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BRIEF REPORT

Association of Superficial Cartilage Transverse Relaxation Time With Osteoarthritis Disease Progression: Data From the Foundation for the National Institutes of Health Biomarker Study of the Osteoarthritis Initiative

David Fuerst,[1] Wolfgang Wirth,[1] Martin Gaisberger,[2] David J. Hunter,[3] and Felix Eckstein[1]

Objective. To study whether layer-specific cartilage transverse relaxation time (T2) and/or longitudinal change is associated with clinically relevant knee osteoarthritis (OA) disease progression.

Methods. The Foundation for the National Institutes of Health Biomarker Consortium was a nested case–control study on 600 knees from 600 Osteoarthritis Initiative participants. Progressor knees had both medial tibiofemoral radiographic joint space width (JSW) loss (≥0.7 mm) and a persistent increase in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (≥9 on a 0–100 scale) at 24–48 months from baseline (n = 194). Multiecho spin-echo (MESE) magnetic resonance images (MRIs) for cartilage T2 analysis had been acquired in the right knees only (97 progressor knees). These were compared to 104 control knees without JSW or pain progression. Fifty-three knees had JSW progression, and 57 pain progression only. Cartilage thickness segmentations obtained from double-echo steady-state MRI were matched to MESE MRI to extract superficial and deep femorotibial cartilage T2. Superficial medial femorotibial compartment (MFTC) T2 at baseline was the primary, and change in deep MFTC T2 between baseline and 12 months was the secondary analytic outcome of this post hoc exploratory study.

Results. Baseline superficial MFTC T2 was significantly elevated in progressor knees (adjusted mean 47.2 msec [95% confidence interval (95% CI) 46.5, 48.0]) and JSW progression only knees (adjusted mean 47.3 msec [95% CI 46.3, 48.3]), respectively, versus non-progressor knees (45.8 msec [95% CI 45.0, 46.5]) after adjustment for age, sex, body mass index, WOMAC pain score, and medial joint space narrowing grade (analysis of covariance). Change in T2 was not significantly associated with case status.

Conclusion. Baseline superficial, but not deep, medial cartilage T2 is associated with clinically relevant disease progression in knee OA.

INTRODUCTION

Knee osteoarthritis (OA) severely affects quality of life and is responsible for substantial health care utilization and cost; although some risk factors of knee OA have been identified, disease progression is slow, and current diagnostic methods are limited in associating periods of symptomatic and radiographic progression (1).

Biomarkers that can predict longer term, clinically important outcomes can be important in medical practice and for selecting

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[1]David Fuerst, PhD, Wolfgang Wirth, PhD, Felix Eckstein, MD: Paracelsus Medical University Salzburg and Nuremberg, Salzburg, Austria, and Chondrometrics, Ainring, Germany; [2]Martin Gaisberger, PhD: Paracelsus Medical University Salzburg and Nuremberg, Salzburg, Austria; [3]David J. Hunter, MBBS: Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, New South Wales, Australia.

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SIGNIFICANCE & INNOVATIONS

- This is a novel study in an exceptionally large cohort that determines whether baseline or longitudinal change in cartilage transverse relaxation time (T2) is associated with clinically relevant osteoarthritis (OA) progression. The sample studied is well established and has reported a large number of other imaging and molecular biomarkers in the context of disease progression for comparison.
- This study applies a registration technique for determining superficial and deep cartilage T2 based on morphologic cartilage segmentations.
- Baseline superficial medial cartilage T2 is identified to be associated with clinically relevant (medial) disease progression of >2 years and may hence be used to identify OA patients with subsequent progression of knee OA.
- Deep cartilage T2, in contrast, is not found to be associated with disease progression, so superficial and deep cartilage T2 properties should always be determined separately.

participants for clinical trials that evaluate treatment efficacy of disease-modifying OA drugs. The Foundation for the National Institutes of Health (FNIH) OA Biomarkers Consortium study was conducted to evaluate the association of imaging and molecular biomarkers with structural (radiographic) and symptomatic (pain) progression in knee OA (1). Previously, we have shown that medial femorotibial compartment (MFTC) cartilage thickness loss over 24 months was associated with combined radiographic and symptomatic progression, with a stronger association for radiographic progression (1). Further work revealed that 24-month change in bone shape, semiquantitative measures of cartilage damage, synovitis, and meniscal pathology were also associated with progression in the consortium sample (2).

