Research article

Baseline structural tissue pathology is not strongly associated with longitudinal change in transverse relaxation time (T2) in knees without osteoarthritis

Frank W. Roemer[a,b,*], Felix Eckstein[c,d], Georg N. Duda[e], Ali Guermazi[b], Susanne Maschek[c,d], Wolfgang Wirth[c,d]

[a] Department of Radiology, Friedrich-Alexander University Erlangen-Nürnberg (FAU) & Universitätsklinikum Erlangen, Maximiliansplatz 3, 91054, Erlangen, Germany
[b] Quantitative Imaging Center, Department of Radiology, Boston University School of Medicine, FGH Building, 3rd Floor, 820 Harrison Avenue, 02118, Boston, MA, USA
[c] Institute of Anatomy, Paracelsus Medical University Salzburg & Nuremberg, Strubergasse 21, 5020, Salzburg, Austria
[d] Chondrometrics GmbH, 83404, Ainring, Germany
[e] Julius Wolff Institute, Charité-Universitätsmedizin Berlin, Augustenburger Platz 1, 13353, Berlin, Germany

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ABSTRACT

Purpose: To evaluate whether baseline MRI-defined structural abnormalities are associated with subsequent change in laminar femorotibial cartilage transverse relaxation time (T2) of participants without radiographic signs, symptoms or risk factors for knee osteoarthritis (OA).
Method: We studied all right knees with longitudinal MRI data of the refined Osteoarthritis Initiative Healthy Reference cohort. Baseline osteophytes, effusion-synovitis, Hoffa-synovitis, bone marrow lesions, cartilage lesions, and meniscus morphology and - extrusion were scored semiquantitatively from MR images by an expert reader. Deep and superficial layer cartilage T2 was computed in the medial and lateral femorotibial compartment (MFTC/LFTC) at baseline and at 1- and 4-year follow-up from multi-echo spin-echo MR images. Statistical analyses were performed using UNIANOVA.
Results: 82 participants (age 54.1 ± 7.2y, BMI 24.2 ± 3.0 kg/m^2; 61% women, bilateral Kellgren-Lawrence 0) were studied. Number of baseline MRI pathologies was not significantly associated with longitudinal change in MFTC or LFTC cartilage T2 over 1 or 4 years. Feature-specific analyses suggested that presence of baseline MFTC osteophytes may be associated with prolongation in superficial MFTC cartilage T2 over one (0.8 vs. 0.0 ms, p = 0.02) and four years (2.3 vs. 0.9 ms, p = 0.01), and that MFTC meniscal damage or extrusion may be associated with prolongation in deep layer T2 times over the first year (0.7 vs. 2.1 ms, p = 0.02).
Conclusions: Our study does not provide evidence that, in knees without radiographic OA, baseline structural MRI abnormalities are strongly related to compositional progression during normal aging and/or the potentially earliest phases of the disease as measured by cartilage T2.

1. Introduction

Compositional magnetic resonance imaging (MRI) techniques enable evaluation of the biochemical or ultrastructural composition of articular cartilage and therefore have the potential to supplement clinical MRI sequences in identifying cartilage degeneration at an earlier stage than is possible today using conventional morphologic sequences only [1]. To date, compositional MRI is not in standard clinical use despite its availability for many years, but it is being used with increasing frequency in osteoarthritis (OA) research particularly for

'pre-structural' evaluation of cartilage and, for example and beyond other applications, to assess biochemical response of joint tissue to loading through physical activity [2,3]. Articular cartilage spin-spin (transverse) relaxation time (T2) represents a widely used imaging marker of cartilage composition related to hydration, collagen integrity and orientation, and cartilage mechanical properties [1]. T2 quantification has recently gained interest as it is available on most clinical MRI systems and may provide a potential imaging biomarker for detecting and monitoring "early" structural disease progression at stages of osteoarthritis (OA) at which no morphologic cartilage loss has yet

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* Corresponding author at: Department of Radiology, Friedrich-Alexander University Erlangen-Nürnberg (FAU) & Universitätsklinikum Erlangen, Maximiliansplatz 3, 91054, Erlangen, Germany.
  E-mail addresses: frank.roemer@uk-erlangen.de, froemer@bu.edu (F.W. Roemer).

occurred, and at which therapeutic interventions are potentially more promising compared to later disease stages [2,4]. Some studies have reported the ability of T2 to differentiate between subjects with and without radiographic OA (ROA) whereas others were unable to confirm such differences or found no differences for different radiographic OA stages [5–7]. Knee cartilage T2 was reported to be prolonged and more heterogeneous in subjects at risk of developing OA than in healthy reference subjects, despite similar prevalence of cartilage, bone marrow or meniscus lesions in both groups [8]. One study suggested that increases in T2 values were able to predict radiographic disease onset in a cohort of subjects at risk [9].

Recently, a longitudinal increase in T2 was reported in healthy reference participants from the Osteoarthritis Initiative (OAI) over one-year, suggesting deterioration in cartilage composition, whereas no significant longitudinal change was observed in ROA and non-ROA knees with risk factors of OA, a finding challenging to interpret [10]. One study reported cartilage T2 to significantly increase over 2 years in subjects with and without OA risk factors, but neither the presence of risk factors nor the presence of baseline cartilage lesions were significantly associated with increase in T2 [11]. Because cartilage, subchondral bone, meniscal changes and possibly inflammation are frequent findings in knees without pain or radiographic OA, but have been related to knee OA incidence [12], we here hypothesize that presence of one or more baseline MRI-detected structural articular pathologies may be associated with longitudinal change in femorotibial cartilage T2 in knees without apparent other risk factors of OA.

