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Total Knee Replacement as a Knee Osteoarthritis Outcome: Predictors Derived from a 4-Year Long-Term Observation following a Randomized Clinical Trial Using Chondroitin Sulfate

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Abstract

Objective. To predict, using clinical and qMRI data, the incidence of total knee replacement (TKR) during the long-term follow-up of knee osteoarthritis (OA) patients who formerly received chondroitin sulfate (CS) or placebo treatment. *Design*. A post hoc intention-to-treat analysis to evaluate the incidence of TKR was done on knee OA patients who had participated in a 12-month trial evaluating the impact of CS (800 mg/d) versus placebo for 6 months, followed by a 6-month open-phase in which all patients received CS. Additionally, the clinical and qMRI predictors of TKR were determined. *Results*. Thirteen TKRs were performed in the population after a 4-year follow-up. More TKRs were performed in the placebo group than in the CS group (69% vs. 31%, $P = 0.150$, logistic regression). The statistically significant predictors of TKRs were, at baseline, higher WOMAC pain and function scores, presence of bone marrow lesions (BMLs), and higher C-reactive protein levels. Loss of medial cartilage volume and increase in WOMAC pain and function at one-year were also predictors of TKR. Multivariate analyses revealed that baseline presence of BML and higher WOMAC pain score were independent predictors. Time to occurrence of the TKR also favored the CS group versus placebo (log-rank, $P = 0.094$). *Conclusion*. Symptoms such as knee pain and function, presence of BML, and cartilage volume loss predict the long-term occurrence of a "hard" outcome such as TKR.

Keywords

knee osteoarthritis, MRI, chondroitin sulfate, knee replacement

Introduction

Osteoarthritis (OA) treatment remains largely symptomatic. Studies using x-rays, which are still recommended by regulatory agencies for disease-modifying OA drug (DMOAD) trials, have shown that some drugs may have disease (structure) modifying effects in knee OA patients.[1-3] In recent years, a number of studies have used MRI technology to assess the structural changes in knee OA and identify risk factors associated with cartilage volume loss.[4-12] We recently reported the results of phase III trials in knee OA patients that used MRI to explore the DMOAD effects of chondroitin sulfate (CS)[13] and licofelone,[14] a lipoxygenase–cyclooxygenase (LOX-COX) inhibitor, which provide a strong rationale for the use of quantitative MRI in knee DMOAD studies.

The guidelines from the regulatory agencies require that joint structure modification also translate into a significant clinical benefit for the patient before allowing the claim of DMOAD.[15,16] To this end, the prevention of patient

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disability and prevention of the need for joint replacement have been suggested as possible clinically relevant outcomes.[17] Others have used baseline variables to predict possible long-term joint replacement as an outcome[18-22] or post hoc analyses of previous therapeutic interventions to predict total knee replacement (TKR).[23]

We thus elected to use the data from the recently published study[13] to conduct a post hoc analysis addressing the important question about whether the occurrence of TKR can be predicted using clinical and MRI data from long-term follow-up of knee OA patients in a randomized clinical trial.

Methods

Patient Selection and Time to Total Knee Replacement Procedure

Data were collected from the intention-to-treat (ITT) patient populations of the original recently published study.[13] This study was a randomized controlled trial (RCT; NIH registered NCT00604539), approved by the local ethics committees, and all patients gave their oral and written informed consent to participate.

The ITT cohort included 57 patients of the original 70 enrolled in the trial who were randomized and had at least one dose of the assigned medication: CS 800 mg (Condrosan, CS Bio-Active, Bioibérica S.A., Barcelona, Spain) or placebo once daily for the first 6 months (double-blind phase) followed by 6 months of treatment with 800 mg CS once daily for both groups (open-label phase). Among these patients, 51 fully adhered to the study regimen of 6 months, representing the according to protocol (ATP) cohort. With regard to baseline demographics, these 57 patients did not differ significantly from the 70 patients enrolled in the original trial (data not shown). The patients were recruited from outpatient rheumatology clinics in the province of Quebec, Canada. The enrolment period of the clinical trial started in January 2008 and the last patient entered in the study completed the 6-month phase of the trial in December 2008. Phone interviews were completed by December 2011, 4 years after the study inception. Thirteen patients were unreachable, including 6 who were completely lost to follow-up, 6 who failed to answer the phone call, and 1 death. These post hoc phone interviews were approved by the local ethics committees. Assessors from the centers, blinded to treatment, asked the patients the following specific questions: Did you have a total knee replacement? If so, which knee (left or right or both)? And if so, on which date was the surgery performed? Determination of the study knee was assessed from the original log book. The CS compounds provided as per protocol for the original 6-month trial and for the open-label phase were not offered to patients afterward. It is possible that patients were taking CS compounds available over-the-counter and at different dosages after the trial up to the phone interview but this was not evaluated by the assessor. The patients were not informed after the 6-month trial completion into which arm (CS or placebo) they were randomized.