Magnetic resonance imaging (MRI) transverse relaxation time (T2) has been proposed as an imaging biomarker for the detection of alterations in articular cartilage composition (3,4). T2 is thought to reflect collagen integrity, orientation, and hydration, with higher values indicating early cartilage damage, and it was shown to be associated with cartilage histologic grading and mechanical properties (5,6). Superficial cartilage displayed significantly longer T2 than deep-zone cartilage (6,7), with the superficial cartilage being more sensitive to the presence of semiquantitatively graded cartilage lesions (8). However, whether cartilage T2 is associated with disease progression in knees with established OA remains controversial (9–11).

Whether layer-specific (superficial versus deep cartilage T2) is associated with clinically relevant OA progression has not been examined in a large sample. In a study of radiographically normal knees, we reported that baseline superficial T2 was more sensitive to contralateral radiographic status than deep T2, whereas longitudinal change in deep T2 was more sensitive to change than superficial T2 (12). Similar trends were observed in knees with radiographic OA (10). The specific purpose of the current study was therefore to test, in the FNIH Biomarker Consortium sample (1), whether baseline superficial T2 and/or longitudinal (1-year) change in deep T2 was associated with radiographic and/or symptomatic progression.

MATERIALS AND METHODS

Study design. The Osteoarthritis Initiative (OAI) Biomarker Consortium was a nested case–control study (1) that used data from the OAI (13). Eligible participants had ≥1 knee with baseline Kellgren/Lawrence (K/L) grade 1–3 from central radiographic readings and availability of baseline and 24-month knee radiographs, knee MRI, serum and urine specimens, and clinical data (1). Fixed-flexion knee radiographs were assessed for K/L and Osteoarthritis Research Society International (OARSI) joint space narrowing (JSN) grades (1). Medial radiographic progression was defined by a loss in minimum radiographic joint space width (JSW) of ≥0.7 mm from baseline to 24, 36, or 48 months (1). Knee pain was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale, with progression defined as a persistent (≥2 time points) increase of ≥9 points on a 0–100 normalized score from baseline at 24, 36, 48, or 60 months (1). Knees with radiographic and pain progression by 12 months were excluded so that biomarker change could be studied longitudinally before progression criteria were met (1). Therefore, the current analysis on the predictive (but not concurrent) validity of T2 includes baseline and 12 months, but not 24 months data.

In the FNIH Biomarker Consortium study, primary cases were 1) knees that had both radiographic and pain progression; control knees did not have this combination and included 2) knees with neither radiographic nor pain progression, 3) knees with radiographic progression only but not pain progression, and 4) knees with pain progression only but not radiographic progression (1). For better covariate balance, the knees selected for the 4 groups were frequency matched, using K/L grade and body mass index (BMI) strata (1). Because cartilage thickness and bone shape biomarkers were previously shown to be more strongly associated with radiographic than with pain progression (1), only

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Address correspondence to David Fuerst, PhD, Institute of Anatomy & Cell Biology, Paracelsus Medical University, Strubergasse 21, A-5020 Salzburg, Austria. Email: fuerst.d@gmx.at.

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knees with neither radiographic nor pain progression were used as controls in the current study, whereas sensitivity analyses were conducted to explore whether T2 was predictive of partial progressors, i.e., JSW progression only, or pain progression only. Please note that the FNIH cohort included left and right knees (1), whereas the OAI acquired the multiecho spin-echo (MESE) MRI acquisitions that support the analysis of cartilage T2 only in the right knees (13).

Cartilage thickness and T2 measurement. Femorotibial cartilage thickness segmentation in the FNIH Biomarker study relied on sagittal double-echo steady-state (DESS) imaging, with blinding to group assignment and order of acquisition (1). To extract cartilage T2, existing cartilage segmentations of the DESS (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24627) were registered to the MESE MRIs using a recently validated algorithm (14). The segmentations comprised the entire medial tibia (MT) and lateral tibia (LT) and the central (weight-bearing) part of the medial femoral (cMF) and lateral femoral (cLF) condyles, defined as 75% of the distance between the intercondylar notch and the posterior end of the condyles. The registration process required automated trimming of the DESS segmentations in the joint periphery and in the depth of the cartilage because we discovered an underestimation of the total cartilage thickness by the MESE (14). The quality of the registration results was validated visually and quantitatively by checking the final Mattes Mutual Information metrices (15). Once trimmed and registered, superficial and deep femorotibial cartilage T2 was extracted based on the local distance between the cartilage surface and bone interface (14) (see Supplementary Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.24627). The deep zone covered 50% of cartilage close to the bone surface, while the superficial zone included the remaining 50%. T2 was computed for each voxel, as described previously (10,12), with T2 values exceeding the range of plausible values of articular cartilage (<5 or >120 msec) being excluded (15). Superficial and deep T2 was determined across the 4 plates, averaging MT and cMF for the MFTC, LT, and cLF for the lateral compartment (LFTC) and all plates for the total femorotibial (FT) joint.

