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Research Article (Non-Member)

Cartilage quantitative T2 relaxation time 2 to 4 years following isolated anterior cruciate ligament reconstruction¹

Running title: Cartilage T2 following isolated ACLR

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Graphical abstract Cartilage quantitative T2 relaxation time 2 to 4 years following isolated anterior cruciate ligament reconstruction

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Twenty-eight individuals with isolated ACL reconstruction (ACLR) exhibited significantly ($p < 0.05$) higher T2 relaxation time values – suggestive of cartilage degeneration - in the deep layer of the medial femoral condyle compared with controls ($n = 9$) at 2-3 years post-surgery. Somewhat surprisingly, ACLR individuals ($n = 16$) showed a significant decrease in T2 values in the deep layer of the lateral tibia from 2 to 4 years post-surgery, suggesting a partial improvement in cartilage composition.

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Abstract

Cartilage T2 relaxation time in isolated anterior cruciate ligament reconstruction (ACLR) without concomitant meniscal pathology and their changes over time remain unclear. The purpose of this exploratory study was to: 1) compare cartilage T2 relaxation time (T2 values) in people with isolated ACLR at 2-3 years post-surgery (baseline) and matched healthy controls and; 2) evaluate the subsequent 2-year change in T2 values in people with ACLR. Twenty-eight participants with isolated ACLR and 9 healthy volunteers underwent knee magnetic resonance imaging (MRI) at baseline; 16 ACLR participants were re-imaged 2 years later. Cartilage T2 values in full thickness, superficial layers, and deep layers were quantified in the tibia, femur, trochlear and patella. Between-group comparisons at baseline were performed using analysis of covariance adjusting for age, sex and body mass index. Changes over time in the ACLR group were evaluated using paired sample t-tests. ACLR participants showed significantly higher ($p = 0.03$) T2 values in the deep layer of medial femoral condyle at baseline compared to controls (mean difference 4.4ms [13%], 95% CI 0.4, 8.3ms). Over 2 years, ACLR participants showed a significant reduction ($p = 0.04$) in T2 value in the deep layer of lateral tibia (mean change 1.4ms [-7%], 95% CI 0.04, 2.8ms). The decrease in T2 values suggests improvement in cartilage composition in the lateral tibia (deep layer) of ACLR participants. Further research with larger ACLR cohorts divided according to meniscal status and matched healthy cohorts are needed to further understand cartilage changes post-ACLR.

Key words: Anterior cruciate ligament reconstruction; Post-traumatic osteoarthritis; Magnetic resonance imaging; T₂ mapping

Introduction

Anterior cruciate ligament (ACL) rupture is a common knee injury, and surgical ACL reconstruction (ACLR) is frequently performed to restore knee stability and function^{1,2}. However, ACL rupture is strongly associated with an increased risk of early onset knee osteoarthritis (OA) even after ACLR^{3,4}. Thus, the ACLR knee constitutes an ideal model for elucidating the pathogenesis of early OA and the potential for disease-modifying interventions.

Early-stage cartilage degeneration is characterised by a loss of proteoglycans, collagen disorganisation and increasing water content⁵. Advanced compositional magnetic resonance imaging (MRI) techniques, such as T2 relaxation time, T1 rho relaxation time and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), can quantify cartilage biochemical changes and detect early degeneration non-invasively⁶. T2 relaxation time, or T2 value, reflects the water content and collagen fibril orientation; thus, an elevated T2 value suggests increased water mobility as well as collagen damage early in the cartilage degenerative process⁷⁻⁹. Laminar analysis of T2 values also allows investigation of cartilage changes throughout the depth of the tissue, which is important given the different structural and biomechanical properties of the superficial and deep layer of articular cartilage¹⁰⁻¹³.

Previous studies have assessed cartilage T2 values in different knee regions from 1 to 3 years after ACLR^{12, 14-23}. Results from these studies demonstrated elevated T2 values, suggestive of degenerative changes particularly in the lateral tibia^{12, 17} and medial femoral condyle^{17, 20} in the first 2 years after ACLR. At 2 to 3 years post ACLR, Li et al.¹⁴ reported higher cartilage T2 values in all knee compartments of ACLR participants compared to healthy controls. Another study performed laminar analysis and demonstrated higher T2 values in the deep layer of lateral tibia in ACLR patients at 2-years post-surgery compared with healthy

controls¹⁷. Importantly, ACLR patients included in the aforementioned studies were not sub-grouped with respect to meniscal pathology. However, a recent study compared ACLR patients (3 years post-surgery) with and without concomitant meniscal injury and demonstrated higher cartilage T2 values in those with “combined” meniscal injury¹⁵, thereby supporting the notion that concomitant meniscal pathology is an important contributor to potential OA development^{3,24}. To date, no studies have compared cartilage T2 values from ACLR patients without concomitant meniscal injury to uninjured individuals, nor have longitudinal changes in cartilage T2 values been investigated in ACLR individuals without meniscal injury.