The Predicting (Independent) Variables

Knee MRI Acquisitions. The original RCT MRI scans were performed using a 1.5 T clinical scanner (Siemens, Erlangen, Germany or General Electric, Milwaukee, WI) with a standard knee coil as previously described.[13]

The protocols to assess cartilage and bone marrow lesions (BMLs) were sagittal 3D FISP with water excitation (Siemens, TR/TE = 22/9 ms, flip angle = 14°, field of view = 160 mm, slice thickness = 1.5 mm, matrix = 512 pixels, receiver bandwidth = 100-110 Hz/pixel), and sagittal 3D SPGR with fat saturation (GE, TR/TE = 42/7 ms, flip angle = 20°, field of view = 160 mm, slice thickness = 1.5 mm, matrix = 512 pixels, receiver bandwidth = 100-110 Hz/pixel or 25.2 kHz and 28.1 kHz).

Cartilage volume was measured by 2 trained readers using a specially developed computer program (Cartiscope; ArthroLab Inc., Montreal, Quebec, Canada) as previously described.[6] The readers were blinded to treatment and to MRI examination time points except for baseline. The change in knee cartilage volume was obtained by subtracting the follow-up volume from the initial (baseline) volume. The change in cartilage volume over time was calculated for the entire knee (global) and for each of the medial and lateral compartments. The reproducibility of the method has previously been demonstrated to be excellent (intrareader reliability: root mean square coefficient of variation [RMS CV%] of 1.6 for the medial compartment of the knee).[6]

Subchondral bone marrow abnormalities were assessed comparing the surface of the lesion with the surface of the subregion in the corresponding image. If the lesion was depicted in multiple slides, the one with the largest extent was chosen. When the maximal extent of the lesion was oriented along the lateromedial direction, a reconstructed axial image was used for the evaluation. A semiquantitative scoring system was used with a scale from 0 to 3 based on the Whole-Organ Magnetic Resonance Imaging Score, or WORMS,[4] where 0 = absence, 1 = <25%, 2 = 25% to 50%, and 3 = >50% of the surface of the respective region regardless of the presence of additional smaller lesions.

Bone marrow lesions were assessed in 10 subregions, 5 for either medial or lateral, leading to a maximal total score of 30. The 5 subregions for either medial or lateral were the tibial plateau, the patella and anterior, central (weight bearing) and posterior femur. The cartilage volume was assessed in the same subregions with the exception of the patella.

Clinical Evaluation

Patients were assessed at baseline and 1 year for height, weight, and body mass index (BMI) as well as disease symptoms using the Western Ontario and McMaster Universities OA Index (WOMAC) pain, stiffness, function, and total score,[24] visual analogue scale for patient global assessment (0 = very good; 100 = very bad), and the pain experienced on the day of the visit (patient pain score: 0 = no pain; 100 = most severe pain). There was a 24-hour washout of analgesic medications prior to the clinical evaluation.

C-Reactive Protein

Blood samples were collected and the levels of C-reactive protein (CRP) were assessed for each serum sample collected at baseline and 1 year as previously described.[25]

Statistical Analysis

Data were entered into a computerized database using a blinded double-entry procedure, after which descriptive statistics for patient characteristics were tabulated. The primary efficacy outcome measure comparing structure modification of CS to placebo was the rate of TKR of the studied joint within the ITT cohort. The TKR incidence assessment was performed 4 years after patient enrolment and drug allocation. Univariate and multivariate logistic regressions were done to find baseline predictors of TKR. For the cartilage volume loss at 1 year, a cutoff value of 7% was selected a posteriori for prediction of TKR occurrence as previously reported.[25] The Kaplan–Meier survival analysis was also used to compare the cumulative incidences of TKR over time between the 2 treatment groups and a log-rank test was used to test for significance. Cox regression analysis was used to find predictors using survival of having a TKR over time as an outcome. For further explanation of the study, similar analyses were performed for the ATP cohort. All statistical analyses were done using SAS software, version 9.1 (SAS Institute Inc., Cary, NC). All tests were 2-sided, and a $P \leq 0.05$ was considered statistically significant. Analyses were not adjusted for multiple comparisons.