The purpose of the current study, therefore, was to relate the baseline presence of MRI-defined structural tissue abnormalities, including osteophytes, effusion-synovitis, Hoffa-synovitis, bone marrow lesions (BMLs), prevalent cartilage damage, and meniscus damage and extrusion, to subsequent longitudinal change in laminar (superficial and deep layer) cartilage T2 in the femorotibial joint in participants without radiographic signs, symptoms or risk factors for knee OA.

2. Methods

2.1. Study participants

The participants for this analysis were selected from the Osteoarthritis Initiative cohort (OAI; https://nda.nih.gov/oai/) [13]. The OAI is a multicenter, longitudinal, prospective observational study of knee OA. This Initiative is a public-private partnership between the NIH and private industry that seeks to develop a public-domain research resource to facilitate the scientific evaluation of biomarkers for osteoarthritis as potential surrogate endpoints for disease onset and progression. All OAI visits have been completed as of January 1, 2015: Baseline, 12-month, 24-month, 36-month, and 48-month visits in clinic with biospecimen collection and imaging; 60-month and 84-month visits via mailed questionnaires and telephone interviews; 72-month visit in clinic with biospecimen collection and imaging; 96-month visit in clinic with imaging [14].

Data and images have been publicly released by the OAI co-ordinating center at the University of California, San Francisco and the National Institute of Mental Health Data Archive, through the OAI online website [14]. All OAI participants provided written informed consent and this study was carried out in accordance with the IRB-approved OAI data user agreement. At baseline, the OAI cohort included 4796 participants aged 45–79 years that were recruited at one of four clinical sites [13]. Exclusion criteria were inflammatory arthritis, severe bilateral joint space narrowing, total knee replacement and severe contralateral narrowing, bilateral total knee replacement or plan for it in the next 3 years, MRI and joint radiography contraindications, inability to provide a blood sample, aids other than 1 straight cane for > 50% of ambulation, comorbid conditions precluding participation, and current participation in a double-blind trial. Of the 4796 participants, the 1390 participants enrolled in the progression cohort

had both symptomatic (i.e. pain, aching or stiffness in the past year) and radiographic OA (osteophytes and/or joint space narrowing in fixed-flexion radiographs) in one or both of their knees. The 3284 incidence cohort participants were at risk of developing knee OA, but did not have both symptomatic and radiographic OA at baseline in either knee. The remaining 122 participants of the OAI were selected as "non-exposed", healthy controls and had no radiographic abnormalities in either knee according to the OAI clinical site readings. These participants also were free of clinical signs of knee OA, and not exposed to risk factors for developing knee OA, such as obesity, knee injury, knee surgery, a family history of total knee arthroplasty in a biological parent or sibling, Heberden's nodes, or repetitive knee bending during daily activities. [13]. At each of five subsequent annual visits the OAI collected clinical data and acquired MRI of the knees and bilateral fixed-flexion radiographs [15].

From the group of 122 knees as described above our study included the right knees of 82 participants that were confirmed to be free of radiographic OA by the central expert readings (Kellgren-Lawrence (KL) grades 0 in both knees) and that had any MRI follow-up available. Baseline and year-one (Y1) follow-up MRIs were available for all 82, while year-four (Y4) follow-up was available for only 57 of 82 participants.

2.2. MRI acquisition

MRIs of both knees were performed on identical 3 T systems (Siemens Trio, Erlangen,

Germany). The MRI protocol used for this study included a coronal two-dimensional intermediate-weighted (IW) turbo spin-echo (TSE), sagittal three-dimensional (3D) dual-echo at steady-state (DESS), coronal and axial multiplanar reformations of the 3D DESS, and sagittal IW fat saturated (fs) TSE sequences [15]. Further, a sagittal two-dimensional multi-echo spin-echo sequence (MESE) was acquired in the right knee with seven different echos (10–70 ms) for generating T2 maps [14]. A detailed overview of imaging parameters of the OAI is presented in Appendix 1 in Supplementary material.

2.3. MRI analysis

Baseline effusion-synovitis, Hoffa-synovitis, femorotibial BMLs, femorotibial cartilage damage, osteophytes, meniscus morphology and meniscus extrusion were assessed by one musculo-skeletal radiologist with 15 years' experience in standardized semi-quantitative knee OA evaluation (initials blinded) using the semi-quantitative MRI Osteoarthritis Knee Score (MOAKS) scoring system [16].

Segmentation of the cartilage of the medial and lateral tibia and the medial and lateral weight-bearing femoral condyles using the MESE images was performed manually by one trained image analyst with 16 years' experience in MRI-based image segmentation of cartilage (initials blinded). All segmentations were quality controlled by a second experienced reader and adjudicated excluding obvious surface defects [10]. Because cartilage T2 is known to display spatial variation with tissue depth, the segmented cartilages were computationally divided into superficial and deep 50%, 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 non-linear method, with the 1 st 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.