The primary aim of this study was to compare the cartilage T2 values (full-thickness and lamellar) between individuals with isolated ACLR performed 2-3 years previously and healthy controls. The secondary aim was to examine the change in cartilage T2 values over the subsequent 2 years in these ACLR individuals. It was hypothesised that ACLR individuals would exhibit higher knee cartilage T2 values compared with controls (H_1), and that cartilage T2 values would change over 2 years in the ACLR individuals (H_2).

Methods

Participants

This prospective cohort study (level 2) was approved by the University of Melbourne Human Research Ethics Committee, and all participants provided written informed consent. Twenty-eight participants with isolated ACLR (i.e., without concomitant meniscal pathology) were recruited from two experienced orthopaedic surgeons specialising in ACLR surgery in Melbourne, Australia. These participants were a subgroup of a larger longitudinal cohort study, and the joint morphology at baseline has been published²⁵. Inclusion criteria for ACLR participants were: (i) aged 18–40 years; (ii) ACLR performed for an acute ACL tear

within 6 months of injury; (iii) ACLR performed arthroscopically using ipsilateral semitendinosus and gracilis (hamstring) autograft; and (iv) ACLR performed 2-3 years previously. Participants were excluded if they had: (i) International Cartilage Repair Society (ICRS) cartilage defects grade > 2 noted by the surgeon at the time of ACLR; (ii) other musculoskeletal, cardiovascular or neurological conditions; (iii) previous ACL surgery or subsequent knee surgery on the involved leg; (iv) body mass index (BMI) > 34 kg/m² (to minimise effects of adiposity on gait assessment reliability in the larger study); and (v) contraindications to MRI. All ACLRs were performed using the same arthroscopically assisted technique with hamstring autograft. Meniscal pathology was assessed at the time of ACLR surgery using arthroscopy, and participants with meniscal pathology were excluded. No chondral surgery was undertaken as all lesions were less than ICRS grade 3. A post-surgical rehabilitation protocol emphasising rapid restoration of knee joint range of motion and quadriceps (particularly vastus medialis) function was prescribed²⁵.

Nine healthy participants were recruited at baseline as the control group. Inclusion criteria for control participants were: (i) aged between 18-40 years; (ii) BMI < 34 kg/m². Exclusion criteria for healthy controls were: (1) prior knee surgery, (2) known lower limb injury or abnormality, and (3) contraindications to MRI.

Measurements

Anthropometric measures and sports activity

Body mass and height were used to calculate BMI (kg/m²). The sports activity rating scale from the Cincinnati knee rating system was completed to assess the activity level of the participants by considering both the frequency of play and type of sports²⁶. Higher scores indicate higher level of sports participation (0-100).

MRI assessment

ACLR participants underwent MRI assessment at 2-3 years post-ACLR (baseline) and at follow-up 2 years later, while the control group underwent MRI assessment only at baseline. Quantitative T2 mapping was performed using one 3-T MRI unit (Siemens Magnetom Verio, Erlangen, Germany) with an 8-channel knee coil. T2 mapping used a sagittal multi-echo spin echo sequence, implementing a slice thickness of 3 mm; spacing between slices 3.6mm; inter-slice gap 0.6 mm; five echo /repetition times of 13.8, 27.6, 41.4, 55.2, and 69.0/1200 milliseconds; flip angle 180 degrees; field of view 159 mm; in-plane resolution: 0.42×0.42 mm; and acquisition time of 8 min 16 sec. The current study also performed morphological sequences including T1-weighted 3D gradient recall in the sagittal plane and proton density (PD)-weighted fat-saturated spin echo acquisition in the coronal plane²⁵. Thus, the T2 mapping scan was performed after 10-15 mins resting in sitting position and 15 minutes in the supine position following the morphology sequence. T2 mapping images were constructed from the multi-spin-echo sequence using vendor-supplied software (Siemens syngo MapIt, Erlangen, Germany). The Siemens software fitted a mono exponential function to the signal intensity decay over all five echoes to extract the decay value, representing it as a pixel in the T2 mapping “image.” Cartilage was directly segmented on the T2 mapping images by manually tracing the boundary in six compartments: medial tibia, medial femoral condyle, lateral tibia, lateral femoral condyle, trochlea and patella using OsiriX (Pixmeo SARL, Geneva, Switzerland) at window level 40 and window width 100. Segmentations were subsequently overlaid on the first echo images (TE=13.8ms) for visualization as shown in Figure 1. After delineating the full-thickness cartilage, the entire layer was further divided into two equally spaced layers (i.e., superficial layer and deep layer) by an in-house program developed in Matlab (The Mathworks, Inc. Mass., USA) using the Image Processing Toolbox (Figure 2). Pixels with