Statistical analysis. Baseline superficial MFTC T2 was a priori defined as the primary, and longitudinal change in deep MFTC T2 between baseline and 12 months as the secondary analytic outcome between full progressor case and non-progressor control knees in this post hoc analysis. All other comparisons, including sensitivity analyses of partial progressors versus controls were considered exploratory. Statistical testing was performed using an analysis of covariance to identify notable changes between adjusted means. Age, sex, BMI, WOMAC pain score, and medial JSN grade at baseline were used as covariates. Demographic, clinical, and radiographic variables were compared between all groups using 1-way analysis of variance or chi-square tests.

RESULTS

Of 600 FNIH biomarker study knees, 311 were right knees. Of those, 97 were full progressor knees with JSW and pain progression, while 104 were control knees without JSW or pain progression. The remaining 110 knees were partial progressors, subdivided into 53 knees with JSW progression only and 57 knees with pain progression only. The demographic characteristics, radiographic status, and pain status of these groups are shown in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24627. There were statistically significant differences in age between subgroups (P = 0.02) but not in the BMI or WOMAC pain scores, nor in sex, K/L grade, or medial JSN distribution between these (P = 0.11–0.83).

Baseline superficial MFTC T2 was statistically significantly elevated in progressor knees (adjusted mean 47.2 msec [95% confidence interval (95% CI) 46.5, 48.0]) and JSW progression only knees (adjusted mean 47.3 msec [95% CI 46.3, 48.3]), respectively, versus non-progressor knees (45.8 msec [95% CI 45.0, 46.5], P values = 0.01 and 0.02) (Table 1). Yet, no notable difference was observed for deep MFTC T2 (Table 1). Among exploratory end points, superficial T2 in the FT joint, MT, and cLF were notably elevated in progressor versus non-progressor knees (Table 1). Further, none of the deep layer T2 baseline values in the cartilage plates, compartments, or total joint differed notably between progressor and non-progressor knees (Table 1).

The exploratory sensitivity analyses revealed that in the JSW progression only group, superficial T2 was notably elevated versus control knees in the MFTC, cMF, and FT joint, but not in the MT. A notable elevation in the superficial T2 in the JSW progression only group was also observed in the cLF but not in the LT or the LFTC. The pain progressor only knees did not display notable differences in superficial T2 versus controls in any of the regions studied (Table 1). Further, none of the deep layer T2 values differed notably between full or partial progressor versus control knees (Table 1).

Although the adjusted longitudinal change in deep layer MFTC T2 between baseline and 12 months increased in the progressor knees (0.15 msec [95% CI –0.52, 0.83]) and decreased in non-progressor knees (–0.47 msec [95% CI –1.13, 0.19]), this difference did not reach statistical significance (P = 0.21) (Table 2). The only exploratory longitudinal end point that revealed a notable difference was the change in superficial T2 in the FT joint between pain only progressor versus control knees (Table 2); none of the other superficial or deep T2 change measures differed notably between full or partial progressors versus control knees (Table 2).

Table 1. Layer-specific adjusted mean (control) and between-group differences with 95% confidence interval of cartilage transverse relaxation time (T2) at baseline in knees without joint space width (JSW) or pain progression (controls), in knees with both JSW and pain progression (JSW + pain), in knees with JSW progression only (JSW only), and in knees with pain progression only (pain only)*