2.4. Analysis approach

Due to the relatively low frequencies of specific knee joint structural pathologies in this sample and the relatively small sample size, the ordinal MOAKS subscales were dichotomized into presence or absence
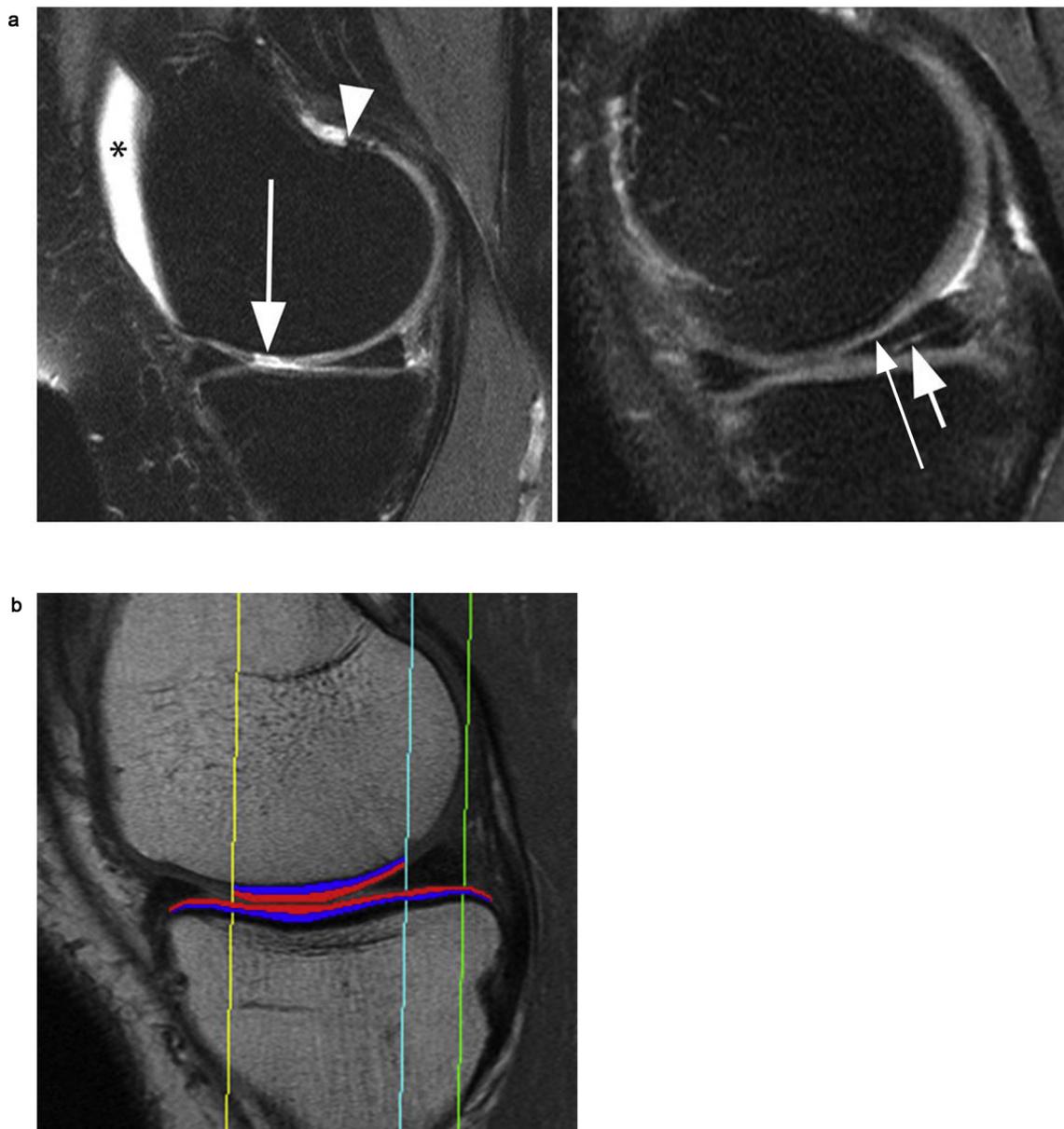
Fig. 1. A. Baseline predictors. Sagittal intermediate-weighted fat suppressed image on the left depicts a full thickness focal cartilage lesion in the medial femur (long arrow) and moderate joint effusion (asterisk). In addition there is a tiny posterior femoral osteophyte (arrowhead). Image on the right of panel shows a different knee with a horizontal-oblique meniscal tear of the posterior horn (short arrow) and discrete superficial thinning of the adjacent femoral cartilage (long arrow) B. T2 as longitudinal outcome. Sagittal T2 MESE image after segmentation showing the region of interest used to define the central weight-bearing part of the medial femur (vertical yellow and blue lines) and the medial tibia (vertical yellow and green lines). The superficial cartilage layer is depicted in red, the deep layers in blue.

of the respective features. Only intrameniscal signal alterations not reaching the meniscal surface (i.e. MOAKS grade 1) and thus, not clearly representing a meniscal tear were not considered as pathologic. The association between the number of specific baseline structural pathologies (i.e. non-zero scores for all features but meniscus damage where scores of ≥2 were considered) and ipsi-compartmental longitudinal T2 change over 1 and 4 years was considered the primary analytic focus. The association between specific structural pathologies and change in the number of lesion types between baseline and year 1 vs. longitudinal T2 change and the association between baseline T2 and 4-year change in number of lesion types were considered exploratory.