T2 values greater than 100 ms were removed to reduce artefacts^{14,27}. Mean full-thickness and laminar T2 values were then calculated using the same program. Those T2 values were then averaged from the middle five slices of cartilage in each of the four tibiofemoral compartments, 10 slices in the patella, and the central three slices for the trochlear groove using axial plane images transformed by OsiriX. A trained examiner (XW) performed all T2 segmentation. The intra-rater reliability for cartilage volume (expressed as intra-class correlation coefficients, ICCs) was 0.94-0.99 for all regions of interest.

Cartilage defects at baseline were graded on the medial tibial plateau, medial femoral condyle, lateral tibial plateau, lateral femoral condyle and patella using the T1-weighted 3D gradient recall with ICRS score²⁵. The ICRS score was as follows: grade 0 normal cartilage; grade 1 focal blistering and intra-cartilaginous low signal intensity area with an intact surface and base; grade 2 irregularities on the surface or base and loss of thickness <50 %; grade 3 deep ulceration, with >50 % loss of thickness; and grade 4 full-thickness cartilage wear with exposure of subchondral bone²⁸. Intra-observer and inter-observer agreement values ranged between 0.85 and 0.94²⁵.

Statistical analysis

Means and standard deviations were presented for continuous variables with normal distribution, while median and interquartile range presented for continuous variables that were not normally distributed. For descriptive variables, Chi square, Mann-Whitney U or independent samples t-tests were used to compare between groups, where appropriate.

Analysis of covariance (ANCOVA) was used to compare differences in baseline T2 values between ACLR participants and controls after adjusting for age, sex and BMI, given that these covariates are associated with cartilage T2 values²⁹. Paired samples t-test was used to examine the longitudinal change of cartilage T2 value in ACLR participants. All statistical

analyses were performed using SPSS package (version 22.0, SPSS, Chicago, IBM). A significance level of $P < 0.05$ was used with no adjustments for multiple statistical testing given the exploratory nature of the study.

Results

A comparison of the participant demographic characteristics in the ACLR and control groups is shown in Table 1. The mean time from injury to ACLR was 0.2 ± 0.1 years, and the time from surgery to baseline MRI was 2.4 ± 0.4 years. Several ICRS grade 2 cartilage defects were recorded at the time of ACLR: 1 in medial femoral condyle and 2 in patella. Only cartilage defects with cartilage loss were recorded; thus, ICRS grade 1 cartilage soft was not included.

Participants in the ACLR group had a higher BMI than those in the control group ($p = 0.01$). No significant between-group differences were found for the other variables, including the cartilage defects at baseline assessment (Table 1).

Sixteen ACLR participants returned for follow-up assessment two years later. There were no significant differences in demographics between the completers and non-completers (Table 2).

Comparison of cartilage T2 value in ACLR and control groups

Cartilage T2 values at baseline in ACLR and control groups, together with between-group differences adjusted for age, sex and BMI are shown in Table 3. The ACLR group exhibited significantly higher T2 values in the deep layer of the medial femoral condyle (mean difference 4.4ms [13%]; 95% CI 0.4, 8.3ms; $p = 0.03$) with no significant between-group differences observed at other sites. The results were similar when including

physical activity level (Actigraph GT3X, Pensacola, FL, USA) as an additional covariate (data not shown).

Longitudinal changes in T2 values in ACLR participants over 2 years

ACLR participants exhibited a significant decrease in T2 values in the deep layer of the lateral tibia (mean change 1.4ms [-7%]; 95% CI 0.04, 2.8ms; $p = 0.04$) (Table 4). No significant changes in T2 values were identified at the other measured sites.

Discussion

This study investigated early knee cartilage compositional changes following ACLR using T2 relaxation time values from MRI. Results showed that ACLR participants had significantly higher T2 values in the deep layer of medial femoral condyle at 2-3 years following surgery compared to healthy controls. Over the subsequent two-year period, ACLR participants showed a significant reduction in T2 value in the deep layer of lateral tibia. The results support both hypotheses.

