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Is Laminar Cartilage Composition as Determined by T2 Relaxometry Associated with Incident and Worsening of Cartilage or Bone Marrow Abnormalities?

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Abstract

Objective. To test the hypothesis that superficial cartilage composition (T2) is associated with subsequent incidence or worsening of cartilage damage, and deep T2 with that of bone marrow lesions (BMLs) in knees without radiographic osteoarthritis (ROA). *Design*. A total of 201 knees from the Osteoarthritis Initiative without ROA were included: 78 from the healthy reference cohort, 60 without ROA but with risk factors, and 63 without ROA but with contralateral ROA. Year 1 (Y1) superficial and deep cartilage T2 were derived in the medial and lateral (weightbearing) femur (MF/LF) and tibia (MT/LT), using sagittal multiecho spin echo magnetic resonance images. Cartilage and BMLs were assessed in the medial (MFTJ) and lateral femorotibial joint (LFTJ) at Y1 and 3 years later. Binary logistic regression statistics were applied. *Results*. Incidence or worsening of cartilage damage was more frequent (MFTJ 15%, LFTJ 13%) than incidence or worsening of BMLs (6.0%, 4.5%). In knees with incident or worsening cartilage lesions in the MF and LT, deep layer T2 in the same plate was elevated (MF, 43.6 ± 4.0 vs. 41.3 ± 3.8 ms, $P = 0.047$; LT, 33.8 ± 2.3 vs. 32.0 ± 2.2 ms, $P = 0.008$) compared to those without. In knees with incident or worsening of BMLs in the LFTC and LT, superficial layer T2 was elevated (LFTJ, 49.6 ± 4.8 vs. 46.7 ± 3.1 ms; LT, 47.4 ± 4.9 vs. 44.0 ± 3.3 ms, both *P*s = 0.04). *Conclusions*. Contrary to our hypothesis, increased deep layer cartilage T2 was associated with subsequent worsening of cartilage damage, whereas superficial layer T2 was related to subsequent BML worsening. Yet, this relationship was observed in some, but not in all cartilage plates.

Keywords

MRI, osteoarthritis, risk factors, progression

Introduction

Compositional magnetic resonance imaging (MRI) techniques, including T2 relaxometry, have been developed to characterize the cartilage matrix quality at a stage where abnormal findings are early and possibly reversible, allowing intervention to potentially protect from disease incidence and halt progression at an early stage.[1] Studies have shown that T2 measurements are elevated in knees with early stages of osteoarthritis (OA) or risk factors for

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incident OA.[2-5] Moreover, elevated T2 values have been reported to predict radiographic OA (ROA) over a 4-year period.[6] Identification of specific regions of cartilage with a high risk of incident focal surface damage will potentially help in identifying individuals that are likely to benefit from preventive interventions before the onset of such macroscopic lesions.

A small recent study based on Osteoarthritis Initiative (OAI) data showed that mean local T2 values are persistently elevated compared with the surrounding cartilage prior to morphological lesion onset in the same location. This relationship reached significance 1 year prior to lesion development in cases, but not in controls without lesion incidence, suggesting that focal T2 elevation predicts incident cartilage lesions at the same location.[7] However, the authors did not differentiate the superficial from the deep cartilage layer, and not all knees were free of ROA. To address the question whether laminar, that is, deep and superficial, elevation in T2 are relevant for prediction of incident or progression cartilage lesions in the same articular compartment or plate we included 3 different samples from the OAI without ROA: (1) the so-called "healthy reference cohort" without ROA in either knee (i.e., Kellgren-Lawrence [K-L] 0) and being free of risk factors, (2) those with K-L 0 in both knees but with risk factors of incident knee OA,[5] and (3) those with K-L 0 in one knee, and ROA in the contralateral knee.[8] As several authors suggested that K-L 1 may already be a reflection of early, ongoing disease, we did not include knees without ROA but K-L 1.[9-11] Given the concept of the osteochondral unit, we hypothesize that superficial T2 is elevated in cartilage plates with subsequent cartilage surface damage incidence or worsening, and that deep layer T2 is elevated for those with subsequent subchondral bone marrow lesion (BML) development or worsening.[12]

Thus, the primary purpose was to analyze whether knees with subsequent incident or worsening cartilage damage and BMLs exhibit greater superficial and/or deep layer T2 compared with those that do not develop such structural damage in the same compartment or cartilage plate 3 years later. In additional sensitivity analyses, we studied (1) whether knees with prevalent cartilage damage or BMLs exhibit elevated T2 values in the same plate (i.e., medial femur [MF], medial tibia [MT], lateral femur [LF], or lateral tibia [LT]) or compartment (i.e., medial femoro-tibial compartment [MFTC] or lateral femoro-tibial compartment (LFTC]); (2) whether compartments or plates without prevalent cartilage damage or BMLs show differences in T2 between those that develop cartilage damage or BMLs and those that do not develop these structural changes; (3) whether compartments or plates with preexisting cartilage damage or BMLs show differences in T2 between those that show worsening versus those that do not; and finally (4) whether the results differed when taking into account compartments with or without prevalent meniscal damage or extrusion.

