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Subregional laminar cartilage MR spin–spin relaxation times (T2) in osteoarthritic knees with and without medial femorotibial cartilage loss – data from the Osteoarthritis Initiative (OAI)

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SUMMARY

Objective: To explore whether subregional laminar femorotibial cartilage spin–spin relaxation time (T2) is associated with subsequent radiographic progression and cartilage loss and/or whether one-year change in subregional laminar femorotibial cartilage T2 is associated with concurrent progression in knees with established radiographic OA (ROA).

Methods: In this case-control study, Osteoarthritis Initiative (OAI) knees with medial femorotibial progression were selected based on one-year loss in both quantitative cartilage thickness Magnetic resonance imaging (MRI) and radiographic joint space width (JSW). Non-progressor knees were matched by sex, Body mass index (BMI), baseline Kellgren-Lawrence-grade (2/3), and pain. Baseline and one-year follow-up superficial and deep cartilage T2 was analyzed in 16 femorotibial subregions using multi-echo spin-echo MRI.

Results: 37 knees showed medial femorotibial progression whereas 37 matched controls had no medial or lateral compartment progression. No statistically significant baseline differences between progressor and non-progressor knees in medial femorotibial cartilage T2 were observed in the superficial (48.9 ± 3.0 ms; 95% CI: [47.9, 49.9] vs 47.8 ± 3.6 ms; 95% CI: [46.6, 49.0], $P = 0.07$) or deep cartilage layer (40.8 ± 3.6 ms; 95% CI: [39.5, 42.0] vs 40.1 ± 4.7 ms; 95% CI: [38.5, 41.6], $P = 0.29$). Concurrent T2 change was more pronounced in the deep than the superficial cartilage layer. In the medial femorotibial compartment (MFTC), longitudinal change was greater in the deep layer of progressor than non-progressor knees (1.8 ± 4.5 ms; 95% CI: [0.3, 3.3] vs −0.2 ± 1.9 ms; 95% CI: [−0.8, 0.5], $P = 0.02$), whereas no difference was observed in the superficial layer.

Conclusion: Medial compartment cartilage T2 did not appear to be a strong prognostic factor for subsequent structural progression in the same compartment of knees with established ROA, when appropriately controlling for covariates. Yet, deep layer T2 change in the medial compartment occurred concurrent with medial femorotibial progression.

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Introduction

Magnetic resonance imaging (MRI) spin–spin (transverse) relaxation time (T2) has been proposed as an imaging biomarker for the detection of alterations in cartilage composition before the onset of knee osteoarthritis (OA), to differentiate stages of OA, and to monitor or predict disease progression[1–3]. T2 is known to reflect cartilage composition (collagen integrity, orientation, and hydration)[1,3,4], and to correlate with histological grading[5,6] and mechanical properties[1,7] of articular cartilage.

Several studies investigated the association between cartilage T2 times and incidence or progression of knee OA. In a nested case-control study of knees with Kellgren Lawrence grade (KLG) 0 at baseline, Liebl *et al.* reported baseline T2 times to be significantly greater in most knee compartments of KLG 0 knees that developed radiographic OA (ROA) over 4 years than in non-incident control knees[8], in particular in the superficial layer[8]. Joseph *et al.*[9] reported prevalence of MRI structural pathology to increase over time in subjects with risk factors for OA and the authors also reported that

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greater baseline cartilage T2 predicted longitudinal change in cartilage, meniscus, and bone marrow lesion scores. Based on a cohort including 55 knees with KLG 0–3 at baseline, Prasad *et al.*[10] reported significantly longer baseline T2 (and T1rho) times in the 27 case knees with progression over 2 years (incidence or worsening of existing cartilage lesions) than in 28 control knees without progression using a modified WORMS scoring system. No statistically significant differences were, however, found between progressor and non-progressor knees, when T2 times were compared separately in knees with and without ROA[10]. It is well-known that the likelihood of progression is associated with radiographic disease stage[11–13], and it may thus be that the differences in baseline radiographic disease stages were responsible for the observed differences in baseline T2[14–16] rather than progression *per se*. Prasad *et al.* did not report statistically significant differences in demographic data or baseline pain between progressor and non-progressor knees[10], but a study on the relationship of T2 with structural progression should ideally rule out potential bias from risk factors of OA structural progression, since high BMI or knee pain have been associated with both progression[11,17,18] and with cartilage T2[19–22]. Also, previous studies on the relationship between cartilage T2 and OA progression have analyzed bulk cartilage T2 of entire cartilage plates, albeit T2 is known to vary strongly between superficial and deep laminae[23], and subregional differences in cartilage T2 are to be expected based on local variations in collagen architecture[24].