Whilst T2 relaxation time methodologies are somewhat different between studies and can affect T2 values³⁰, our range of T2 values are comparable to those reported in the bulk of other ACLR-related studies, most of which have used very similar methodology^{12, 14, 15, 17, 20}. Our comparatively higher cartilage T2 values in the medial femoral condyle of participants 2-3 years following ACLR compared to controls is suggestive of degenerative changes, namely damage to the collagen network and increased water mobility⁷⁻⁹. In particular, higher T2 values derived from laminar analysis suggest that cartilage degeneration is apparent in the deep layer. The cartilage degeneration in the deep calcified layer is important, given that the interaction between cartilage and underlying subchondral bone is thought to contribute to

degenerative changes associated with OA³¹. In healthy cartilage, the flow of fluid enables nutrients and oxygen to diffuse in the tissue, and the deep calcified cartilage layer functions as a physical barrier for diffusion and angiogenesis (i.e., invasion of blood vessels) between cartilage and subchondral bone^{32,33}. However, in diseased OA cartilage, fluid permeability increases as a result of angiogenesis in the deep calcified cartilage and contributes to deleterious changes in cartilage mechanical properties^{32,34,35}. Higher T2 values in the deep cartilage layer are possibly related to increased hydraulic permeability in the cartilage-subchondral bone unit, which has been associated with OA progression. In further support, increased cartilage T2 values in the deep layer has been found in combination with degradation of underlying bone in patients with isolated meniscal tears³⁶.

Previous studies demonstrated similar higher T2 value in medial femoral condyle at 0.5 to 2.4 years post ACLR compared with healthy controls^{14,17,19-21}. Other compositional MRI studies using T1rho value and dGEMRIC have also noted cartilage degeneration (i.e., proteoglycan loss) from 3 weeks to 2 years following ACLR^{12,17,37-39}. Li et al. (2015) found higher medial femoral condyle T2 values in those with meniscal pathology at 2 to 4.2 years post-ACLR compared to those with intact menisci¹⁵. Taken together, the findings suggest that medial femoral condyle cartilage is more susceptible to early degeneration post-ACLR.

With respect to longitudinal cartilage compositional change in ACLR participants, the current study found a decreased T2 value in the deep layer of lateral tibia over the 2-year follow-up period. These findings suggest a dynamic change in cartilage composition towards improvement (i.e. decreased mobile water content) in the deep layer of lateral tibia from 2.4 to 4.4 years following surgery. This may be related to increased synthesis of collagen and proteoglycan as part of the cartilage repair process, evident in the early stages of OA⁴⁰⁻⁴². In a previous study, laminar analysis of T2 showed decreased values at lateral tibia in the

superficial layer; however, the T2 value tended to increase in the deep layer during the first 2 years following ACLR¹⁷. Hence, there may be different biochemical responses and recovery mechanisms in superficial and deep layers. Our results imply that the cartilage composition in the deep cartilage layer may change towards improvement during the follow-up period. However, even if the process of cartilage synthesis may have commenced, newly synthesised cartilage is different from healthy cartilage in that new cartilage exhibits poorer mechanical properties and, as such, is susceptible to degeneration in the longer-term^{5, 40, 43}.

Cross-sectional comparisons and longitudinal changes in cartilage T2 values were not significant at other knee sites, and this was probably due to study timing and the current ACLR patient cohort. A recent study investigated cartilage thickness changes over the first 5 years following ACLR; maximal thickness increase and decrease were greater over the first 2 years than over the subsequent 3 years, suggesting that major perturbations in cartilage homeostasis occur earlier than the later 2-year window in the current study⁴⁴. Thus, the cartilage T2 value change, reflecting cartilage compositional change from 2.4 to 4.4 years post-ACLR in the present study, may be less pronounced compared to earlier changes in the first 2 years^{12, 17}. Furthermore, the relatively small differences in cartilage T2 values between groups and T2 value change over time in the ACLR group might be attributed to our patient cohort. Specifically, we allowed only ACLR participants without meniscal pathology or severe cartilage defects in order to increase the homogeneity of our cohort, given that combined meniscal pathology and cartilage defects increases the risk of knee OA^{24, 45}.

