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Trajectory of cartilage loss within 4 years of knee replacement – a nested case–control study from the Osteoarthritis Initiative

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SUMMARY

Objective: Knee replacement (KR) represents a clinically important endpoint of knee osteoarthritis (KOA). Here we examine the 4-year trajectory of femoro-tibial cartilage thickness loss prior to KR vs non-replaced controls.

Methods: A nested case–control study was performed in Osteoarthritis Initiative (OAI) participants: Cases with KR between 12 and 60 month (M) follow-up were each matched with one control (without KR through 60M) by age, sex, and baseline radiographic stage. Femoro-tibial cartilage thickness was measured quantitatively using magnetic resonance imaging (MRI) at the annual visit prior to KR occurrence (T_0), and at 1–4 years prior to T_0 (T_{-1} to T_{-4}). Cartilage loss between cases and controls was compared using paired *t*-tests and conditional logistic regression.

Results: Hundred and eighty-nine knees of 164 OAI participants [55% women; age 64 ± 8.7; body mass index (BMI) 29 ± 4.5] had KR and longitudinal cartilage data. Comparison of annualized slopes of change across all time points revealed greater loss in the central medial tibia (primary outcome) in KRs than in controls [94 ± 137 vs 55 ± 104 μm; $P = 0.0017$ (paired *t*); odds ratio (OR) 1.36 (95% confidence interval (CI): 1.08–1.70)]. The discrimination was stronger for $T_{-2} \rightarrow T_0$ [OR 1.61 (1.33–1.95), $n = 127$] than for $T_{-1} \rightarrow T_0$, and was not statistically significant for intervals prior to T_{-2} [i.e., $T_{-4} \rightarrow T_{-2}$, OR 0.97 (0.67–1.41), $n = 60$]. Results were similar for total medial femoro-tibial cartilage loss (secondary outcome), and when adjusting for pain and BMI.

Conclusions: In knees with subsequent replacement, cartilage loss accelerates in the 2 years, and particularly in the year prior to surgery, compared with controls. Whether slowing this cartilage loss can delay KR remains to be determined.

Introduction

Knee osteoarthritis (KOA) is estimated to affect >10% of the population in the United States[1] and, although commonly regarded as a disease of the elderly, symptomatic KOA is diagnosed today at a mean age of only 56 years, with a lifetime risk of 45%[2]. KOA is

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associated with substantial functional limitations and disability[3,4], causes significant morbidity, mortality, and reduction in the quality of life[5], and substantial health care utilization[6]. In absence of effective disease modifying therapies, a large portion of the costs involved in managing KOA is driven by knee replacements (KRs), and KR therefore represents a clinically important endpoint[7]. The number of annual KRs in the US has doubled in the last decade, with a disproportionate increase amongst younger adults; its prevalence now is considerably greater than that of rheumatoid arthritis[8].

Few studies have examined cartilage loss quantitatively with magnetic resonance imaging (MRI) prior to KR[7,9–12]. However, these prospective cohort studies generally did not adequately adjust for the fact that knees with advanced radiographic disease exhibit greater cartilage loss[13–15] and also are more likely to receive KR than those being at an earlier stage of disease. Using a case/control design with matching for baseline radiographic disease stage [Kellgren Lawrence grade (KLG)], sex, and age, we have reported that cartilage thickness loss was significantly greater in the year prior to KR than in control knees that did not subsequently undergo KR[16]. However, KOA is a slowly evolving disorder, and 1 year of observation represents a relatively short time period in relation to the time between incident symptoms or radiographic signs and need for KR. Elucidating the trajectory of cartilage loss over several years prior to KR can help in the understanding of how structural change in KOA progresses prior to that knee reaching a critical clinical state. Further, this analysis may help in characterizing potential time windows for structure modification of cartilage by therapeutic intervention with disease modifying drugs (DMOADs) or other measures.

The purpose of this study therefore was to examine the trajectory of cartilage loss over 4 years prior to KR, compared with matched controls that did not undergo KR during this observation interval. Specifically, we asked whether cartilage loss between KRs and control knees differs during observation intervals >1 year prior to KR.

Methods

Study design

This study was ancillary to the Osteoarthritis Initiative (OAI) multi-center longitudinal cohort study (OAI) (http://www.oai.ucsf.edu/)[16,17]. The participants were recruited at four centers[16–18] and studied annually over 4 years, using 3 T MRI[16–19] and other methods. OAI participants were 45–79 years old and with (or at risk of symptomatic KOA) in at least one knee[17]. The study was approved by the local Institutional Review Boards at each of the sites, and all participants gave informed consent[17]. OAI participants were examined and interviewed annually about having received a KR in the preceding 12 months (M). This was confirmed by radiography, or from hospital records when radiographs were not available.