Statistical analyses were performed using univariate analyses (UNIANOVA) adjusted for age, sex and BMI, with T2 change as dependent variable and structural MRI pathology as the predictor (Fig. 1). Statistical analyses were conducted using IBM SPSS 22 software (IBM Corporation, Armonk, NY).

3. Results

The sample included 82 participants (age 54.1 ± 7.2 years, BMI $24.2 \pm 3.0 \, kg/m^2$; 61% women).

3.1. Baseline structural pathology

"Any" baseline cartilage lesion in the medial femoro-tibial compartment (MFTC) was observed in 15 (18%) participants and in 26 (32%) in the lateral femoro-tibial compartment (LFTC). 39 (48%) knees had any baseline Hoffa-synovitis, 13 (16%) any effusion-synovitis, 7 (9%) knees had medial and 3 (4%) had lateral femoro-tibial BMLs, 7 (9%) had medial and 3 (4%) lateral meniscal damage (excluding intrameniscal signal alterations) or meniscus extrusion (extrusion > 3 mm only). Only few of these lesions were high-grade. Two (2.4%) knees did not have any lesion type present at baseline, 9 knees (11%) had 1 lesion

Table 1
Baseline structural pathology.

		Patella n (%)	Trochlea n (%)	cMF n (%)	cLF n (%)	pMF n (%)	pLF n (%)	MT n (%)	LT n (%)
Cartilage scores									
	0.0	39 (47.6)	60 (73.1)	70 (85.4)	82 (100)	82 (100)	81 (98.8)	77 (93.9)	57 (69.5)
	1.0	7 (8.5)	15 (18.3)	9 (11.0)	0	0	0	0	7 (8.5)
	1.1	1 (1.2)	3 (3.7)	1 (1.2)	0	0	1 (1.2)	0	1 (1.2)
	2.0	28 (34.1)	3 (3.7)	2 (2.4)	0	0	0	5 (6.1)	6 (7.3)
	2.1	3 (3.7)	1 (1.2)	0	0	0	0	0	0
	2.2	4 (4.9)	0	0	0	0	0	0	0
BML Size									
	0	63 (76.8)	70 (85.4)	78 (95.1)	82 (100)	81 (98.8)	80 (97.5)	80 (97.5)	81 (98.8)
	1	15 (18.3)	11 (13.4)	4 (4.9)	0	1 (1.2)	1 (1.2)	2 (2.4)	1 (1.2)
	2	4 (4.9)	1 (1.2)	0	0	0	1 (1.2)	0	0
Osteophytes									
	0	44 (53.7)	81 (98.8)	81 (98.8)	72 (87.8)	28 (34.1)	71 (86.6)	82 (100)	82 (100)
	1	38 (46.3)	1 (1.2)	1 (1.2)	10 (12.2)	54 (65.9)	11 (13.4)	0	0

			Medial n (%)		Lateral n (%)
Meniscus Morphology					
	0		19 (23.2)		69 (84.1)
	1		59 (72.0)		10 (12.2)
	2		2 (2.4)		1 (1.2)
	3		2 (2.4)		2 (2.4)
Meniscus Extrusion					
	0		61 (74.4)		82 (100)
	1		18 (22.0)		0
	2		3 (3.7)		0

Inflammation	Hoffa Synovitis n (%)	Effusion synovitis n (%)
0	43 (52.4)	69 (84.1)
1	38 (46.3)	12 (14.6)
2	0	1 (1.2)
3	1 (1.2)	0.0

Lesion Score	MFTC n (%)	LFTC n (%)	FemTib n (%)	FemPat n (%)	Knee n (%)
0	26 (31.7)	27 (32.9)	5 (6.1)	9 (11.0)	2 (2.4)
1	28 (34.1)	29 (35.4)	26 (31.7)	24 (29.3)	9 (11.0)
2	17 (20.7)	17 (20.7)	17 (20.7)	20 (24.4)	20 (24.4)
3	10 (12.2)	8 (9.8)	17 (20.7)	17 (20.7)	24 (29.3)
4	0	1 (1.2)	15 (18.3)	8 (9.8)	17 (20.7)
5	1 (1.2)	0	1 (1.2)	4 (4.9)	8 (9.8)
6	0	0	0	0	1 (1.2)
7	0	0	1 (1.2)	0	1 (1.2)

BML – bone marrow lesion; cMF – central medial femur; cLF –central lateral femur; pMF – posterior medial femur; pLF – posterior lateral femur; MT- medial tibia, LT –lateral Tibia; MFTC – medial femoro-tibial compartment; LFTC – lateral femoro-tibial compartment; FemTib – femoro-tibial joint (i.e. both medial and lateral femoro-tibial compartment); FemPat – femoropatellar compartment.

type, 20 (24.4%) knees had 2, 24 (29.3%) had 3, 17 (20.7%) 4, 8 (8.9%) 5, one knee (1.2%) had 6 and one (1.2%) knee had 7 lesion types; lesion types included cartilage damage, BMLs, osteophytes, meniscal damage, meniscal extrusion, Hoffa-synovitis and effusion-synovitis. Baseline frequencies of OA features between the entire sample and the subset with Y4 follow-up data available (n = 57) did not differ significantly (p ≥ 0.51). A detailed overview of the baseline structural pathology is presented in Table 1.

