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Brief report

Radiographically normal knees with contralateral joint space narrowing display greater change in cartilage transverse relaxation time than those with normal contralateral knees: a model of early OA? – data from the Osteoarthritis Initiative (OAI)

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SUMMARY

Objective: To develop a model of early osteoarthritis, by examining whether radiographically normal knees with contralateral joint space narrowing (JSN), but without contralateral trauma history, display greater longitudinal cartilage composition change (transverse relaxation time; T2) than subjects with bilaterally normal knees.

Methods: 120 radiographically normal knees (Kellgren Lawrence grade [KLG] 0) from the Osteoarthritis Initiative were studied. 60 case knees displayed definite contralateral radiographic knee osteoarthritis (KLG $\geq$ 2) whereas 60 reference subjects were bilaterally KLG0, and were matched 1:1 to cases based on age, sex, and BMI. All had multi-echo spin-echo MRI acquired at year (Y) 1 and 4 follow-up, with cartilage T2 being determined in superficial and deep cartilage layers across 16 femorotibial subregions. T2 across all regions was considered the primary analytic focus.

Results: Of 60 KLG0 case knees (30 female, age: 65.0 ± 8.8 y, BMI: 27.6 ± 4.4 kg/m^2), 21/22/13/4 displayed contralateral JSN 0/1/2/3, respectively. The longitudinal increase in the deep layer cartilage T2 between Y1 and Y4 was significantly greater ($P = 0.03$; Cohen's D 0.50) in the 39 KLG0 case knees with contralateral JSN (1.2 ms; 95% confidence interval [CI] [0.4, 2.0]) than in matched KLG0 reference knees (0.1 ms; 95% CI [−0.5, 0.7]). No significant differences were identified in superficial T2 change. T2 at Y1 was significantly greater in case than in reference knees, particularly in the superficial layer of the medial compartment.

Conclusions: Radiographically normal knees with contralateral, non-traumatic JSN represent an applicable model of early osteoarthritis, with deep layer cartilage composition (T2) changing more rapidly than in bilaterally normal knees.

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Introduction

Evaluating treatment for modifying the structural progression of "early" osteoarthritis (OA) requires models that display subtle alterations in articular tissue over time. These alterations must occur at an early disease stage, preferably before the actual onset, and their progression should be detectable using *in vivo* methods. Otherwise, sample sizes become formidable, rendering clinical trials on preventive structure and disease modification inefficient.

In the absence of local risk factors, such as injuries from a previous trauma, knee OA typically affects both joints.[1,2] Based on this concept, it was demonstrated that radiographically normal knees

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(Kellgren Lawrence grade [KLG] 0) with definite radiographic OA (ROA, KLG $\geq$ 2) of the contralateral (CL) knee have a greater likelihood of incident ROA than KLG0 knees from subjects with bilaterally normal knees.[2] The former also displayed greater rates of cartilage loss than the latter, and the effect was strongest when the CL knee displayed advanced ROA, i.e. joint space narrowing (JSN).[3]

Magnetic resonance imaging (MRI) transverse (spin–spin) relaxation time (T2) has been proposed as an imaging biomarker for detection of alterations in articular cartilage composition before the onset of ROA.[4,5] Cartilage T2 reflects collagen integrity, orientation, and hydration[4,6], with an increase in the relaxation time indicating (early) damage; T2 was shown to be associated with cartilage histological grading[4,7] and mechanical properties.[4,8] Elevated baseline cartilage T2 predicts the onset of ROA[9] and the progression of degenerative cartilage abnormalities in early OA[10], while longitudinal change in T2 has been proposed to be particularly suitable of monitoring "progression" during early OA, before advanced structural changes occur.[5]

The purpose of the current study was therefore to develop a model of "early" OA, by examining whether radiographically normal (KLG0) knees with idiopathic, contralateral knee OA, that is without a relevant contralateral trauma history, display a greater longitudinal increase in cartilage T2 (as well as a greater cartilage T2 at baseline) compared with subjects with bilaterally normal knees. Specifically, we tested the hypothesis that T2 change was greater in KLG0 case knees with CL radiographic JSN than in KLG0 reference knees from bilaterally normal subjects.[3] Such a model of "early" knee OA, together with sensitive imaging methodology for monitoring progression during early disease stages, will potentially enable evaluating the efficacy of preventive structure-modifying (or structure-preserving) therapies, before the actual onset of more advanced OA.