To our knowledge, no study to date has evaluated the cross-sectional and longitudinal relationship of cartilage T2 with structural progression as defined by quantitative radiographic and/or MRI outcomes (i.e., radiographic JSW or MRI-based cartilage thickness or volume) and no previous study has evaluated the relationship of cartilage T2 with structural progression separately for deep and superficial cartilage and/or for different femorotibial subregions. Because loss in radiographic JSW or cartilage thickness is typically observed in knees with established ROA (KLG $\geq$2) and because participants with established ROA are those typically enclosed in clinical trials[25], we used a matched case-control design of participants with established (but without end-stage [KLG 4]) radiographic OA (KLG 2/3), to study whether (subregional) laminar medial femorotibial compartment (MFTC) cartilage T2 times.

a) are associated with subsequent medial compartment structural progression
b) change concurrently in knees with subsequent medial compartment structural progression
c) show a greater concurrent change in knees with subsequent medial compartment structural progression than in knees without such progression.

Based on previous reports that T2 is limited in monitoring progression once an advanced disease stage is reached[2], we performed sensitivity analyses with stratification for baseline KLG.

Methods

Study design and sample selection

The study participants were selected from the Osteoarthritis Initiative (OAI) cohort (OAI; http://www.oai.ucsf.edu/, clinicaltrials.gov: NCT00080171)[26], which was approved by the Committee on Human Research, the Institutional Review Board (IRB) for the University of California, San Francisco (UCSF). All OAI participants provided written informed consent and this study was carried out in accordance with the IRB-approved OAI data user agreement. OAI participants were 45–79 years old, with or at risk of symptomatic knee OA in at least one knee. General exclusion criteria were rheumatoid or inflammatory arthritis, bilateral end-stage knee OA, inability to walk without aids, and MRI contraindications.

The inclusion criteria for the current nested case-control sample have been described previously: Knees with and without medial femorotibial progression were selected from a sample of 725 right knees from OAI participants, for which MRI-based cartilage thickness measurements were available for the baseline and the one-year follow-up visit (Fig. 1). At the baseline visit, these knees were KLG 2–4[12,17,25] according to the OAI clinical site radiographic readings[17,25]. Of these 725 right knees studied with MRI, 625 also had quantitative JSW measurements from fixed-flexion radiographs[27] that we used here to ensure that apparent change in cartilage loss was not due to MRI-specific precision errors or artifacts, so that structural progression was confirmed by a second, independent method.

Based on smallest detectable change (SDC) thresholds[28,29] for MRI-based MFTC cartilage thickness (>102 μm) and for radiographic medial minimum joint space width (mJSW) loss (>328 μm), we selected progressor knees that exceeded both thresholds. Non-progressor knees were defined as knees that did not exceed the SDC thresholds for either cartilage thickness loss or mJSW loss in the MFTC and that also did not exceed the SDC threshold for lateral femorotibial compartment (LFTC) cartilage loss (92 μm). Because the objective of this study was to determine, whether cartilage T2 is associated with subsequent structural progression in knees with established ROA, the current study included knees with definite, but not end stage ROA, whereas knees with KLG 1 and 4 at baseline were excluded. The radiographic inclusion/exclusion relied on the central KLG readings (release 0.5), which are deemed more reliable than the clinical site readings that were used to select the initial sample of 725 knees[25].

Of the 625 knees for which both MRI-based cartilage thickness and radiography-based mJSW measurements were available, 404 knees did not exceed any SDC threshold, 80 exceeded only the MFTC SDC threshold for MRI-based cartilage loss, 87 exceeded only the SDC threshold for radiography-based mJSW loss, and 54 knees exceeded the MFTC SDC threshold for both MRI-based cartilage loss and radiography-based mJSW loss (Fig. 1). Cartilage loss exceeding the LFTC SDC threshold was observed in 64 of the 404 knees that did not display MFTC loss. After excluding knees without definite radiographic OA (KLG<2) or with end-stage radiographic OA (KLG 4) at baseline, 46 of the 54 knees with MFTC progression and 229 of the 340 knees without MFTC or LFTC progression qualified for inclusion in this study.

In order to reduce the potential bias introduced by covariates (e.g., sex, BMI, pain), knees with and without structural progression were matched 1:1 by the same sex, body height (±3 cm), BMI (±5 kg/m^2), baseline KLG (2 or 3), and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores (±5; scale from 0 to 20). An appropriate matching control was found for 37 of the 46 progressor knees. Because all knees fulfilling the selection criteria were included in this study and because no information about the expected effect size for laminar (and subregional) cartilage T2 was available, no a-priori power analysis was performed.

T2 analysis of femorotibial cartilage

The right knees of the OAI participants had sagittal 3 T multi-echo spin-echo (MESE) MR images acquired[26,30] (Fig. 2). The repetition time was 2700 ms and the echo times were 10, 20, 30, 40, 50, 60, and 70 ms (slice thickness 3.0 mm, in-plane resolution 0.3125 mm). T2 was computed for each voxel by fitting a mono-exponential decay curve to the measured signal intensities using

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