	Control, msec	JSW + pain, msec	JSW only, msec	Pain only, msec
FT joint				
Deep	42.0 (41.5, 42.4)	0.4 (–0.3, 1.1)	0.8 (–0.0, 1.6)	0.3 (–0.5, 1.1)
Superficial	45.3 (44.8, 45.9)	1.0 (0.2, 1.8)†	1.1 (0.2, 2.1)†	0.3 (–0.6, 1.2)
MFTC				
Deep	44.3 (43.6, 45.0)	0.4 (–0.6, 1.4)	1.0 (–0.2, 2.2)	0.0 (–1.1, 1.1)
Superficial	45.9 (45.2, 46.6)	1.3 (0.3, 2.4)†	1.4 (0.2, 2.6)†	0.3 (–0.8, 1.5)
LFTC				
Deep	39.6 (39.1, 40,1)	0.4 (–0.3, 1.1)	0.6 (–0.3, 1.4)	0.6 (–0.2, 1.4)
Superficial	44.8 (44.2, 45,4)	0.7 (–0.2, 1.5)	0.9 (–0.2, 1.9)	0.3 (–0.7, 1.2)
MT				
Deep	36.4 (35.6, 37.2)	–0.2 (–1.4, 1.0)	0.3 (–1.2, 1.7)	–0.3 (–1.6, 1.1)
Superficial	37.8 (37.1, 38.5)	1.49 (0.5, 2.5)†	0.9 (–0.3, 2.2)	0.1 (–1.0, 1.3)
cMF				
Deep	52.2 (51.2 53.3)	1.0 (–0.4, 2.5)	1.8 (–0.0, 3.5)	0.3 (–1.4, 2.0)
Superficial	54.0 (53.0, 55.0)	1.2 (–0.3, 2.6)	1.9 (0.1, 3.6)†	0.5 (–1.2, 2.2)
LT				
Deep	34.0 (33.4, 34.6)	0.5 (–0.4, 1.3)	0.5 (–0.6, 1.5)	0.3 (–0.7, 1.3)
Superficial	41.6 (40.9, 42.4)	0.3 (–0.8, 1.4)	0.2 (–1.1, 1.5)	0.2 (–1.0, 1.5)
cLF				
Deep	45.1 (44.5, 45.8)	0.4 (–0.6, 1.3)	0.6 (–0.5, 1.8)	0.9 (–0.1, 2.0)
Superficial	47.9 (47.2, 48.6)	1.1 (0.1, 2.0)†	1.5 (0.4, 2.7)†	0.3 (–0.8, 1.4)

* Adjusted values are given for the whole femorotibial (FT) joint, the medial femorotibial compartment (MFTC), the lateral femorotibial compartment (LFTC), and all femorotibial cartilage plates: medial tibia (MT), weight-bearing (central) medial femur (cMF), lateral tibia (LT), and weight-bearing (central) lateral femur (cLF).
† Notable differences between the full or partial progressor group versus controls.

Table 2. Layer-specific adjusted longitudinal changes (control) and between-group differences with 95% confidence interval of cartilage transverse relaxation time (T2) between baseline and year 1 (in msec) in knees without joint space width (JSW) or pain progression (controls), in knees with both JSW and pain progression (JSW + pain), in knees with JSW progression only (JSW only), and in knees with pain progression only (pain only)*

	Control (n = 102)	JSW + pain (n = 88)	JSW only (n = 52)	Pain only (n = 55)
FT joint				
Deep	–0.36 (–0.79, 0.06)	0.3 (–0.3, 1.0)	0.1 (–0.7, 0.8)	0.7 (0.0, 1.4)†
Superficial	0.04 (–0.37, 0.45)	–0.2 (–0.8, 0.5)	0.3 (–0.4, 1.0)	0.2 (–0.4, 0.9)
MFTC				
Deep	–0.47 (–1.13, 0.19)	0.6 (–0.4, 1.6)	0.0 (–1.1, 1.2)	0.9 (–0.2, 2.0)
Superficial	0.22 (–0.43, 0.88)	–0.1 (–1.0, 0.9)	0.4 (–0.8, 1.5)	0.2 (–0.9, 1.3)
LFTC				
Deep	–0.25 (–0.63, 0.12)	0.0 (–0.5, 0.6)	0.1 (–0.5, 0.8)	0.6 (–0.0, 1.2)
Superficial	–0.15 (–0.51, 0.22)	–0.2 (–0.7, 0.3)	0.2 (–0.4, 0.9)	0.3 (–0.3, 0.9)
MT				
Deep	–0.58 (–1.51, 0.36)	0.5 (–0.9, 1.9)	0.3 (–1.4, 1.9)	0.9 (–0.7, 2.4)
Superficial	–0.02 (–0.84, 0.81)	–0.2 (–1.4, 1.0)	1.0 (–0.4, 2.4)	1.0 (–0.4, 2.3)
cMF				
Deep	–0.37 (–1.22, 0.48)	0.7 (–0.5, 2.0)	–0.2 (–1.7, 1.3)	0.9 (–0.5, 2.3)
Superficial	0.46 (–0.50, 1.43)	–0.0 (–1.4, 1.4)	–0.3 (–1.9, 1.4)	–0.5 (–2.1, 1.0)
LT				
Deep	–0.31 (–0.81, 0.18)	0.1 (–0.6, 0.9)	0.3 (–0.6, 1.2)	0.5 (–0.3, 1.4)
Superficial	0.14 (–0.36, 0.65)	–0.2 (–1.0, 0.5)	0.5 (–0.4, 1.4)	–0.3 (–1.1, 0.6)
cLF				
Deep	–0.19 (–0.67, 0.28)	–0.1 (–0.8, 0.8)	–0.1 (–0.9, 0.7)	0.6 (–0.2, 1.4)
Superficial	–0.43 (–0.93, 0.06)	–0.2 (–0.9, 0.6)	0.0 (–0.8, 0.9)	0.8 (–0.0, 1.6)

* cLF = central lateral femur; cMF = central medial femur; FT = femorotibial; LFTC = lateral femorotibial compartment; LT = lateral tibia; MFTC = medial femorotibial compartment; MT = medial tibia.
† Notable differences between the full or partial progressor group versus controls.