Methods

Study design

The study was based on data from the Osteoarthritis Initiative (OAI), a prospective, observational cohort study (https://nda.nih.gov/oai/). The OAI enrolled 4,796 participants aged 45–79 at four clinical centers, and provides clinical information, 3 T MRI, and fixed-flexion radiographs (of both knees).[11]

The sample selection (Online Fig. 1) relied on the central radiographic readings (Boston University, version 1.8). 150 OAI participants had unilateral ROA (one knee KLG0, the other KLG $\geq$ 2) at Y1 follow-up, did not report a relevant trauma history of the KLG $\geq$ 2 knee (OAI variable INJR/INJL), and had MRI available at the year 1 (Y1) and Y4 follow-up visit.[3] In 4 knees, radiographic evaluation was missing at Y1, so that KLGs were taken from baseline and Y2 readings. Amongst these 150, the right knee was KLG0 in 63 participants (with the left knee KLG $\geq$ 2), and the left knee was KLG0 in the other 87 participants (with the right knee KLG $\geq$ 2). Only right knees in the OAI had multi-echo spin-echo (MESE) MRIs for cartilage T2 analyses acquired.[11] Therefore, 63 KLG0 case knees (with contralateral KLG $\geq$ 2) were available for cartilage T2 analysis. Of these, 60 were matched 1:1 with 60 right KLG0 reference knees from OAI incidence cohort participants who were bilaterally KLG0, and had MRIs at Y1 and Y4[3] (criteria: same sex, same pain frequency, similar age [±5 y], and similar BMI [±5 kg/m^2]).

Analysis of femorotibial cartilage T2

Sagittal 3 T multi-echo spin-echo (MESE) MR images of the right knees were acquired[11] (Fig. 1), with a repetition time of 2700 ms, and echo times of 10, 20, 30, 40, 50, 60, and 70 ms (slice thickness 3.0 mm, in-plane resolution 0.3125 mm $\times$ 0.3125 mm). Segmentation of medial and lateral tibial and weight-bearing femoral cartilage were performed manually (S.M.) by tracing the cartilage surface and bone interface using custom software.[12] Baseline and follow-up images were analyzed with reference to each other, but with blinding to acquisition order and CL knee radiographic status. Because cartilage T2 varies spatially with tissue depth[4,13], the cartilage layers were computationally divided into top (superficial) and bottom (deep) 50% after segmentation (Fig. 1), based on the local distance of each voxel between the segmented cartilage surface and bone interface.[12] T2 was computed for each voxel by fitting a mono-exponential decay curve to the measured signal intensities, with the 10 ms echo being excluded to reduce impact of stimulated echoes.[4,12] The deep and superficial T2 was also determined across 16 femorotibial subregions (Fig. 1), as described previously.[3,11,12] Averages were provided for the medial and lateral compartment (MFTC/LFTC) and the total femorotibial joint (FTJ). Location-independent T2 lengthening and shortening scores were computed by summing all negative/positive changes across the 16 subregions within each knee, equivalent to the analysis of location-independent cartilage thinning and thickening scores.[3,14] Location-independent ordered values (OVs) of T2 change were derived by ordering the T2 changes observed in the 16 subregions within each knee in ascending order.[14] OV1 therefore represented the subregion with the largest T2 decrease within each knee and OV16 the subregion with the greatest T2 increase within each knee. Cartilage thickness measures at Y1 and Y4 were available for 58 of the 60 knees.[3]