Methods

Study Participants

The participants for this analysis were selected from the OAI cohort (http://www.oai.ucsf.edu).[13] All OAI participants provided written informed consent and this study was carried out in accordance with the institutional review board–approved OAI data user agreement. At baseline, the OAI cohort included 4796 participants aged 45 to 79 years who were recruited at 1 of 4 clinical sites. At each of 5 subsequent annual visits the OAI collected clinical data and acquired MRI of the knees and bilateral fixed-flexion radiographs.[13]

We included 201 right knees that had no signs of ROA (K-L 0), semiquantitative MRI Osteoarthritis Knee Score (MOAKS) assessments at the year 1 (Y1) and year 4 (Y4) OAI follow-up visits and cartilage T2 measurements at the Y1 OAI follow-up visit available. Of these, 78 knees were from subjects from the so-called "nonexposed" healthy reference cohort of the OAI, confirmed to be free of any sign of ROA by the central expert readings (i.e., K-L grades 0 in both knees) as well as free of knee pain and relevant risk factors of incident OA, 60 knees had no signs of ROA in both of their knees but had risk factors for developing knee OA,[5] and 63 knees had definite ROA (i.e., K-L $\geq$2) in the contralateral knee.[8]

MRI Acquisition

MRIs of both knees were acquired at 4 sites on identical 3-T systems (Siemens Magnetom Trio, Erlangen, Germany). The MRI pulse sequence protocol included a coronal 2-dimensional intermediate-weighted (IW) turbo spin-echo (TSE), sagittal 3-dimensional (3D) dual-echo at steady-state (DESS), coronal and axial multiplanar reformations of the 3D DESS, sagittal IW fat-suppressed (fs) TSE sequences and a sagittal multi-echo spin echo (MESE) sequence of the right knee for T2 quantification. Details of the OAI MRI protocol have been published.[14]

MRI Assessment

Cartilage damage, meniscal damage and extrusion, and subchondral BMLs were assessed for Y1 (i.e., reference visit in this analysis) and Y4 visits in chronological order by one experienced radiologist using the semiquantitative MOAKS scoring system.[15] The reason for choosing Y1 and Y4 was that readings for double K-L 0 knees without ROA, but with risk factors, were available from a published study.[16]

Inter- and intrareader reliability for MOAKS has been described previously for the same reader and all of the measures showed substantial (0.61-0.8) or reached almost perfect agreement (0.81-1.0).[15]

Segmentation of the cartilage of the medial and lateral tibia and the medial and lateral weightbearing femoral condyles was performed manually using the MESE images by one trained and validated image analyst with 18 years' experience in MRI-based image segmentation of cartilage. All segmentations were quality controlled by a second experienced reader and adjudicated (blinded) excluding obvious surface defects.[4] Because cartilage T2 is known to display spatial variation with tissue depth, the segmented cartilages were computationally divided into superficial and deep layers (each comprising 50% of cartilage thickness), based on the distance between the segmented cartilage surface and bone interface. Cartilage T2 was computed for each voxel by fitting a mono-exponential decay curve to the measured signal intensities using a nonlinear, 2-parameter fitting method, with the first echo excluded to reduce the impact of stimulated echoes. Voxels with $R^2 < 0.66$ for the curve fitting were eliminated, to avoid contribution from voxels with low image quality or noise.

Analytic Approach

Statistical analyses were performed for the medial and lateral femoro-tibial compartment and on a plate level, that is, MF, MT, LF and LT. Incidence of cartilage damage or BMLs was defined as occurrence of features between the Y1 and Y4 follow-up visits in knees that had no presence of the respective features in the respective regions (e.g., incidence of cartilage damage at Y4 in at least one MFTC MOAKS subregion in knees that had no cartilage damage in any MFTC MOAKS subregion at Y1). Worsening of cartilage damage or BMLs was defined as an increase of a MOAKS score in a subregion that already exhibited that feature at Y1. Any worsening or incidence was considered as primary outcome and was defined as any increase in cartilage damage or BML scores between Y1 and Y4.