This study is the first to compare T2 cartilage values between isolated ACLR participants and healthy controls at 2.4 years following surgery, and to explore changes over the subsequent 2 years. Importantly, whilst ACLR participants in previous studies were heterogeneous with respect to meniscal pathology and ACL graft type, the current study only included ACLR participants without meniscal pathology and with the same hamstring graft. One previous

study investigated T2 values in ACLR participants with various meniscal statuses at similar follow-up timing post-surgery¹⁴. These authors found that ACLR participants had higher T2 value in all knee compartments (i.e. medial tibia, medial femoral condyle, lateral tibia, lateral femoral condyle, patella and trochlea) compared to the healthy controls. Their findings differ from the current study where higher values were found only for the deep medial femoral condyle layer. We compared ACLR participants to healthy controls; the contralateral knee used as reference in some studies^{18, 22, 46}, may give a different impression, given that the contralateral knee may also showed longitudinal T2 changes, possibly due to altered biomechanics and neuromuscular function in the contralateral limb after ACLR²³.

This study has several limitations. First, as this was an exploratory study, the sample size was small, reducing the statistical power of the study. Because of this, statistical corrections were not made to account for multiple comparisons. Our findings need to be confirmed in larger cohort studies with longer follow-up. Second, only 16 of the 28 ACLR participants (57%) returned for follow-up testing; however, there were no differences in demographics between completers and non-completers. Third, T2 results can be affected by the methodology used³⁰. Like the bulk of the other ACLR T2 studies^{12, 14, 15, 17, 20}, the current study fitted the exponential T2 relaxation across all five echoes. Although some protocols⁴⁷ have suggested exclusion of the first echo or other compensation techniques for the T2 decay calculation, our methods and actual T2 values are consistent with most of the previous T2 studies after ACLR.

In summary, individuals with isolated ACLR exhibited higher T2 values – suggestive of cartilage degeneration - in the deep layer of the medial femoral condyle compared with controls at 2-3 years post-surgery. ACLR individuals showed decreased T2 values in the deep layer of the lateral tibia from 2 to 4 years following ACLR, which suggests a partial improvement of cartilage composition.

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Competing interests

The authors have no competing interests.

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Table 1 Demographics comparing the isolated ACLR and control groups

Characteristics	ACLR (n = 28)	Controls (n = 9)	<i>p</i> value
Age	29.8 (± 6.3)	26.0 (± 4.7)	0.10
Male, n (%)	17 (61)	4 (44)	0.46
Body mass index (kg/m ²)	24.2 (± 2.5)	21.3 (± 3.1)	0.01*
Sports activity level	85 (80, 95)	95 (87, 100)	0.08
Time from injury to surgery (yr)	0.2 (± 0.1)	N/A	N/A
Time from surgery to baseline assessment (yr)	2.4 (± 0.5)	N/A	N/A
Cartilage defects at baseline assessment			
Medial tibia	Grade 0	26 (93%)	9 (100%)
	Grade 1	2 (7%)	0
			1.0

	Grade 0	19 (68%)	9 (100%)	
Medial femoral condyle	Grade 1	7 (25%)	0	0.26
	Grade 2	2 (7%)	0	
	Grade 0	19 (68%)	7 (78%)	
Lateral tibia	Grade 1	6 (21%)	2 (22%)	0.85
	Grade 2	3 (11%)	0	
	Grade 0	17 (61%)	8 (89%)	
Lateral femoral condyle	Grade 2	11 (39%)	1 (11%)	0.22
	Grade 0	19 (68%)	7 (78%)	
Patella	Grade 1	9 (32%)	2 (22%)	0.70

Data were presented as mean (\pm standard deviation) or number (%). Sports activity level was presented as median (interquartile range). Sport activity level ranges from 0 to 100 with higher scores indicating higher level of sports participation. N/A=not applicable.

Table 2 Demographics between ACLR participants who returned for follow-up and those who withdrew

Characteristics	Completed follow-up (n = 16)	Lost to follow-up (n = 12)	<i>p</i> value
Age	30.5 (\pm 6.9)	29.0 (\pm 5.7)	0.55
Male, n (%)	10 (63)	7 (58)	0.14
Body mass index (kg/m ²)	23.9 (\pm 3.1)	24.4 (\pm 1.8)	0.63
Sports activity level	85 (80, 95)	90 (76, 95)	0.94
Time from surgery to baseline assessment (yr)	2.5 (\pm 0.4)	2.4 (\pm 0.5)	0.79
Time from baseline to follow-up assessment (yr)	2.1 (\pm 0.3)	N/A	N/A

Parametric data were presented as mean (\pm standard deviation), and sports activity level was presented as median (interquartile range). N/A=not applicable.