Statistical analysis

Given previous findings on deep layer cartilage T2 change with progression in established knee OA[12], the primary analytic focus of this exploratory study was the comparison of the longitudinal change in the deep layer across the total FTJ between the 39 KLG0 case knees with contralateral radiographic JSN $\geq$ 1[3] and their matched KLG0 reference knees; superficial T2 was considered a co-primary focus. The secondary analytic foci were location-independent T2 lengthening scores. Given the 1:1 paired matching for key variables, a paired *t*-test was used to evaluate whether the observed longitudinal differences were significantly different between case and reference knees. Effect size was estimated using Cohen's D. All other comparisons were considered exploratory. Linear regression analysis was used to relate longitudinal change in T2 with that of the location-independent cartilage thinning score.[3]

Results

Demographics and radiographic status

Of 60 KLG0 case knees (age: 5.0 ± 8.8 y, BMI: 27.6 ± 4.4 kg/m^2), 30 were from female participants, all displayed contralateral KLG $\geq$ 2 per definition, and 21/22/13/4 contralateral JSN 0/1/2/3, respectively. Of the 60 KLG0 references knees with contralateral KLG0 (age 65.0 ± 8.6 y; BMI 27.3 ± 4.1 kg/m^2), 30 were from women (per matching criteria). The MFTC/LFTC cartilage thickness was 3.51 ± 0.48 mm/3.93 ± 0.61 mm for the case and 3.46 ± 0.58 mm/3.87 ± 0.65 mm for the reference knees. Of the 58 case and 57 reference knees with Y4/Y6 or Y8 follow-up KLGs available, 21% case and only 4% reference knees developed ROA (KL $\geq$ 2, $P < 0.01$ [chi-squared test]).

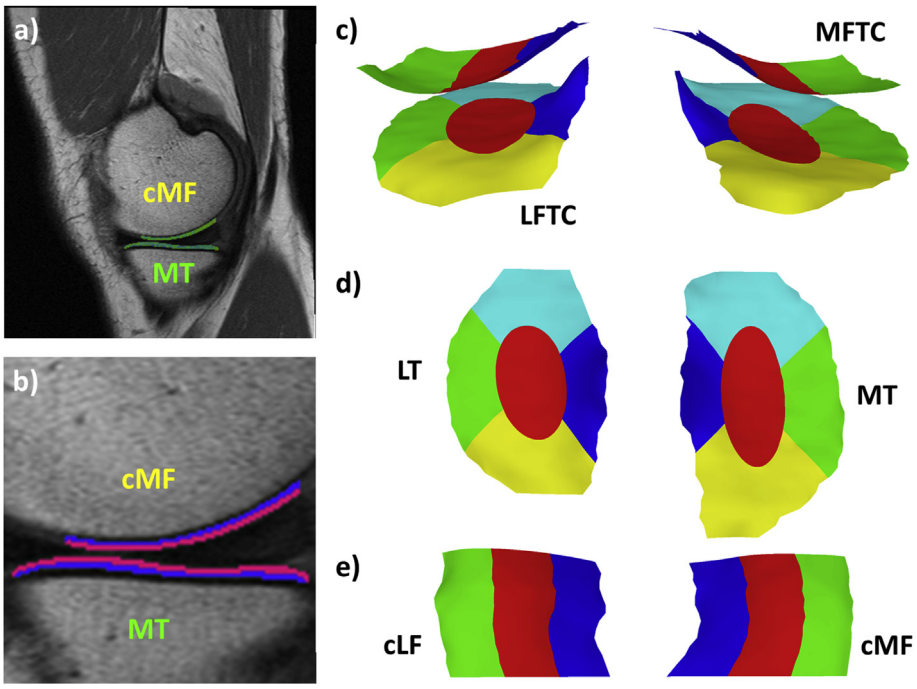

Fig. 1. Illustration showing the cartilage T2 measurements in the central part of the medial femoral condyle (cMF) and the medial tibia (MT) and the subregional analysis; a) color-coded T2 map, b) superficial (magenta) and deep (blue) cartilage layers, c) Illustration of the 16 subregions in the medial (MFTC) and lateral (LFTC) femorotibial compartment, d) Illustration showing the central (red), external (green), internal (blue), anterior (turquoise), and posterior (yellow) subregions of the medial (MT) and lateral tibia (LT), e) Illustration showing the central (red), external (green), internal (blue) subregions of the medial (cMF) and lateral femoral condyle (cLF).