Statistical analyses were performed using binary logistic regression with presence, incidence, or worsening in MOAKS scores as dependent variable, and cartilage T2 in the respective region and age, body mass index, sex, and sample (contralateral ROA, contralateral K-L 0, healthy reference cohort) as independent variables. Adjusting for sample was deemed necessary to account for differences in cartilage T2 due to different risk factor profiles.[5] In sensitivity analyses, we stratified our sample into knees without meniscal damage or extrusion and those with presence of meniscal damage or extrusion (defined as grade 2 or higher for both features as grade 1 extrusion of up to 3 mm is commonly considered a normal finding and grade 1 mensical damage represents intrameniscal signal only but not a tear or meniscal substance loss[17]). Due to the multiple subgroups and combinations of outcomes and subsequent low frequencies, results are presented for compartments and plates without meniscal damage or extrusion only. A P value <0.05 was considered statistically significant. Due to low n of some of the observed findings regarding prevalence, incidence, or worsening, only those with $n > 5$ are presented as values below that were considered not interpretable in a meaningful manner. Statistical analyses were conducted using IBM SPSS 24 software (IBM Corporation, Armonk, NY).

Results

A total of 201 participants were included. These had a mean age of 61.1 ± 9.4 years, a mean body mass index of 26.3 ± 4.1 m/kg^2, and 109 (56%) were women. None of the knees exhibited damage of the cruciate or collateral ligaments.

Primary Analysis

Any incidence or worsening of cartilage damage was seen in 31 (15.4%) knees in the MFTC and 26 (12.9%) in the LFTC. Any incidence or worsening of BMLs was less frequent and seen in 12 (6.0%) knees in the MFTC and 9 (4.5%) knees in the LFTC. Although the majority of T2 values at Y1 were increased for compartments or plates with incident or worsening of cartilage damage compared to those without, statistically significant T2 prolongation at Y1 was only observed in the deep layer of the MF (43.6 ± 4.0 vs. 41.3 ± 3.8 ms, $P = 0.047$) and the LT (33.8 ± 2.3 vs. 32.0 ± 2.2 ms, $P = 0.008$) plates. No statistically significant differences between knees with versus without incidence or worsening of cartilage damage were observed for superficial layer T2. Differences in T2 at Y1 between knees with and without any incidence or worsening of BMLs were less uniform than for cartilage damage. Elevated T2 at Y1 was observed in the superficial layer of the LFTC (49.6 ± 4.8 vs. 46.7 ± 3.1 ms, $P = 0.044$) and the LT plate (47.4 ± 4.9 vs. 44.0 ± 3.3 ms, $P = 0.039$) of knees with any incidence or worsening of BML. No statistically significant differences between knees with versus without incidence or worsening of BMLs were observed for deep layer T2. Details of these results are presented in **Table 1**.

Sensitivity Analysis: Presence of Cartilage Damage and BMLs at Y1

Prevalent MFTC cartilage damage at Y1 was observed in 69 (34.3%) and LFTC cartilage damage in 79 (39.3%) of the knees at Y1. BMLs were less frequent with 18 (9.0%) knees showing prevalent BMLs in the MFTC, and 19 (9.5%) in the LFTC. All compartments and plates with presence of cartilage damage or BMLs showed elevated T2.

Table 1. Incidence or Worsening of Cartilage Damage and BMLs from Y1 to Y4 ($n = 201$ Knees).