Results

Patient Baseline Characteristics, Change at 1 Year, and Risk of Total Knee Replacement

From the ITT population of the original study,[13] 57 patients (81.4%) were contacted, of whom 13 (18.6%) had undergone TKR of the knee including one who had TKR of the contralateral knee. The clinical and MRI data, however, were not available for that contralateral knee. The first occurrence of a TKR was noted one year after the original study completion. The effect of the initial 6-month treatment with CS when compared with placebo may have been protective, as 4 patients had the procedure compared with 9 patients treated with placebo in the follow-up time frame ($P = 0.150$, univariate logistic regression). Patients from the 2 original treatment groups were combined in the present post hoc study since they had similar baseline demographics and disease characteristics (data not shown). With regard to baseline symptom characteristics (**Table 1**), a greater TKR incidence was associated with knee symptoms as measured by WOMAC baseline pain (64.6 vs. 50.0, $P = 0.012$, univariate logistic regression) and function (67.1 vs. 55.7, $P = 0.045$). Higher CRP levels seen at baseline also predicted TKR (4.0 vs.2.3, $P = 0.055$). With regard to knee structural assessment, the BML score at baseline as measured in the medial compartment (2.9 vs. 1.1, $P = 0.016$) and, to a lesser extent, the global knee score (3.8 vs. 2.1, $P = 0.031$), were associated with TKR. Changes at 1 year, including less improvement in the WOMAC pain (−8.1 vs. −26.5, $P = 0.016$) and function (−-5.4 vs. −24.2, $P = 0.020$) and the loss of at least 7% of cartilage volume in the medial compartment (80% vs. 28%, $P = 0.046$) were also associated with TKR. The volume loss of at least 7% in the medial compartment was associated with the highest odds ratio for a TKR (odds ratio [OR] = 10.333, confidence interval [CI] = 1.046-102.079). Neither the BML nor the CRP changes at 1-year follow-up were associated with TKR. Analyses of the ATP population revealed similar results (data not shown).

Multivariate analyses of the ITT cohort (target knee only) controlling for age, gender, and BMI at baseline (**Table 2**) revealed that baseline presence of BML (OR = 2.107, CI = 1.255-3.535, $P = 0.005$) and greater WOMAC pain (OR = 1.101, CI = 1.027-1.180, $P = 0.007$) were independent and strong predictors of TKR.

Survival Analyses: Risk of Total Knee Replacement over Time for the Intention-to-Treat Cohort

The length of time after a patient was enrolled in the study and the influence of treatment (initial CS vs. placebo administration) on the occurrence of a TKR were examined. The Kaplan–Meier survival curves of patients (**Fig. 1**) showed that over time the 2 curves tend to separate from each other, suggesting a protective effect of a 6-month CS administration versus placebo, even though the placebo group received CS for the remaining 6 months. Despite the small number of TKRs that occurred ($n = 13$), a log-rank test revealed a trend toward difference ($P = 0.094$). A multivariate Cox regression model to assess the independence of the effect of this treatment (**Table 3**) demonstrated that, while controlling for age, gender, and BMI, at baseline the WOMAC pain

Table 1. Intention-to-Treat Cohort Univariate Analyses.