Longitudinal analysis of T2 change

The longitudinal increase in deep layer T2 across the FTJ was significantly greater ($P = 0.03$; Cohen's D 0.50) in the 39 case knees with contralateral JSN (+1.2 ms; 95% confidence interval [CI] [0.4, 2.0] ms) than in matched reference knees (+0.1 ms; 95% CI [−0.5, 0.7] ms; Table I; Fig. 2). A similar effect size (Cohen's D 0.49) was observed for the location-independent T2 lengthening score across all femorotibial subregions (Table I). Whereas differences in longitudinal T2 changes between case and reference knees were statistically significant in the LFTC, the effect size in the MFTC was weaker and not significant (Table I). Differences in the T2 shortening score and in OV1 or 16 were not statistically significant (Table I). For the superficial layer, no statistically significant differences were identified between case and reference knees (Fig. 2, Table I). The increase in deep layer T2 lengthening score was significantly correlated with the location-independent cartilage thinning score in case knees ($r = -0.31$, $P = 0.01$).

When analyzing all 60 knees, including the 21 without CL JSN, the longitudinal effects seen for deep layer T2 became weaker and only the lengthening score differed statistically significantly between case and reference knees (Online Table I).

Cross-sectional analysis

In the 39 case knees with contralateral JSN, the deep layer T2 at Y1 was somewhat longer in the case than in the reference knees, but the differences were not statistically significant (Table II; Fig. 2). Superficial cartilage T2 was, however, significantly longer in case knees with CL JSN than in matched reference knees across the TFJ

Table I
Longitudinal change in superficial and deep layer cartilage T2 (in ms) over 3 years of observation in KLG0 knees from participants with contralateral (CL) JSN ($n = 39$) and KLG0 knees from matched participants with CL KLG0 ($n = 39$)

		KLG0 with CL JSN				KLG0 with CL KLG0				Difference	
		Mean	SD	95% CI		Mean	SD	95% CI		*P*	Cohen D
Deep layer	FTJ	1.2	2.5	0.4	2.0	0.1	1.8	−0.5	0.7	0.03	0.50
	Lengthening score	32.9	29.6	23.3	42.5	21.8	12.8	17.6	25.9	0.05	0.49
	MFTC	1.4	3.4	0.3	2.5	0.4	2.4	−0.4	1.2	0.15	0.34
	LFTC	1.0	2.5	0.2	1.8	−0.1	1.8	−0.7	0.5	0.02	0.53
	Shortening score	−12.8	13.2	−17.1	−8.5	−18.4	17.2	−23.9	−12.8	0.11	0.36
	OV 16	7.4	7.7	4.9	9.9	5.4	2.7	4.5	6.3	0.14	0.35
	OV 1	−4.3	2.8	−5.2	−3.4	−5.0	3.6	−6.2	−3.8	0.37	0.21
Superficial layer	FTJ	0.9	1.9	0.3	1.5	0.9	1.5	0.4	1.4	0.98	0.01
	Lengthening score	31.2	17.7	25.5	36.9	29.7	18.0	23.9	35.6	0.71	0.08
	MFTC	1.3	2.5	0.5	2.2	1.3	2.2	0.6	2.0	0.98	0.00
	LFTC	0.5	2.2	−0.2	1.3	0.5	1.9	−0.1	1.1	0.99	0.00
	Shortening score	−15.5	16.2	−20.7	−10.2	−14.9	10.2	−18.2	−11.6	0.85	−0.04
	OV 16	8.4	4.6	6.9	9.8	6.7	3.3	5.7	7.8	0.08	0.41
	OV 1	−4.9	4.6	−6.4	−3.4	−5.2	2.4	−6.0	−4.4	0.73	0.08