	No					Yes				
	n	Mean	SD	95% CI		*n*	Mean	SD	95% CI	*P*
Cartilage										
Superficial layer										
MFTC	170	47.4	3.9	46.8	48.0	31	48.5	3.7	47.2	49.9	0.611
LFTC	175	46.8	3.2	46.3	47.3	26	47.4	3.4	46.0	48.7	0.937
MT	185	43.2	3.1	42.7	43.6	16	43.6	2.5	42.3	45.0	0.902
MF	183	51.7	5.4	50.9	52.5	18	53.6	5.6	50.8	56.4	0.486
LT	179	44.0	3.4	43.5	44.5	22	44.7	3.2	43.3	46.1	0.475
LF	194	49.6	3.7	49.1	50.1	7	51.0	5.3	46.1	55.9	0.932
Deep layer										
MFTC	170	37.4	2.5	37.1	37.8	31	38.4	2.6	37.5	39.4	0.139
LFTC	175	36.4	2.3	36.1	36.8	26	37.5	2.6	36.4	38.5	0.296
MT	185	33.7	2.2	33.3	34.0	16	33.4	2.4	32.1	34.7	0.564
MF	183	41.3	3.8	40.8	41.9	18	43.6	4.0	41.6	45.6	0.047*
LT	179	32.0	2.2	31.7	32.3	22	33.8	2.3	32.8	34.8	0.008*
LF	194	40.9	3.3	40.5	41.4	7	40.7	3.3	37.6	43.8	0.208
BMLs										
Superficial layer										
MFTC	189	47.6	3.9	47.0	48.1	12	47.7	3.5	45.5	49.9	0.323
LFTC	192	46.7	3.1	46.3	47.2	9	49.6	4.8	46.0	53.3	0.044*
MT	194	43.2	3.1	42.8	43.6	7	43.5	2.7	41.1	46.0	0.718
MF	195	51.9	5.4	51.2	52.7	6	51.0	6.0	44.7	57.2	0.971
LT	193	44.0	3.3	43.5	44.4	8	47.4	4.9	43.3	51.5	0.039*
LF	200	49.6	3.8	49.1	50.2	1			n/a		
Deep layer										
MFTC	189	37.6	2.5	37.2	38.0	12	37.6	2.3	36.1	39.0	0.827
LFTC	192	36.5	2.3	36.2	36.8	9	38.1	3.0	35.8	40.5	0.101
MT	194	33.6	2.2	33.3	34.0	7	33.7	1.6	32.2	35.2	0.975
MF	195	41.6	3.9	41.0	42.1	6	40.8	3.8	36.8	44.8	0.844
LT	193	32.1	2.3	31.8	32.5	8	33.3	2.0	31.6	34.9	0.497
LF	200	40.9	3.3	40.4	41.4	1			n/a[a]		

BML = bone marrow lesion; MFTC = medial femoro-tibial compartment; LFCT = lateral femoro-tibial compartment; MT = medial tibia; MF = medial femur; LT = lateral tibia; LF = lateral femur; n/a = not applicable.
[a]Values not presented. No meaningful interpretation possible due to low *n*.
*Statistically significant at $P < 0.05$.

Statistically significant differences in T2 between those with vs. those without cartilage damage presence at Y1 were observed particularly in the superficial layer (both compartments and all plates but LF) and in the deep LT layer. Statistically significant T2 differences at Y1 were seen in those with BMLs in both the superficial and deep MFTC layer (superficial, 49.8 ± 2.5 vs. 47.3 ± 3.9 ms, $P = 0.038$; deep, 38.8 ± 2.2 vs. 37.5 ± 2.5 ms, $P = 0.030$) and both the superficial and deep MF layer (superficial, 55.5 ± 4.4 vs. 51.7 ± 5.4 ms, $P = 0.008$; deep, 43.6 ± 4.0 vs. 41.4 ± 3.9 ms, $P = 0.014$), while statistically significant T2 differences at Y1 in the LFTC compartment were seen in the deep layer of the LT plate only (33.7 ± 2.3 vs. 32.1 ± 2.2 ms, $P = 0.009$). **Table 2** shows these findings regarding Y1 prevalence in detail.

Sensitivity Analysis: Incidence of Cartilage Damage and BMLs

Incidence of FT cartilage damage in previously not affected compartments (132 MFTC and 122 LFTC) from Y1 to Y4 was observed in 15 (11.4%) knees medially and 2 (1.6%) knees laterally. Incidence of femoro-tibial BMLs in previously not affected subregions (183 MFTC, 182 LFTC) from Y1 to Y4 were seen in 11 (6.0%) knees medially and 6 (3.3%) knees laterally. Statistically significant differences in Y1 T2 were observed only for those with incident cartilage damage the deep layer of the MFTC (39.7 ± 2.1 vs. 37.1 ± 2.5 ms, $P = 0.002$) and the MF plate (45.4 ± 4.4 vs. 41.0 ± 3.8 ms, $P = 0.015$) but not in the superficial layer or in those knees with incident BMLs. These results are presented in detail in **Table 3**.

Table 2. Presence of Cartilage Damage and BMLs at Year 1.