	Knee Replacement			If $P < 0.05$	
	Yes	No	P^a	OR	95% CI
Baseline characteristics					
	($n = 13$)	($n = 44$)			
Male, % (n)	23.0 (3)	41.0 (18)	0.249		
Age (years), mean (SD)	65.8 (7.5)	62.4 (10.5)	0.284		
BMI (kg/m^2), mean (SD)	31.5 (3.8)	30.5 (5.1)	0.513		
WOMAC, mean (SD)					
Pain	64.6 (14.3)	50.0 (17.2)	0.012	1.056	1.012-1.102
Stiffness	64.8 (25.0)	55.1 (21.0)	0.170		
Function	67.1 (16.8)	55.7 (17.1)	0.045	1.042	1.001-1.085
CRP biomarker (mg/L), mean (SD)	4.0 (3.6)	2.3 (2.1)	0.055	1.265	0.995-1.607
Treatment effect, % (n)			0.150		
Chondroitin sulfate	31.0 (4)	59.0 (26)			
Placebo	69.0 (9)	41.0 (18)			
BML score, mean (SD)					
Medial compartment	2.9 (2.3)	1.1 (2.0)	0.016	1.423	1.069-1.893
Lateral compartment	0.2 (0.4)	0.4 (0.9)	0.354		
Global knee	3.8 (2.8)	2.1 (2.2)	0.031	1.343	1.027-1.757
Variable 1-year change					
WOMAC, mean (SD)[b]					
Pain (change)	−8.1 (27.3)	−26.5 (18.8)	0.016	1.045	1.008-1.083
Stiffness	−51.5 (34.7)	−39.2 (27.3)	0.199		
Function	−5.4 (21.9)	−24.2 (22.2)	0.020	1.042	1.007-1.079
CRP biomarker (change %), mean (SD)	52.0 (108.9)	42.1 (139.9)	0.818		
Cartilage volume, % (n)					
Medial compartment (reduction of at least 7%)	80.0 (4)	28.0 (12)	0.046	10.333	1.046-102.079
Lateral compartment (reduction of at least 7%)	0.0 (0)	19.0 (8)	0.967		
Global knee (reduction of at least 7%)	0.0 (0)	19.0 (8)	0.967		
BML score, mean (SD)[b]					
Medial compartment	−1.0 (1.7)	−0.3 (1.2)	0.219		
Lateral compartment	0.2 (0.4)	0.1 (1.1)	0.858		
Global knee	−0.8 (2.2)	−0.1 (2.1)	0.484		

Note: OR = odds ratio; CI = confidence interval; SD = standard deviation; BMI = body mass index; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; CRP = C-reactive protein; BML, bone marrow lesion.
[a]Logistic regression to predict a knee (target) replacement.
[b]Changes in WOMAC and BML are reported in absolute values, a negative sign denotes improvement over time for the WOMAC and the BML scores. $n = 12$ for BML and cartilage volume since the contralateral knees are not included.

Table 2. Predictors of Knee Replacement: Intention-to-Treat Cohort Multivariate Analyses.

Baseline Predictors	OR	95% CI	P^a
Age (years)	1.052	0.937-1.182	0.388
BMI (kg/m^2)	1.038	0.823-1.308	0.755
BML medial compartment	**2.107**	**1.255-3.535**	**0.005**
WOMAC pain	**1.101**	**1.027-1.180**	**0.007**
CRP	1.522	0.972-2.384	0.066

Note: OR = odds ratio; CI = confidence interval; BMI = body mass index; BML = bone marrow lesion; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; CRP = C-reactive protein.
[a]Logistic regression to predict a knee (target) replacement. $n = 12$ as data from the contralateral knees are not included. Statistically significant values are given in boldface.

(OR = 1.101, CI = 1.042-1.164, $P = 0.001$) and presence of BML in the medial compartment (OR = 2.132, CI = 1.379-3.296, $P = 0.001$) were strongly associated with the occurrence of a TKR over time.

Discussion

The aim of this post hoc study was to examine the long-term effect of CS on the occurrence of TKR in knee OA patients. Similar studies have been done using TKR as an outcome and its feasibility has been demonstrated. Bruyere et al[23] demonstrated that 3 years of glucosamine sulfate treatment may prevent the occurrence of a TKR up to 5 years after drug discontinuation. Our group[25] also recently published