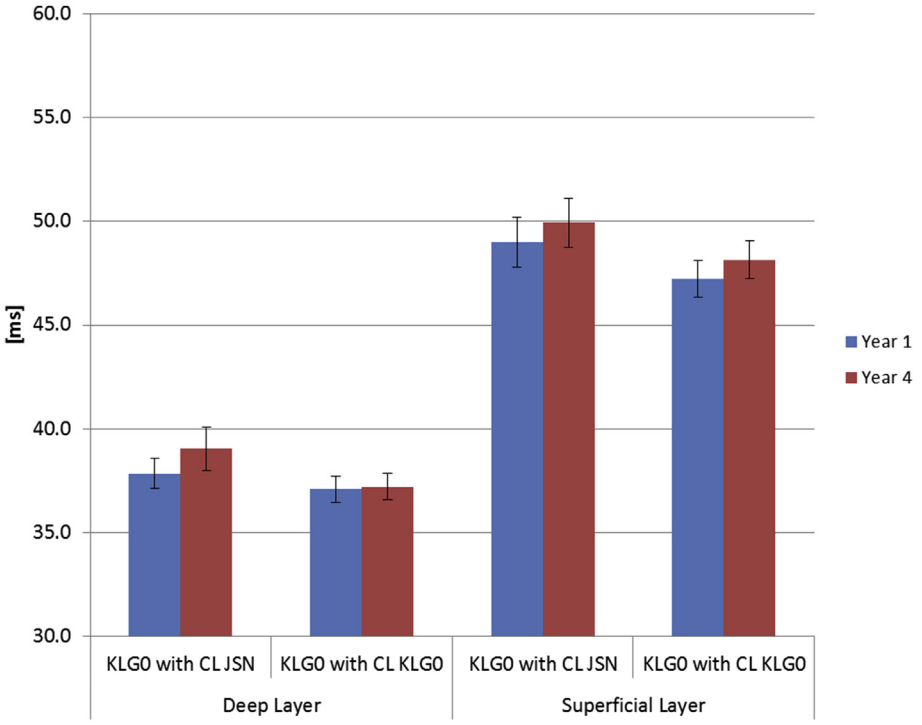

Fig. 2. Bar graphs showing the cartilage T2 times in the superficial and deep layer of the entire femorotibial joint at the Y1 and the Y4 visit in case knees with CL JSN ($n = 39$) and in matched reference knees ($n = 39$).

($P < 0.01$; Cohen's D 0.53; Fig. 2), in the MFTC ($P = 0.02$; Cohen's D 0.46), and the LFTC ($P = 0.01$, Cohen's D 0.48, Table II).

When including all 60 case knees in the analysis, the effect size became less for superficial layer T2, but the differences in deep layer T2 became statistically significant for the TFJ and the LFTC (Online Table II).

Discussion

This is the first study to explore whether the transverse relaxation time (T2) is sensitive to identifying compositional change in cartilage in a model of "early" knee OA, specifically a KLG0 knee with CL non-posttraumatic JSN. Although the sample size was small (due to the relatively rare occurrence of non-post-traumatic unilateral OA and the OAI providing T2 MRI in right knees only), statistically significant effects were identified in longitudinal and cross-sectional analyses. Another limitation is that the T2 changes seen in case knees may represent the adaptation to altered weight-bearing in patients with OA in the contralateral knee. Yet, the T2 changes seen were significantly associated with greater cartilage loss in case than in reference knees[3], and the case knees displayed a 5-fold incidence of ROA up to year 8 follow-up. These observations strengthen the assumption that the above model represents "early OA".