Table 3 T2 values in ACLR and control groups at baseline

	Full-thickness T2 (ms)			Superficial layer T2 (ms)			Deep layer T2 (ms)		
	ACLR	Controls	Adjusted difference # (95% CI)	ACLR	Controls	Adjusted difference # (95% CI)	ACLR	Controls	Adjusted difference # (95% CI)
Medial tibia	32.4 ± 4.2	29.3 ± 4.8	2.0 (-1.8, 5.9)	39.2 ± 4.9	36.7 ± 5.4	0.3 (-3.9, 4.6)	25.5 ± 4.7	21.6 ± 4.6	3.8 (-0.4, 8.1)
Medial femoral condyle	42.0 ± 3.8	38.9 ± 3.9	3.2 (-0.3, 6.6)	45.9 ± 4.1	43.0 ± 5.0	2.1 (-1.9, 6.1)	37.9 ± 4.7	34.6 ± 4.0	4.4 (0.4, 8.3)*
Lateral tibia	28.8 ± 4.0	29.2 ± 4.2	-1.0 (-4.7, 2.6)	36.8 ± 5.1	37.9 ± 5.6	-2.1 (-6.7, 2.5)	20.2 ± 3.4	19.9 ± 3.4	0.2 (-3.0, 3.4)
Lateral femoral condyle	42.7 ± 4.3	40.8 ± 3.5	0.8 (-3.0, 4.5)	47.3 ± 4.5	45.0 ± 4.4	0.6 (-3.4, 4.6)	37.8 ± 4.8	37.1 ± 4.0	0.6 (-3.6, 4.8)
Trochlear	46.2 ± 3.8	47.8 ± 6.1	1.1 (-4.1, 6.3)	50.3 ± 6.0	48.0 ± 3.1	1.3 (-3.8, 6.4)	45.0 ± 7.0	44.1 ± 5.4	0.7 (-5.4, 6.8)
Patella	36.1 ± 4.9	37.6 ± 4.1	-2.3 (-6.7, 2.1)	43.1 ± 5.4	44.6 ± 4.5	-2.3 (-7.2, 2.5)	29.2 ± 5.1	30.7 ± 4.2	-2.3 (-6.9, 2.2)

T2 values are presented as mean (± standard deviation). 95% CI=95% confidence interval. * Significant difference between the two groups ($P < 0.05$). # Adjusting for age, gender and BMI.

Table 4 Two-year change of T2 value in ACLR participants from baseline to follow-up using paired-t test

	Full-thickness T2 (ms)				Superficial layer T2 (ms)				Deep layer T2 (ms)			
	BL	FU	Mean change (95% CI)	P value	BL	FU	Mean change (95% CI)	P value	BL	FU	Mean change (95% CI)	P value
Medial tibia	32.2 ± 4.8	32.0 ± 4.8	-0.2 (-1.6, 1.1)	0.7	39.0 ± 5.4	39.5 ± 6.1	0.5 (-1.0, 2.0)	0.5	25.3 ± 5.1	24.1 ± 4.4	-1.5 (-3.5, 0.6)	0.19

Medial femoral condyle	41.1 ± 3.0	41.1 ± 3.7	0.01 (-1.3, 1.5)	0.9 8	44.8 ± 3.9	46.0 ± 4.9	1.2 (-0.4, 2.8)	0.1 3	37.1 ± 4.1	35.8 ± 4.0	-1.3 (-3.0, 0.4)	0.13
Lateral tibia	29.0 ± 3.2	27.7 ± 2.3	-1.3 (-2.9, 0.4)	0.1 3	36.9 ± 4.2	35.7 ± 4.0	-1.2 (-3.3, 0.9)	0.2 5	20.4 ± 2.7	19.0 ± 1.6	-1.4 (-2.8, -0.04)	0.04
Lateral femoral condyle	42.4 ± 4.5	42.3 ± 4.2	-0.1 (-1.2, 1.4)	0.8 8	47.0 ± 4.9	47.2 ± 4.7	-0.3 (-1.0, 1.5)	0.6 3	37.1 ± 4.8	37.0 ± 5.0	-0.2 (-1.9, 1.5)	0.81
Trochlear	46.0 ± 5.0	45.3 ± 5.2	-0.7 (-3.2, 1.8)	0.5 7	48.4 ± 5.8	47.6 ± 5.7	-0.8 (-3.4, 1.7)	0.5 0	43.3 ± 5.7	42.6 ± 5.3	-0.7 (-3.5, 2.2)	0.63
Patella	36.2 ± 5.4	36.6 ± 3.9	0.4 (-1.5, 2.2)	0.6 7	42.4 ± 5.9	43.2 ± 4.4	0.8 (-1.0, 2.7)	0.3 4	30.1 ± 5.3	29.8 ± 4.0	-0.3 (-2.3, 1.7)	0.77

T2 values presented as mean (± standard deviation). 95% CI=95% confidence interval. Change of T2=follow-up T2–baseline T2, thus negative values represent a decrease in T2 while positive values represent an increase. BL=Baseline; FU=Follow-up.