DISCUSSION

In this study, we explored the predictive relationship of layer-specific cartilage T2 for clinically relevant OA progression in a relatively large sample. Baseline superficial, but not deep MFTC T2 (or LFTC T2), was associated with (combined) medial radiographic and symptomatic progression, with higher T2 indicating worse histopathologic and mechanical cartilage properties (6). Given that progressor knees were defined by medial JSW progression (1), the predictive finding of baseline MFTC T2 is plausible. Sensitivity analyses suggest that the differences between progressor and non-progressor knees are mainly driven by JSW but not pain progression. Yet, both are difficult to disentangle because most OA patients exhibit radiographic and symptomatic progression together, with partial progressor groups representing rare cases in which pain progression may originate from a different source than OA with JSW progression being actively ruled out. The discrimination of superficial MFTC was already investigated in a previous pilot study (10) and confirmed in this work. Longitudinally, deep MFTC T2 increased more strongly between baseline and 12 months in progressor knees than superficial T2, but the difference versus controls was not significant. This may potentially be attributed to the loss of superficial cartilage with the longest T2 time in progressor knees, which may lead to a shift of the cartilage layers (each 50% of cartilage thickness) toward the deep cartilage, and which may thereby cancel the signal from cartilage T2 prolongation. Yet, the pilot study detected a significant increase in deep (not superficial) MFTC T2 in progressor versus non-progressor knees over 1 year, concurrent with progression, when a relatively large difference in MRI cartilage and JSW loss was present at 1 year already (10).

A limitation of the current study is that only right knees could be included because the left ones did not have MESE acquisitions according to the OAI protocol. Another limitation is that (for exploratory reasons) multiple comparisons were done in parallel, but the study had an a priori–defined primary and secondary analytic end point. The *P* values were only computed for those end points. Finally, the clinically important difference in T2 is currently unknown.

A strength of the current study is that an automated registration method was used that relied on DESS segmentations that have been validated for cartilage thickness analysis (14). Although the segmentations had to be adapted to match the MESE, this was done in a consistent manner and did not rely on manual segmentation of the cartilage surface or bone interface using the MESE. Another strength is that not only the bulk, but layer-specific analyses were provided given that T2 values differ by a large amount (~10 msec) between superficial and deep cartilage, likely due to differences in hydration and collagen orientation (7). Although preferably, 3 layers should have been analyzed, but the limited in-plane resolution of the MESE (0.3125 mm) (13) did not permit such a division, particularly in OA knees.

The longitudinal predictive interval (baseline to 12 months) was relatively short and partially overlapping with progression. Although none of the knees met the progressor definition at 12 months (1), this period was still partially measuring concurrent change. Given limited test–retest precision (7), measurement of T2 change may not be reliable over relatively short periods such as 1 year. Twenty-four–month T2 or 2-year change from baseline were deliberately not included because this period would have been concurrent with progression in a large number of knees (1), whereas the current analysis focused on predictive association. A clear strength of using the OAI Biomarker Consortium sample and its design is that the results can be compared with those of other imaging and molecular biomarkers (1). Also, the sample size was fairly large and therefore resolves some of the controversy of whether cartilage T2 is associated with subsequent disease progression, which had already been suggested by previous studies (9,10).

In conclusion, superficial cartilage T2, measured at the baseline visit in the affected (medial) compartment, was associated with subsequent clinically relevant (medial) disease progression of >2 years and may hence be used to identify OA patients with subsequent progression of knee OA. Deep cartilage T2, in contrast, is not found to be associated with disease progression, neither at baseline nor when measured longitudinally. The results also emphasize that superficial and deep cartilage T2 properties should always be determined separately.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Fuerst 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.

Study conception and design. Fuerst, Eckstein.
Acquisition of data. Wirth.
Analysis and interpretation of data. Gaisberger, Hunter.

ADDITIONAL DISCLOSURES

Authors Fuerst, Wirth, and Eckstein are employees of Chondrometrics.

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