3.2. Baseline structural pathology and longitudinal change in T2

A longitudinal increase in T2 was observed in both compartments and layers. Over the 1st year, the longitudinal change (mean [95% confidence intervals]) in superficial and deep layer T2 was 0.6 [0.1, 1.0] ms and 0.8 [0.5, 1.2] ms in the MFTC, and 0.5 [0.1, 0.8] ms and 0.7 [0.4, 1.1] ms in the LFTC. Over the 4-year period, the changes were 1.8 [1.3, 2.3] ms and 1.2 [0.8, 1.7] ms in the MFTC, and 1.2 [0.8, 1.6] ms and 1.0 [0.5, 1.6] ms in the LFTC. Table 2 gives a detailed overview of the associations between baseline structural morphology and subsequent change in T2 from baseline to Y1 and concurrent structural

worsening and change in T2. Table 3 shows the details regarding the respective changes from baseline to Y4.

The number of "any" baseline MRI pathologies was not significantly associated with longitudinal change in superficial or deep MFTC (or LFTC) cartilage T2 over the 1- or 4-year observation period (p ≥ 0.22). Further, no statistically significant associations were observed between most MRI structural features and 1- or 4-year change in ipsi-compartmental cartilage T2.

Presence of baseline MFTC osteophytes appeared to be associated with prolongation in superficial layer T2 over the first year (0.8 [0.4, 1.3] ms vs. 0.0 [−1.0, 1.0] ms, p = 0.02), and the 4-year observation period (2.3 [1.6, 3.0] ms vs. 0.9 [0.3, 1.6] ms, p = 0.01). Further, the presence of baseline MFTC meniscal damage or extrusion appeared to be associated with a prolongation in deep layer T2 at year 1 (2.1 [0.6, 3.7] ms vs. 0.7 [0.3, 1.1] ms, p = 0.02), but not at year 4 (2.0 [1.1, 3.0] ms vs. 1.1 [0.7, 1.6] ms, p = 0.21).

3.3. Worsening of structural pathology and longitudinal change in T2

Ipsi-compartmental worsening of semiquantitatively assessed MRI

Table 2
Baseline structural pathology and change in T2 values from baseline to year 1.

Baseline structural pathology		N	Change in T2 values from baseline to year 1					
			Superficial Layer			Deep Layer		
			Mean	[95% CI]	P-Value	Mean	[95% CI]	P-Value
Medial tibio-femoral compartment								
Hoffa synovitis	No	43	0.2	[−0.3, 0.8]	0.07	0.9	[0.3, 1.4]	0.87
	Yes	39	0.9	[0.3, 1.6]		0.8	[0.3, 1.3]	
Effusion synovitis	No	69	0.5	[0.0, 0.9]	0.68	0.9	[0.5, 1.3]	0.30
	Yes	13	1.0	[−0.5, 2.4]		0.5	[−0.3, 1.2]	
Cartilage damage	No	67	0.3	[−0.2, 0.8]	0.09	0.7	[0.3, 1.1]	0.15
	Yes	15	1.5	[0.7, 2.3]		1.4	[0.6, 2.2]	
BML	No	75	0.7	[0.2, 1.1]	0.08	0.9	[0.6, 1.3]	0.11
	Yes	7	−0.7	[−2.9, 1.4]		−0.2	[−1.9, 1.6]	
Osteophytes	No	28	0.0	[−1.0, 1.0]	*0.02	0.6	[-0.2, 1.4]	0.32
	Yes	54	0.8	[0.4, 1.3]		0.9	[0.6, 1.3]	
Meniscus (extrusion/morphology)	No	75	0.5	[0.0, 1.0]	0.55	0.7	[0.3, 1.1]	*0.02
	Yes	7	1.0	[−0.3, 2.4]		2.1	[0.6, 3.7]	
Number of baseline MRI features	0	10	−0.6	[−2.1, 0.9]	0.08	0.4	[−1.1, 1.9]	0.71
	1	31	0.4	[−0.3, 1.2]		1.0	[0.4, 1.6]	
	2	23	0.8	[−0.1, 1.7]		0.6	[0.0, 1.3]	
	3+	18	1.1	[0.3, 1.9]		1.0	[0.3, 1.7]	
Worsening of MRI features[1]	No	67	0.7	[0.3, 1.2]	0.69	0.9	[0.6, 1.3]	0.69
(baseline → year 1)	Yes	11	0.6	[−1.0, 2.2]		0.7	[−0.5, 1.8]	
Lateral tibio-femoral compartment								
Hoffa synovitis	No	43	0.4	[0.0, 0.9]	0.75	0.8	[0.3, 1.2]	0.98
	Yes	39	0.5	[−0.1, 1.0]		0.7	[0.2, 1.2]	
Effusion synovitis	No	69	0.5	[0.1, 0.8]	0.70	0.8	[0.4, 1.1]	0.41
	Yes	13	0.4	[−0.7, 1.6]		0.5	[−0.6, 1.5]	
Cartilage damage	No	56	0.5	[0.1, 0.9]	0.95	0.8	[0.3, 1.2]	1.00
	Yes	26	0.4	[−0.2, 1.1]		0.7	[0.1, 1.3]	
BML	No	79	0.5	[0.2, 0.8]	N/A[3]	0.8	[0.5, 1.1]	N/A[3]
	Yes	3	−0.5	[−4.7, 3.8]		−0.8	[−5.7, 4.2]	
Osteophytes	No	62	0.5	[0.1, 0.9]	0.76	0.8	[0.4, 1.2]	0.90
	Yes	20	0.3	[−0.4, 1.1]		0.7	[−0.1, 1.4]	
Meniscus (extrusion/morphology)	No	79	0.4	[0.1, 0.8]	N/A[3]	0.7	[0.4, 1.1]	N/A[3]
	Yes	3	1.2	[−7.1, 9.6]		0.8	[−5.2, 6.8]	
Number of baseline MRI features	0	23	0.7	[0.1, 1.3]	0.22	0.9	[0.3, 1.6]	0.87
	1	31	0.4	[−0.1, 0.9]		0.8	[0.2, 1.3]	
	2	13	−0.3	[−1.3, 0.7]		0.4	[−0.5, 1.2]	
	3+	15	0.9	[−0.1, 2.0]		0.7	[−0.2, 1.6]	
Worsening of MRI features[2]	No	70	0.6	[0.3, 1.0]	*0.04	0.9	[0.6, 1.3]	*0.01
(baseline → year 1)	Yes	10	−0.4	[−1.6, 0.7]		−0.3	[−1.5, 0.8]	