	No				Yes				
	n	Mean	SD	95% CI	*n*	Mean	SD	95% CI	*P*
Cartilage									
Superficial layer									
MFTC	132	46.7	3.5	46.1 47.3	69	49.3	4.0	48.3 50.2	0.001*
LFTC	122	46.2	2.8	45.7 46.7	79	47.9	3.7	47.0 48.7	0.017*
MT	181	42.9	3.0	42.5 43.4	20	45.9	2.7	44.6 47.2	0.001*
MF	142	50.9	5.2	50.0 51.7	59	54.3	5.2	53.0 55.7	0.004*
LT	125	43.3	2.9	42.8 43.9	76	45.3	3.7	44.5 46.2	0.004*
LF	183	49.4	3.6	48.9 50.0	18	51.9	4.8	49.5 54.3	0.219
Deep layer									
MFTC	132	37.4	2.6	37.0 37.9	69	37.9	2.5	37.3 38.5	0.376
LFTC	122	36.2	2.2	35.8 36.6	79	37.1	2.5	36.6 37.7	0.121
MT	181	33.6	2.2	33.3 33.9	20	34.3	2.2	33.2 35.3	0.163
MF	142	41.2	4.0	40.6 41.9	59	42.3	3.6	41.4 43.3	0.255
LT	125	31.6	2.0	31.3 32.0	76	33.1	2.4	32.6 33.7	0.000*
LF	183	40.9	3.2	40.4 41.3	18	41.2	3.7	39.3 43.1	0.176
BMLs									
Superficial layer									
MFTC	183	47.3	3.9	46.8 47.9	18	49.8	2.5	48.6 51.1	0.038*
LFTC	182	46.9	3.3	46.4 47.3	19	47.0	3.1	45.5 48.5	0.956
MT	192	43.1	3.1	42.7 43.5	9	45.7	1.9	44.3 47.2	0.073
MF	191	51.7	5.4	50.9 52.5	10	55.5	4.4	52.4 58.7	0.008*
LT	185	44.0	3.4	43.5 44.5	16	45.1	3.5	43.2 47.0	0.297
LF	198	49.7	3.8	49.1 50.2	3			n/a	
Deep layer									
MFTC	183	37.5	2.5	37.1 37.8	18	38.8	2.2	37.7 39.9	0.030*
LFTC	182	36.5	2.4	36.2 36.9	19	36.8	2.0	35.8 37.7	0.478
MT	192	33.6	2.2	33.3 33.9	9	34.9	1.5	33.7 36.0	0.096
MF	191	41.4	3.9	40.9 42.0	10	43.6	4.0	40.7 46.5	0.014*
LT	185	32.1	2.2	31.7 32.4	16	33.7	2.4	32.4 35.0	0.009*
LF	198	40.9	3.3	40.5 41.4	3			n/a[a]	

BML = bone marrow lesion; MFTC = medial femoro-tibial compartment; LFCT = lateral femoro-tibial compartment; MT = medial tibia; MF = medial femur; LT = lateral tibia; LF = lateral femur; n/a = not applicable.
[a]Values not presented. No meaningful interpretation possible due to low *n*.
*Statistically significant at $P < 0.05$.

Sensitivity Analysis: Worsening of Cartilage Damage and BMLs

Preexisting cartilage damage was found in 69 MFT and 79 LFT compartments. Worsening cartilage damage was observed in 12 (17.4%) MFTC and 21 (26.6%) LFTC. Statistically significant differences in Y1 T2 for those with vs. those without worsening cartilage damage were observed neither for the superficial nor for the deep layer in both compartments as shown in **Table 4**. No statistical comparison of Y1 T2 measurements was possible between knees with versus without worsening of BMLs as none of the 18 knees with preexisting BMLs in the MFTJ and only 2 of the 19 knees with preexisting BMLs in the LFTJ showed worsening.

Sensitivity Analysis: Stratification of Knees Taking Into Account Meniscal Damage and/or Extrusion

Forty-six knees (22.9%) had medial meniscal damage or extrusion grade 2 or more, and 24 knees (11.9%) had lateral meniscal damage or extrusion. After excluding these knees and reanalyzing the data for the compartments and plates without meniscal damage or extrusion only, the results did not markedly change. Any incidence or worsening of cartilage damage was seen in 17 of 155 (11.0%) MFTC and in 10.7% in the LFTC. Any incidence or worsening of BMLs was less frequent and seen in 8 (5.2%) knees in the MFTC and 6 (3.4%) knees in the LFTC. For cartilage, no superficial layer differences were seen and deep layer differences

Table 3. Incidence of Cartilage Damage and BMLs in Previously Not Affected Compartments/Plates from Y1 to Y4.