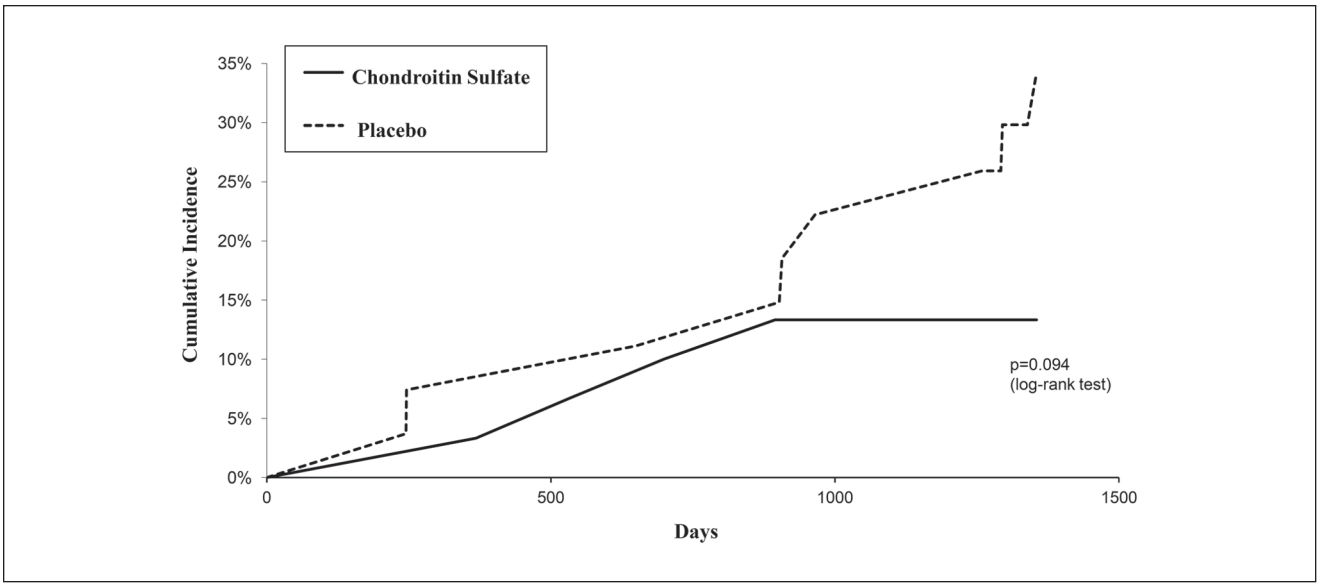

Figure 1. Kaplan–Meier cumulative incidence: Intention-to-treat cohort. Knee replacement not adjusted for covariates. The figure shows cumulative incidence of having a total knee replacement over time since the beginning of study enrolment per treatment group. Survival analysis was done using the Kaplan–Meier cumulative incidence method. A log-rank test was performed to assess statistical relevance between the 2 treatment groups.

Table 3. Predictors of Time to Knee Replacement: Intention-to-Treat Cohort Cox Regression.

Baseline Predictors	HR	95% CI	P[a]
Age (years)	1.054	0.966-1.151	0.238
BMI (kg/m^2)	1.105	0.949-1.288	0.199
BML medial compartment	**2.132**	**1.379-3.296**	**0.001**
WOMAC pain	**1.101**	**1.042-1.164**	**0.001**
CRP	1.238	1.028-1.490	0.024

Note: HR = hazard ratio; CI = confidence interval; BMI, body mass index; BML, bone marrow lesion; Western Ontario and McMaster Universities Osteoarthritis Index; CRP = C-reactive protein.
[a]Cox regression to predict a knee (target) replacement. *n* = 12 as data from the contralateral knees are not included. Statistically significant values are given in boldface.

the protective effect of licofelone on the occurrence of a TKR up to 6 years after the study inception. The present study provides additional information on the possible protective effects of CS on the progression of knee OA structural changes using the "hard" outcome of TKR. Although the protective effect was statistically modest, a trend favoring CS was seen in both the end-point incidence and survival analyses after 4 years. The current findings also indicate that patients who had TKRs had greater incidences at baseline of severe knee symptoms, higher CRP levels, and higher incidence of BML in the medial compartment, and more cartilage volume loss at 1 year, also in the medial compartment. This study also validates the use of MRI in a multicenter study demonstrating its assessment of the effects of drug treatment translating into a "hard" outcome such as a TKR. The present results and those from previous knee OA MRI studies[20-22] bring to light the importance of evaluating cartilage volume loss at earlier stages of the knee OA process in the prediction of TKRs. The medial compartment lesions at baseline such as the presence of BML were strongly predictive of TKR, data that support the role played by biomechanical stress in such an event.[20,21]