[1] n = 4 with improvement excluded.
[2] n = 2 with improvement excluded.
[3] Too few observations.
* Statistically significant at p ≤ 0.05.

features between baseline and year 1 appeared to be associated with T2 shortening in superficial (−0.4 [−1.6, 0.7] ms vs 0.6 [0.3, 1.0] ms, p = 0.04) and deep layer (−0.3 [−1.5, 0.8] ms vs. 0.9 [0.6, 1.3] ms, p = 0.01) LFTC cartilage over 1 year, but not over 4 years. Ipsi-compartmental worsening of MRI features between baseline and Y1 was neither significantly associated with change in T2 from Y1 to Y4 in the MFTC (N = 6, superficial 0.2 [−2.2, 2.6] ms vs. 0.9 [0.3, 1.5] ms, p = 0.35; deep −0.2 [−2.0, 1.5] ms vs. 0.2 [−0.2, 0.6] ms, p = 0.37) nor the LFTC (N = 6, superficial 1.4 [−0.5, 3.4] ms vs. 0.8 [0.4, 1.3] ms, p = 0.44; deep 0.8 [−1.1, 2.7] ms vs. 0.3 [−0.2, 0.8] ms, p = 0.49).

Table 4 illustrates the association between baseline cartilage T2 and change in number of lesion types from baseline to Y4 on a total knee level. Knees with subsequent lesion score worsening were observed to show lower T2 in the superficial layer of the femorotibial joint (43.8 ms vs. 45.4 ms, p = 0.01), that was driven by lower values in the superficial layer of the medial compartment and in particular in the central medial femur (Table 4).

4. Discussion

The OAI healthy reference cohort provides a unique opportunity to study knees without radiographic abnormalities, pain, and risk factors of knee OA for up to 4 years of observation using state of the art imaging technology. In this cohort, longitudinal change in laminar transverse relaxation time (T2) of medial or lateral femorotibial cartilage was not predicted by the number of morphologic structural MRI tissue abnormalities. If any, medial compartment osteophytes detected by MRI (but not by radiography) and possibly meniscal pathology (only over the first year) may be associated with an increase in cartilage T2 (i.e. compositional deterioration), but given the larger number of comparisons that had to be performed when individual features of structural MRI pathology were studied, the latter result needs to be interpreted with great care and to be confirmed in future population-based studies.

In a different, smaller subsample from the OAI comparing participants with and without OA, Stahl et al. found significantly higher T2 relaxation times in the tibio-femoral cartilage of patients with early knee OA compared to healthy controls, allowing for differentiation of patients with and without disease. However, these authors did not

Table 3
Baseline structural pathology and change in T2 values from baseline to year 4.