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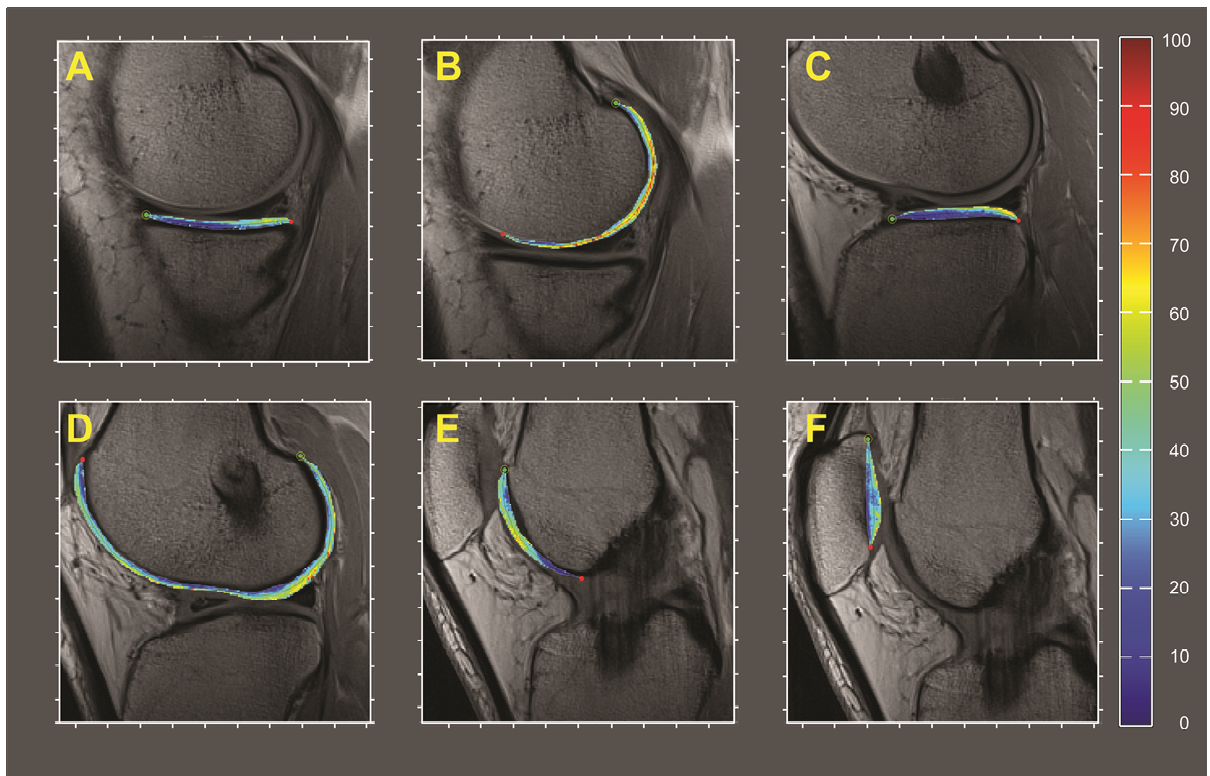


Figure 1 .