		No					Yes				
	Total[a]	*n*	Mean	SD	95% CI		N	Mean	SD	95% CI	*P*
Cartilage											
Superficial layer											
MFTC	132	117	46.4	3.4	45.8	47.0	15	48.5	3.7	46.5	50.5	0.061
LFTC	122	120	46.2	2.8	45.7	46.7	2			n/a[b]		
MT	181	168	42.9	3.0	42.4	43.3	13	43.3	2.6	41.7	44.9	0.748
MF	142	135	50.7	5.1	49.9	51.6	7	54.1	6.7	47.9	60.3	0.334
LT	125	123	43.4	3.0	42.8	43.9	2			n/a[b]		
LF	183	182	49.4	3.6	48.9	50.0	1			n/a[b]		
Deep layer												
MFTC	132	117	37.1	2.5	36.7	37.6	15	39.7	2.1	38.6	40.9	0.002*
LFTC	122	120	36.2	2.2	35.8	36.6	2			n/a		
MT	181	168	33.6	2.2	33.2	33.9	13	33.7	2.2	32.4	35.0	0.993
MF	142	135	41.0	3.8	40.3	41.7	7	45.4	4.4	41.4	49.5	0.015*
LT	125	123	31.6	2.0	31.2	32.0	2			n/a[b]		
LF	183	182	40.9	3.2	40.4	41.3	1			n/a[b]		
BMLs												
Superficial layer												
MFTC	183	172	47.3	3.9	46.7	47.9	11	47.5	3.6	45.1	50.0	0.421
LFTC	182	176	46.8	3.1	46.3	47.2	6	49.9	5.9	43.7	56.1	0.072
MT	192	185	43.1	3.1	42.6	43.5	7	43.5	2.7	41.1	46.0	0.664
MF	191	185	51.7	5.4	50.9	52.5	6	51.0	6.0	44.7	57.2	0.928
LT	185	179	43.9	3.2	43.4	44.4	6	47.2	5.7	41.2	53.2	0.054
LF	198	197	49.7	3.8	49.1	50.2	1			n/a[b]		
Deep layer												
MFTC	183	172	37.5	2.5	37.1	37.9	11	37.4	2.3	35.8	39.0	0.936
LFTC	182	176	36.5	2.3	36.1	36.8	6	38.1	3.6	34.3	41.9	0.250
MT	192	185	33.6	2.3	33.3	33.9	7	33.7	1.6	32.2	35.2	0.920
MF	191	185	41.5	3.9	40.9	42.0	6	40.8	3.8	36.8	44.8	0.885
LT	185	179	32.0	2.2	31.7	32.4	6	32.9	2.2	30.6	35.2	0.674
LF	198	197	40.9	3.3	40.5	41.4	1			n/a[b]		

BML = bone marrow lesion; MFTC = medial femoro-tibial compartment; LFCT = lateral femoro-tibial compartment; MT = medial tibia; MF = medial femur; LT = lateral tibia; LF = lateral femur; n/a = not applicable.

[a]Total number of knees without cartilage damage or BMLs in respective compartment/plate at Y1.

[b]Values for $n < 5$ not presented. No meaningful interpretation possible due to low *n*.

*Statistically significant at $P < 0.05$.

were observed for the MFTC and the LT plate. For BMLs, deep layer differences in T2 were seen only in the LFTC and no superficial layer differences were observed (Supplemental Appendix 1). Regarding presence of cartilage damage at Y1, elevated T2 was seen especially in the superficial layer medially and those with BMLs showed elevated superficial T2 in the MF plate and deep layer T2 in the MFTC, the MF plate and LT plate (Supplemental Appendix 2). For those knees with incidence of cartilage damage or BMLs elevated T2 was observed in the deep layer in the MFTC and MF plate only (Supplemental Appendix 3). For knees with worsening of cartilage or BMLs no significant differences in T2 were observed in superficial or deep layers for cartilage while the BML analyses were not interpretable due to low frequencies (Supplementary Appendix 4).

Discussion

In this sample of knees without ROA and different risk factor profiles, no consistent relationship between laminar cartilage T2 at Y1 and subsequent incidence or worsening of cartilage damage or BMLs from Y1 to Y4 was observed, with statistically significant differences observed only for the deep MF and LT layer for incidence or worsening of cartilage damage and for the superficial LFTJ and LT layers for incidence or worsening of BMLs. These findings were supported by 2 sensitivity analyses that showed statistically

Table 4. Worsening of Preexisting Cartilage Damage and BMLs from Y1 to Y4.