Baseline structural pathology		N	Change in T2 values from baseline to year 4					
			Superficial Layer			Deep Layer		
			Mean	95% CI	P-Value	Mean	95% CI	P-Value
Medial tibio-femoral compartment								
Hoffa synovitis	No	28	1.3	[0.8, 1.8]	0.08	1.0	[0.4, 1.7]	0.49
	Yes	29	2.2	[1.4, 3.0]		1.4	[0.8, 2.0]	
Effusion synovitis	No	47	1.7	[1.1, 2.2]	0.61	1.3	[0.8, 1.8]	0.70
	Yes	10	2.1	[0.5, 3.7]		0.8	[−0.2, 1.8]	
Catilage lesions	No	47	1.7	[1.1, 2.3]	0.78	1.3	[0.8, 1.7]	0.93
	Yes	10	2.1	[0.8, 3.3]		1.0	[−0.5, 2.6]	
BML	No	52	1.9	[1.4, 2.4]	0.14	1.2	[0.8, 1.6]	0.66
	Yes	5	0.7	[−3.0, 4.3]		1.3	[−2.6, 5.2]	
Osteophytes	No	23	0.9	[0.3, 1.6]	*0.01	0.8	[−0.1, 1.6]	0.12
	Yes	34	2.3	[1.6, 3.0]		1.5	[1.1, 2.0]	
Meniscus (extrusion/morphology)	No	52	1.8	[1.2, 2.3]	0.73	1.1	[0.7, 1.6]	0.21
	Yes	5	1.4	[0.0, 2.8]		2.0	[1.1, 3.0]	
Number of baseline MRI features	0	8	1.3	[0.6, 2.0]	0.50	0.8	[−1.1, 2.6]	0.58
	1	22	1.4	[0.7, 2.2]		0.9	[0.2, 1.6]	
	2	14	2.0	[0.5, 3.5]		1.7	[0.8, 2.5]	
	3+	13	2.2	[1.2, 3.3]		1.5	[0.5, 2.5]	
Worsening MRI features[1]	No	48	2.0	[1.5, 2.5]	0.32	1.3	[0.9, 1.8]	0.16
(baseline → year 1)	Yes	6	1.1	[−1.6, 3.8]		0.4	[−1.6, 2.4]	
Lateral tibio-femoral compartment								
Hoffa synovitis	No	28	0.8	[0.2, 1.4]	0.06	0.9	[0.2, 1.6]	0.77
	Yes	29	1.6	[1.1, 2.1]		1.2	[0.3, 2.1]	
Effusion synovitis	No	47	1.1	[0.7, 1.6]	0.41	1.1	[0.5, 1.7]	0.64
	Yes	10	1.5	[0.6, 2.4]		0.6	[−0.9, 2.1]	
Catilage lesions	No	39	1.3	[0.8, 1.8]	0.70	1.1	[0.3, 1.8]	0.87
	Yes	18	1.1	[0.4, 1.8]		1.0	[0.2, 1.9]	
BML	No	55	1.3	[0.8, 1.7]	N/A[3]	1.1	[0.6, 1.7]	N/A[3]
	Yes	2	−0.1	[−4.9, 4.8]		−0.9	[−4.2, 2.4]	
Osteophytes	No	46	1.2	[0.7, 1.6]	0.79	1.0	[0.4, 1.6]	0.82
	Yes	11	1.4	[0.3, 2.4]		1.2	[0.2, 2.3]	
Meniscus (extrusion/morphology)	No	56	1.2	[0.8, 1.6]	N/A[3]	1.1	[0.6, 1.6]	N/A[3]
	Yes	1	2.6	N/A[3]	N/A[3]	−3.7	N/A[3]	N/A[3]
Number of baseline MRI features	0	15	0.6	[−0.4, 1.6]	0.33	1.0	[0.0, 1.9]	0.60
	1	23	1.6	[1.0, 2.1]		1.0	[−0.1, 2.1]	
	2	10	1.2	[0.1, 2.4]		1.7	[0.9, 2.4]	
	3+	9	1.3	[0.3, 2.3]		0.5	[−1.1, 2.0]	
Worsening of MRI features[2]	No	50	1.3	[0.9, 1.7]	0.16	1.1	[0.6, 1.7]	0.25
(baseline → year 1)	Yes	6	0.3	[−1.2, 1.8]		0.0	[−2.7, 2.6]	

[1] n = 3 with improvement excluded.
[2] n = 1 with improvement excluded.
[3] Too few observations.

observe significant change in T2 over one year in either group. Interpretation of these findings seems challenging given the small sample size analyzed [7]. Baum et al., in contrast, reported cartilage T2 to significantly increase over a 2-year period in OAI subjects without OA (K-L 0 in the analyzed knee) with and without OA risk factors, but neither presence of risk factors nor presence of baseline cartilage damage were significantly associated with the T2 increase [11]. These findings are similar to ours with increasing T2 values over time but only few associations with baseline risk factors such as baseline structural pathology as analyzed in our study. We found significant associations only for presence of medial osteophytes and change in superficial layer T2 at year 1 and 4, and medial meniscus morphology and change in deep layer T2 at year 1. In addition, worsening of MRI features from baseline to year 1 was associated with a concurrent decrease in superficial layer T2 at Y1, but did not predict any change at Y4. Pan et al. reported a significant increase in tibiofemoral cartilage T2 in asymptomatic individuals from the OAI reference cohort and demonstrated that an increase in semiquantitative scores of cartilage abnormalities correlated with greater increase in T2 [17]. A recent study looking at differences in healthy knees with or without posterior meniscal horn damage revealed greater T2 increase over one and 2 years in the group with meniscal lesions, a finding that we could confirm only for deep layers of cartilage at Y1 [18].

However, it is unclear whether some currently unknown mechanism may be in place that inhibits an apparently normal age-related increase in cartilage T2 at specific stages of early OA. Our current study does not provide evidence that in such knees baseline structural MRI pathology is related to compositional progression when measured by cartilage T2. This may be because - in an asymptomatic radiographically normal knee without risk factors - structural MRI pathology is not predictive of future progression, or because T2 is insensitive in capturing such progression, or both.

Compositional magnetic resonance imaging (MRI) techniques enable detection of biochemical and microstructural changes in the cartilage extracellular matrix before gross morphological changes occur, which make these techniques potentially attractive as outcome measures for clinical trials focusing on early potentially reversible disease stages. These techniques include relaxometry measurements (T2, T2* and T1ρ mapping), sodium imaging, delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), magnetization transfer contrast (MTC) and glycosaminoglycan specific chemical exchange saturation transfer (gagCEST), diffusion weighted imaging (DWI), diffusion tensor imaging (DTI), and ultrashort echo-time imaging. Among quantitative MRI techniques for evaluating cartilage matrix composition, T_2 relaxometry

Table 4
Association between baseline T2 values and change in structural pathology from baseline to Year 4.

