain	-0.1	-0.2	0.0
Model 4	KL score	6.4	2.5	10.2
	Preoperative pain	0.1	-0.2	0.4
	KL score * preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	5.9	1.6	10.1
	Preoperative pain	0.0	-0.3	0.4
	KL score * preoperative pain	0.0	-0.1	0.1

Multivariate linear regression models
All models were adjusted for preoperative function.
Model 1: KOOS function outcome = β0 + β1*(KL score) + ε

Model 2: KOOS function outcome = β0 + β1*(KOOS preoperative pain) + ε

Model 3: KOOS function outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + ε

Model 4: KOOS function outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + β3*(KL score*KOOS preoperative pain) + ε

Model 5: Model 4 adjusted for preoperative function, BMI, age, gender and SF12 MCS

Supplementary table 3: Preoperative prediction of 2-year postoperative pain; outcomes of original, not-imputed data

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.9	1.8	6.0
Model 2	Preoperative pain	0.2	0.1	0.3
Model 3	KL score	3.9	1.8	6.0
	Preoperative pain	0.2	0.1	0.3
Model 4	KL score	7.3	2.3	12.4
	Preoperative pain	0.5	0.1	0.8
	KL score * preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	7.5	2.2	12.9
	Preoperative pain	0.4	0.1	0.8
	KL score * preoperative pain	-0.1	-0.2	0.0

Multivariate linear regression models
Model 1: KOOS pain outcome = β0 + β1*(KL score) + ε

Model 2: KOOS pain outcome = β0 + β1*(KOOS preoperative pain) + ε

Model 3: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + ε

Model 4: KOOS pain outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + β3*(KL score*KOOS preoperative pain) + ε

Model 5: Model 4 adjusted for BMI, age, gender and SF12 MCS

Supplementary table 4: Preoperative prediction of 2-year postoperative function; outcomes of original, not-imputed data

	Parameters	B	95% CI for B	
			Lower	Upper
Model 1	KL score	3.4	1.4	5.4
Model 2	Preoperative pain	-0.2	-0.3	0.0
Model 3	KL score	3.3	1.3	5.3
	Preoperative pain	-0.2	-0.3	0.0
Model 4	KL score	7.3	2.4	12.2
	Preoperative pain	0.1	-0.2	0.5
	KL score * preoperative pain	-0.1	-0.2	0.0
Model 5	KL score	7.4	2.2	12.5
	Preoperative pain	0.1	-0.3	0.5
	KL score * preoperative pain	-0.1	-0.2	0.0

Multivariate linear regression models
All models were adjusted for preoperative function.
Model 1: KOOS function outcome = β0 + β1*(KL score) + ε

Model 2: KOOS function outcome = β0 + β1*(KOOS preoperative pain) + ε

Model 3: KOOS function outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + ε

Model 4: KOOS function outcome = β0 + β1*(KL score) + β2*(KOOS preoperative pain) + β3*(KL score*KOOS preoperative pain) + ε

Model 5: Model 4 adjusted for preoperative function, BMI, age, gender and SF12 MCS

Supplementary table 5: Comparative analysis of socio-demographic characteristics of the loss to follow-up patient population *versus* eligible patient population.

	Eligible patients (n=559)	Loss to follow-up patients (n=199)	Analysis of variance (p-value)
Female, n (%)	376 (68)	130 (66)	0.697
Age at inclusion, years	67 ±9	66 ±10	0.476
BMI, kg/m^2	25 ±4	25 ±4	0.431
Comorbidities, n (%)			
Muscular	184 (52)	59 (48)	0.544
Non-muscular	334 (72)	118 (78)	0.171
Preoperative painkilling medication usage, n (%)	492 (91)	170 (88)	0.170
Preoperative pain, 0-100 ±SD	39 ±18	37 ±20	0.124
Preoperative function, 0-100 ±SD	45 ±18	42 ±21	0.062
SF-12, 0-100			
Mean MCS	56 ±9	54 ±10	0.010

BMI: Body-mass Index

MCS: mental component summary scale

SF-12: Short Form 12