Cartilage T2 was observed to increase more rapidly over time in KLG0 knees with CL JSN than in bilateral KLG0 reference knees, suggesting accelerated longitudinal perturbation of cartilage composition. These between-group differences were restricted to the deep cartilage layer, and were more prominent in the lateral compartment, in which they were found to be statistically significant. Our observations coincide with greater rates of cartilage loss observed in KLG0 knees with CL JSN than in reference knees in the lateral than the medial femorotibial compartment, and with these differences being stronger when only including knees with CL JSN.[3]

A strength of the current study is the use of layer- and subregion specific analysis of T2[12], as well as a novel extension of the location-independent technology from measuring change in cartilage thickness[3,14] to that in cartilage T2. As for cartilage thickness, this approach permits analysis of cartilage composition without a priori assumptions required on where in the joint the change may occur[12], an approach that is particularly useful at an early disease stage, in which the more affected compartment is not readily identified.

Table II
Superficial and deep layer cartilage T2 (in ms) at the beginning of the observation interval (Y1) in KLG0 knees from participants with contralateral (CL) JSN ($n = 39$) and KLG0 knees from matched participants with CL KLG0 ($n = 39$)

		KLG0 with CL JSN				KLG0 with CL KLG0				Difference	
		Mean	SD	95% CI		Mean	SD	95% CI		*P*	Cohen D
Deep layer	FTJ	37.8	2.3	37.1	38.6	37.1	2.0	36.5	37.7	0.08	0.35
	MFTC	38.4	2.6	37.5	39.2	37.7	2.4	36.9	38.5	0.23	0.25
	LFTC	37.3	2.6	36.5	38.2	36.5	2.3	35.7	37.2	0.10	0.36
Superficial layer	FTJ	49.0	3.8	47.8	50.2	47.2	2.8	46.3	48.1	<0.01	0.53
	MFTC	49.6	4.7	48.1	51.1	47.6	4.0	46.3	48.9	0.02	0.46
	LFTC	48.4	3.7	47.2	49.6	46.8	2.7	46.0	47.7	0.01	0.48

Interestingly, we also observed significant cross-sectional differences between case vs. reference knees at the beginning of the longitudinal observation interval, in the absence of relevant differences in cartilage thickness, suggesting that some compositional degeneration had already taken place in the absence of relevant matrix substance loss. The statistically significant cross-sectional baseline differences observed for the superficial (but not the deep) cartilage layer indicate that the superficial layer may be sensitive for detecting early cartilage detoriation. This is in line with results from a previous study that reported baseline superficial but not deep layer T2 to predict incident ROA.[9] The longitudinal change in superficial T2 observed in case knees in the current study was similar to that observed in the superficial layer of control knees whereas statistically significant differences in longitudinal change were observed in the deep layer. Change in deep layer T2 may thus represent the most sensitive measure for monitoring progression in early OA knees.

We conclude that radiographically normal knees with contralateral non-posttraumatic JSN represent an applicable human model of "early OA", with prolonged T2 in the superficial cartilage layer at baseline and deep layer cartilage composition changing more rapidly than in bilaterally normal knees. Such a model may serve demonstrating the efficacy of preventive structure-modifying (or −maintaining) therapeutic approaches before the onset of more advanced disease.

Author contributions

- Study conception and design: WW, FR, FE
- Acquisition of data: SM, WW
- Analysis & interpretation of data: All authors
- Writing of first manuscript draft: WW and FE
- Critical manuscript revision and approval of final manuscript: All authors

WW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Role of the study sponsor

The statistical analysis and writing of this article was independent from and not contingent upon approval from the study sponsors.

Conflicts of interest

Dr. Maschek and Dr. Wirth are part time employees and co-owners of Chondrometrics GmbH. Dr. Roemer is a part time employee of Chondrometrics, and is shareholder, CMO and Director of Research of Boston Imaging Core Lab (BICL), LLC. Dr. Duda and Dr. Sharma have no conflicts to declare. Dr. Eckstein is CEO/CMO and co-owner of Chondrometrics GmbH, and he has provided consulting services to Merck KGaA, Bioclinica, Samumed, Tissuegene, Servier, Galapagos and Roche. He also has received speaker honoraria from Medtronic.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2019.06.013.

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