Compartment/plate		Change in total number of MOAKS features per knee							
		Δ Lesion score Knee: no change (N = 32)		Δ Lesion score Knee: Worsening (N = 20)		Δ Lesion score Knee: Improvement (N = 5)			
		mean	95% CI	mean	95% CI	Mean	95% CI	P value improvement	P value worsening
FTJ	Deep	36.1	[35.5, 36.7]	35.1	[34.3, 36.0]	35.3	[32.7, 37.9]	0.23	0.34
	Superficial	45.4	[44.7, 46.0]	43.8	[42.8, 44.8]	44.3	[40.0, 48.6]	*0.01	0.32
MFTC	Deep	36.6	[35.8, 37.3]	35.3	[34.1, 36.4]	35.6	[32.8, 38.5]	0.12	0.36
	Superficial	45.2	[44.4, 46.0]	43.4	[42.2, 44.6]	44.5	[40.0, 49.0]	* < 0.01	0.55
LFTC	Deep	35.7	[35.0, 36.4]	35.0	[34.2, 35.8]	35.0	[32.1, 37.8]	0.73	0.47
	Superficial	45.6	[44.8, 46.4]	44.2	[43.2, 45.2]	44.2	[39.8, 48.5]	0.11	0.24
MT	Deep	33.0	[32.4, 33.7]	32.6	[31.7, 33.4]	32.4	[29.4, 35.4]	0.41	0.34
	Superficial	41.0	[40.1, 42.0]	40.1	[38.9, 41.3]	39.8	[36.1, 43.5]	0.06	0.34
cMF	Deep	40.1	[38.7, 41.4]	37.9	[36.3, 39.6]	38.8	[35.7, 42.0]	0.13	0.52
	Superficial	49.3	[48.4, 50.3]	46.7	[45.2, 48.2]	49.2	[43.8, 54.6]	* < 0.00	0.90
LT	Deep	31.2	[30.5, 31.8]	31.0	[30.1, 31.8]	30.6	[28.8, 32.4]	0.69	0.47
	Superficial	42.6	[41.7, 43.5]	41.5	[40.5, 42.5]	42.1	[37.5, 46.6]	0.13	0.67
cLF	Deep	40.2	[39.1, 41.3]	39.1	[37.9, 40.3]	39.3	[34.9, 43.7]	0.50	0.59
	Superficial	48.5	[47.5, 49.6]	47.0	[45.6, 48.3]	46.3	[42.0, 50.5]	0.21	0.12

FTJ – femoro-tibial joint (medial and lateral); MFTC – medial femoro-tibial compartment (femur and tibia); LFTC – lateral femoro-tibial compartment (femur and tibia); MT – medial tibia; cMF – central medial femur; LT – lateral tibia; LF – central lateral femur; 95% CI – 95% confidence interval.

  * Statistically significant at $p \leq 0.05$.

('mapping') has the longest history and has been applied the most widely as it neither requires contrast agent administration nor special hardware, and can easily be performed in a clinical setting. In particular, the application of T_2 mapping in the Osteoarthritis Initiative (OAI) has provided the community a valuable dataset with large sample size and up to 10 years follow up for gaining knowledge and insights of the natural history of OA development and progression, particularly in its earliest phases [19–21].

Our study has several limitations: Due to the small sample size we had to dichotomize baseline structural damage into presence and absence but did not take into account the specific subgrades of the MOAKS scoring system. Furthermore, the OAI acquired T2 MESE sequences of the right knee only and we do not know if the contralateral knee would show a similar pattern of structural damage or T2 composition. Yet, a recent analysis looking at symmetricity suggested a high prevalence of comparable structural damage in both knees [22]. Further, due to the sample selection focusing on knees without radiographic OA the frequencies of structural damage overall were low limiting potential associations with later T2 changes over time.

In conclusion, the current study does not provide convincing evidence that in knees without ROA (and without risk factors for developing OA) baseline structural MRI tissue abnormalities are related to compositional progression during normal aging and/or the potentially earliest phases of the disease as measured by cartilage T2. Exploratory analyses showed a signal for baseline medial compartment osteophytes and meniscal alterations being associated with T2 prolongation over 1 year that was only sustained for osteophytes over 4 years. Further studies are required to elucidate to what extent structural pathology predicts disease progression before the onset of symptomatic and radiographic knee OA, and to what extent cartilage T2 is a useful biomarker of disease progression in early knee osteoarthritis.

Authors contributions

(1) All authors were involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data.
(2) All authors contributed to drafting the article or revising it critically for important intellectual content.
(3) All authors gave their final approval of the manuscript to be submitted.

Additional contributions:
Analysis and interpretation of the data: FWR; FE; SM; GD; AG, WW.
Drafting of the article: FWR; FE; SM; GD; AG; WW.
Provision of study materials or patients: FWR; FE; SM; WW.
Statistical expertise: WW, FWR, FE.
Obtaining of funding: FWR; FE; SM; GD; WW.
Collection and assembly of data: FWR; FE; SM; WW.
Responsibility for the integrity of the work as a whole, from inception to finished article, is taken by F. Roemer, MD.

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Declaration of Competing Interest

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FE is CEO and co-owner of Chondrometrics GmbH. He provides consulting services to MerckSerono, Samumed, Tissuegene, Servier and Roche, and has held educational lectures for Medtronic. He has received funding support (for studies not related to the current one) from Pfizer, Eli Lilly, Stryker, Novartis, MerckSerono, Glaxo Smith Kline,

Appendix A. Supplementary data

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