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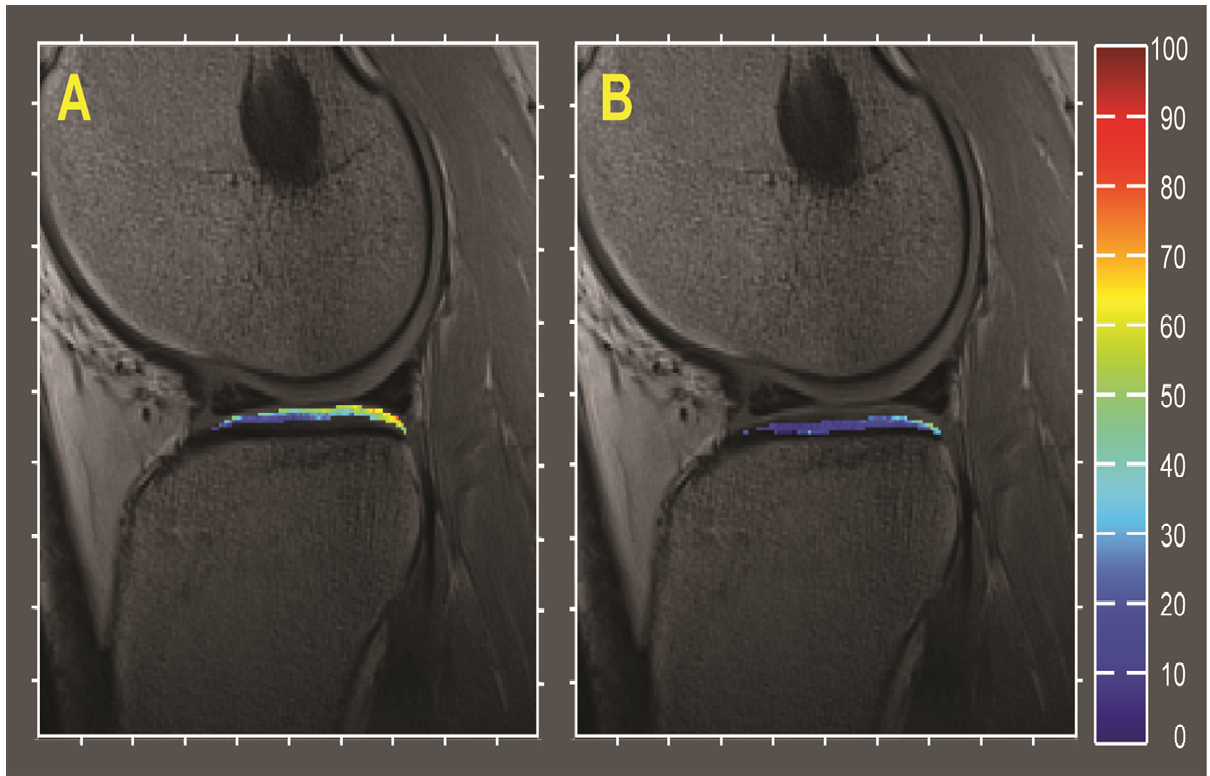
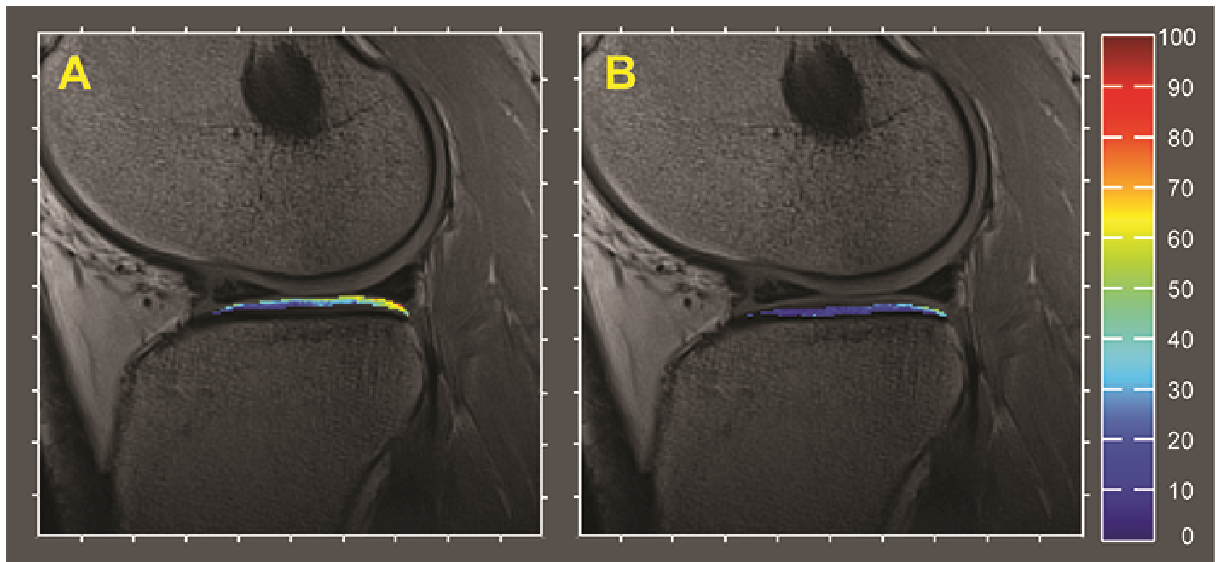


Figure 2 .

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Graphical abstract .

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