		No Worsening					Worsening					
	Total[a]	*n*	Mean	SD	95% CI		*n*	Mean	SD	95% CI		*P*
Cartilage												
Superficial layer												
MFTC	69	57	49.5	4.0	48.4	50.5	12	48.3	4.1	45.7	50.9	0.408
LFTC	79	58	48.0	3.9	47.0	49.0	21	47.5	3.3	46.0	49.0	0.274
MT	20	18	46.0	2.8	44.6	47.4	2			n/a[b]		
MF	59	48	54.6	5.2	53.1	56.1	11	53.3	5.1	49.8	56.7	0.292
LT	76	59	45.4	3.9	44.4	46.4	17	44.9	3.1	43.3	46.5	0.645
LF	18	12	52.3	4.5	49.5	55.2	6	51.2	5.8	45.1	57.2	0.771
Deep layer												
MFTC	69	57	38.0	2.5	37.3	38.6	12	37.6	2.3	36.1	39.0	0.610
LFTC	79	58	37.0	2.4	36.3	37.6	21	37.5	2.6	36.4	38.7	0.973
MT	20	18	34.3	2.4	33.1	35.5	2			n/a[b]		
MF	59	48	42.3	3.7	41.2	43.4	11	42.5	3.5	40.1	44.8	0.777
LT	76	59	33.0	2.4	32.4	33.6	17	33.7	2.3	32.5	34.9	0.458
LF	18	12	41.5	3.9	39.1	44.0	6	40.5	3.6	36.7	44.4	0.494
BMLs												
Superficial layer												
MFTC	18	18	49.8	2.5	48.6	51.1	0	n/a[b]				
LFTC	19	17	46.8	3.2	45.2	48.5	2	n/a[b]				
MT	9	9	45.7	1.9	44.3	47.2	0	n/a[b]				
MF	10	10	55.5	4.4	52.4	58.7	0	n/a[b]				
LT	16	14	44.7	3.6	42.7	46.8	2	n/a[b]				
LF	3	3	47.9	5.1	35.1	60.7	0	n/a[b]				
Deep layer												
MFTC	18	18	38.8	2.2	37.7	39.9	0	n/a[b]				
LFTC	19	17	36.7	2.0	35.7	37.7	2	n/a[b]				
MT	9	9	34.9	1.5	33.7	36.0	0	n/a[b]				
MF	10	10	43.6	4.0	40.7	46.5	0	n/a[b]				
LT	16	14	33.6	2.6	32.1	35.1	2	n/a[b]				
LF	3	3	39.6	3.0	32.1	47.1	0	n/a[b]				

BML = bone marrow lesion; MFTC = medial femoro-tibial compartment; LFCT = lateral femoro-tibial compartment; MT = medial tibia; MF = medial femur; LT = lateral tibia; LF = lateral femur; n/a = not applicable.

[a]Total number of knees with preexisting cartilage damage or BMLs in respective compartment/plate at Y1.

[b]Values not presented. No meaningful interpretation possible due to low *n*.

significant T2 differences for the deep layer of 2 of the regions with incident cartilage damage and no statistically significant differences between knees with versus without incident BMLs, and also no statistically significant differences between knees with versus without worsening of cartilage damage or BMLs. In contrast to these findings regarding the predictive ability of laminar cartilage T2, the sensitivity analysis focusing on laminar cartilage T2 in knees with prevalent cartilage damage or BMLs showed statistically significantly elevated T2 particularly in the superficial layer of regions with cartilage damage and in the medial compartment of knees with BMLs. Thus, while our results suggest that prevalent cartilage damage and BMLs may have an impact on laminar cartilage T2, our data do not support a strong T2 prolongation in knees with subsequent worsening or development of cartilage damage or BMLs when compared with those that do not show progression or lesion onset.