To be eligible as a case, a KR had to be recorded at 24 month (M), 36M, 48M, or 60M follow-up, and MRI acquisitions acceptable for quantitative analysis had to be present for at least two prior (but not necessarily for all preceding) time points (Fig. 1). The annual MRI examination prior to KR occurrence was termed T_0, and the annual examinations preceding T_0 were designated T_{-1} through T_{-4}. KRs detected at 12M were not included, because they did not have longitudinal data prior to KR. KRs detected at the 24M had two prior annual measurements (T_0 and T_{-1}), and those observed at 60M had up to five previous annual measurements (T_0 through T_{-4}; Fig. 1). If both knees of one participant were replaced at the same, or at different time points, both were included in the analysis (for statistical treatment of potentially correlated observations, please see below).

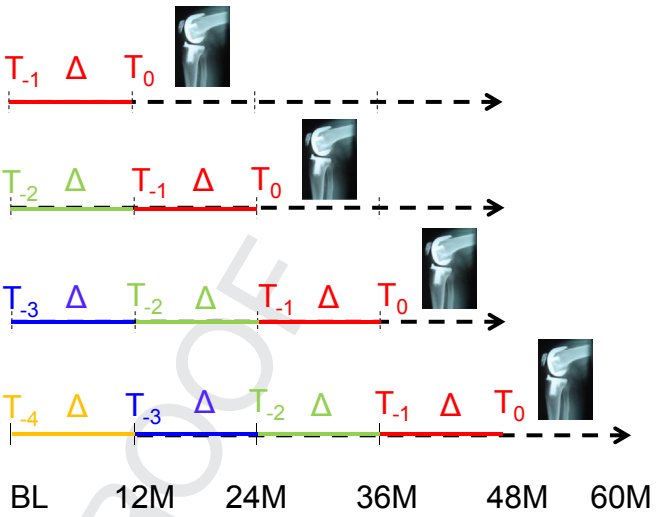

Fig. 1. Graph showing the study design and methods: OAI participants with KR occurrence between 24 and 60 month (M) follow-up had quantitative cartilage analysis at 2–5 prior time points, providing a minimum of one to a maximum of four 1-year observation periods.

Control knees were selected from those without self-reported KR and without evidence of KR on radiographs between baseline and 60M. Knees did not qualify as controls if the opposite knee received a KR during the study. Controls had to have MRIs available at time points corresponding with those of the KR cases (T_0 through T_{-4}). Cases and controls were matched 1:1 by sex, age (±5 years), and radiographic disease stage, documented by central reading at the baseline visit (KLG strata of 0–1, 2, 3, and 4). KLGs from release 0.4 from the central readings of the fixed flexion radiographs (performed at Boston University) were taken[17]. In a second (*post-hoc*) step, attempts were made to match cases with medial joint space narrowing (JSN) to controls with medial JSN, and cases with lateral JSN to controls with lateral JSN: 137 cases could be matched to controls with the same medial/lateral JSN pattern.

Quantitative MRI analysis

The quantitative MR image analysis relied on an oblique sagittal double-echo steady-state (DESS) sequence water excitation[17,19–21]. Segmentation of the medial and lateral femoro-tibial cartilages was performed at one image analysis center (Chondrometrics GmbH, Ainring, Germany), the readers being fully blinded to case/control status and to the acquisition order of the different time points[16,18]. The total area of subchondral bone (tAB) and cartilage surface area (AC) of the weight-bearing femoro-tibial compartment were analyzed[16,18], and all segmentations were quality controlled by one of the two experts (SM or FE)[10,12]. The mean cartilage thickness over the total area of subchondral bone (ThCtAB.Me) was derived after 3D surface reconstruction, using software by Chondrometrics GmbH (Ainring, Germany)[22]. The cartilage thickness was then computed for the medial and lateral (femoro-tibial) compartments, for the medial and lateral tibiae and weight-bearing femoral condyles, and for five tibial (central, external, internal, anterior, posterior) and three femoral subregions (central, external, internal)[22] (Fig. 2). Change in cartilage thickness was computed by subtracting the thickness measured at one time point from that observed at a later time point; absolute cartilage loss hence was expressed as a negative value in μm. The change was not reported in percent (%),

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