The baseline levels of CRP, a demonstrated marker of cartilage volume loss,[12] were approximately twice as high for patients who subsequently had a TKR versus the controls. The cartilage volume loss, especially in the medial compartment, but not the baseline volume (data not shown), was also found to be strongly predictive of a TKR. These findings are in accordance with outcomes such as joint space narrowing, a medial compartment measurement, which have been demonstrated to be predictive of knee OA progression and TKR.[25] Publications have demonstrated that cartilage volume loss correlated with worsening of the WOMAC pain variable.[26-28] The present study suggests that it may also predict the incidence of a TKR, a logical end point of such occurrence. The BML changes at 1 year were not associated with TKR in this particular post hoc study. This contrasts with findings that such BML changes are associated with cartilage volume loss, hence associated with the potential of a later need for a TKR.[11,25]
Interestingly, the results from the analysis of both ATP and ITT cohorts yield, in a univariate way, similar predictive variables for the occurrence of a TKR (data not shown), which strengthens the overall results of the post hoc analysis. Unfortunately, no standardized radiographs with

measurement of the joint space width and long-term joint space narrowing were used to evaluate the structure modifying effect of CS, as stated in the original article.[13] The main reason was that the patients were not followed for enough time to expect any significant x-ray outcome results as previously shown.[14] This represents a study limitation. This study has other limitations. Since this is a post hoc analysis, an RCT with TKR as the primary outcome would be mandatory to evaluate the protective effects of DMOAD agents. Another limitation, related to the design of the original study, is that the placebo arm was maintained for 6 months whereas our assessments were performed at 1 year. Moreover, providing active CS to the placebo group for the open-phase of the trial could have dampened all the different results of this study versus the group taking CS for 12 months. In addition, no written report was specifically collected by our research team to confirm the occurrence of TKR, since only a blinded phone interview directly to the patient was performed. However, the interview specifically asked about the occurrence of a knee replacement and not simply about surgery, which could include arthroscopies or osteotomies. Finally, since not all patients that participated in the original study were reached by phone interview (n = 57, 81.4%) a potential bias is always possible, but the baseline demographics of the 13 lost to follow-up were similar to those of the 57 patients (data not shown). The TKR indication and occurrence is obviously highly dependent on local medical and surgical practices, availability of the procedure, and patient preference. For instance, the 4-year span between the end of the RCT and TKR assessment was completely open and subject to different co-interventions, such as over-the-counter use of CS compounds or any other agents, and comorbidities, including traumatism, that may have influenced the procedure occurrence. Nonetheless, one might expect that these conditions were probably not biased toward the placebo group and that a true CS effect influenced the qMRI and symptom occurrence during the RCT phase of the study and its association with fewer long-term occurrences of TKR.

We intend to repetitively reassess new TKR occurrences in the future to see if such CS protection holds over time. The small patient number resulting in the paucity of TKR occurrences is the major study limitation. For instance, with regard to the multivariate analysis results, it should be taken into account that we could not enter all variables for the model to hold statistically. The enrolment of a larger number of patients would have been ideal, as it might have yielded more convincing evidence and analysis. For example, cartilage volume change used as a continuous variable was not associated with the occurrence of TKR (data not shown), probably because of lack of statistical power. It was the cutoff value of cartilage volume changes at 7% that was selected a posteriori from the data of our previous study[25] that yielded the best prediction of TKR occurrence. These data, however, are interesting as they provide additional support to the findings of that previous study.[25] The lack of statistical power may also explain why only the presence of BML at baseline, and not BML changes over time, was associated with the occurrence of a TKR. This may reflect greater interpatient variability in BML change over time, precluding detection of any predictive signal. The present study was not intended to yield absolute cutoff as a predictor of TKR for future studies but to better understand variables that should be considered when predicting such surgery. Many of the above questions raised by this trial should hopefully be answered by a definitive study presently underway.

Conclusion

In summary, despite its small patient number, our study provides new information regarding the factors that could possibly predict the occurrence of TKR. Symptoms such as baseline knee pain and function, presence of BML, and knee cartilage volume loss over time may predict long-term occurrence of TKR. These data demonstrate that it is possible to predict a "hard" outcome such as TKR from knee OA clinical trial and MRI data. The results are highly encouraging and support the use of MRI to establish new outcomes in DMOAD trials.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article:

J-P. Raynauld and M. Dorais are consultants for ArthroLab Inc., J. Martel-Pelletier and J-P. Pelletier are owners of ArthroLab Inc. and consultants for Bioibérica. B. Haraoui, D. Choquette, A. Beaulieu, L. Bessette, and F. Morin received honoraria from ArthroLab Inc., and F. Abram is an employee of ArthroLab Inc.

Ethical Approval

This study was approved by the local ethics committees.

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