On a tissue level, T2 values of cartilage have been correlated with histological signs of hydration, collagen content and organization.[1] Prolongation and more heterogeneous cartilage T2 values have been observed in patients with risk factors for OA compared with healthy controls, whereas no significant differences have been observed between these groups regarding the prevalence of MRI morphologic abnormalities.[18] The addition of T2-mapping to a routine MRI protocol at 3T has been reported to significantly improve sensitivity for the detection of cartilage lesions from 75% to almost 90% suggesting potential clinical relevance.[19] Given that T2 mapping is capable of showing

intrachondral matrix alterations prior to the appearance of visually detectable surface damage one of the most intriguing questions regarding clinical applicability has been whether T2 is able to predict disease onset and progression of OA. Recently, Kretzschmar *et al*.[7] published a case-control study from the OAI including 57 cartilage plates with newly appearing cartilage lesions from 45 knees that were matched with 52 plates from 26 control knees without cartilage lesion development. T2 values of the location of future lesions and surrounding cartilage was assessed 1 to 4 years prior to lesion onset. The authors observed that the mean local T2 values were persistently elevated compared to the surrounding cartilage prior to lesion onset reaching significance 1 year prior in cases, but not in controls, suggesting focal T2 elevation predicted cartilage lesion development at the same location. While authors mention that most lesions were found in the MF plate, no details on subregional analyses were provided. In addition, no differentiation of the superficial from the deep layer was performed in this study. We tried to fill these gaps by including 3 different samples from the OAI—one that we recently termed "early OA model"—that is, knees without ROA but contralateral ROA, which has been shown to exhibit structural damage more frequently than the unexposed healthy reference cohort,[8] one sample without OA in both knees but risk factors,[5] and an additional sample from the OAI healthy reference cohort. We adjusted for known confounders such as age, body mass index, sex, and also sample but only found minor differences regarding T2 between those knees with and those without lesion worsening and development with a focus on cartilage and BMLs. Based on the concept of the osteochondral unit, that is, the close interrelation between cartilage and the subchondral bone; and previous work that has shown that prevalent cartilage damage as well concomitant BMLs increase risk for subsequent cartilage morphologic damage development or worsening,[20] we hypothesized that knees with BML worsening or development would show higher T2 values in the deep layer and those with cartilage surface damage worsening or development would exhibit T2 changes more commonly in the superficial layer. However, our results did not support this hypothesis. In contrast, differences in *deep* layer T2 were observed in the medial compartment MF plate in knees developing incident cartilage damage versus those that did not but no differences were observed for *superficial* T2. Strengths of our approach included the differentiation in superficial and deep layers as well as the careful matching of T2 and lesion change in the same compartment or plate. Limitations of our approach need mentioning. We did not assess interrelations between plates. Lesion prevalence and incidence overall was rare, which limits interpretation further. Regarding the sensitivity analyses taking into account meniscal damage or extrusion, we focused on those knees without meniscal damage or extrusion as frequencies for the multiple subgroups taking into account those with meniscal damage or extrusion were too small to yield interpretable results. The findings for the subgroup without meniscal damage or extrusion was not markedly different when compared to the results of the entire sample. It has been shown previously that meniscal damage and extrusion is prevalent in persons without ROA and increases risk for OA incidence.[9,10] In our sample, and focusing on intrachondral T2 Y1, meniscal status did not seem to have a relevant impact on Y1 T2 values. Whether meniscal damage predicts worsening of T2 over time was not an aim of our study. In a previous analysis we showed that MFTC meniscal damage or extrusion may be associated with prolongation in deep layer T2 times after 1 year.[21]

In summary, and contrary to our hypothesis, the deep cartilage layer seems to be more relevant for subsequent morphologic cartilage damage development or worsening in the same FT compartment or plate than the superficial layer, which is supported by experimental work emphasizing the role of the subchondral plate and bone marrow alterations in early OA.[22] Overall differences in T2 between those that showed damage development in unaffected compartment or plates and those that showed worsening in previously affected regions were mostly not statistically significant. Furthermore, our sensitivity analyses focusing on compartments without meniscal damage or extrusion did not markedly alter results or their interpretation. While prevalent cartilage damage and BMLs seem to have an impact on cartilage composition in the same compartment or plate cross-sectionally, our data do not support strongly that T2 elevation may be relevant in the context of lesion development or worsening 3 years later.

Authors Contributions

All authors were involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data. All authors contributed to drafting the article or revising it critically for important intellectual content. All authors gave their final approval of the manuscript to be submitted. Analysis and interpretation of the data: FWR, FE, SM, GD, AG, LS, WW. Drafting of the article: FWR, FE, SM, GD, AG, LS, WW. Provision of study materials or patients: FWR, FE, SM, WW. Statistical expertise: WW, FWR, FE. Obtaining of funds: FWR, FE, SM, GD, WW. Collection and assembly of data: FWR, FE, SM, WW.

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Declaration of Conflicting Interests

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Ethical Approval

This study was carried out in accordance with the institutional review board–approved OAI data user agreement.

Informed Consent

All OAI participants provided written informed consent.

Trial Registration

Not applicable.

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