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Quantitative evaluation of the tibiofemoral joint cartilage by T2 mapping in patients with acute anterior cruciate ligament injury vs contralateral knees: results from the subacute phase using data from the NACOX study cohort

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SUMMARY

Objective: Immediate cartilage structural alterations in the acute phase after an anterior cruciate ligament (ACL) rupture may be a precursor to posttraumatic osteoarthritis (PTOA) development. Our aim was to describe changes in cartilage matrix in the subacute phase of the acutely ACL-injured knee compared to the contralateral uninjured knee.
Design: Participants ($n = 118$) aged 15–40 years with an acute ACL injury were consecutively included in subacute phase after acute ACL-injury and underwent MRI (mean 29 days post trauma) of both knees. Mean T2 relaxation times, T2 spatial coefficient of variation and cartilage thickness were determined for different regions of the tibiofemoral cartilage. Differences between the acutely ACL-injured and uninjured knee were evaluated using Wilcoxon signed-rank test.
Results: T2 relaxation time in injured knees was increased in multiple cartilage regions from both medial and lateral compartment compared to contralateral knees, mostly in medial trochlea and posterior tibia (P-value<0.001). In the same sites of injured knees, we observed significantly thinner cartilage. Moreover, injured knees presented shorter T2 relaxation time in superficial cartilage on lateral central femur and trochlea (P-value<0.001), and decreased T2 spatial coefficient of variation in lateral trochlea and load bearing regions of medial-central femoral condyle and central tibia in both compartments.
Conclusion: Small but statistically significant differences were observed in the subacute phase between ACL-injured and uninjured knee in cartilage T2 relaxation time and cartilage thickness. Future longitudinal observations of the same cohort will allow for better understanding of early development of PTOA.
Trial registration number: NCT02931084.

Introduction

A common consequence of anterior cruciate ligament (ACL) injury is early onset knee osteoarthritis (OA)[1,2]. The frequency of post traumatic OA (PTOA) after ACL injury is reported to be as high as 87%[1]. To reduce the risk for knee joint deterioration by secondary prevention[3] it is necessary to understand the complexity and

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multifactorial nature of posttraumatic osteoarthritis (PTOA) development. Acute knee trauma may cause immediate cartilage and subchondral lesions[4] and an outflow of inflammatory cytokines[5], both of which could initiate and facilitate OA development. Since several joint structures in addition to the ACL are usually affected, including other ligaments and menisci, the joint-loading patterns may be substantially altered[6]. This, together with possible re-injuries to the knee[7] may gradually affect the bone remodeling and bone shape[6] and further influence the progression of the disease.

During the past decades magnetic resonance imaging (MRI) has become the method of choice to visualize knee cartilage. In clinical settings, the capability of conventional MRI sequences to detect the changes caused by traumatic impact to the cartilage is limited to macroscopic lesions. Investigating ultrastructural tissue alterations in the acute phase can help in better understanding the development of knee OA secondary to ACL injury. T2 mapping provides a noninvasive means to detect changes in cartilage matrix. Cartilage T2 relaxation time reflects changes in tissue hydration and collagen fibril network, and has been reported to correlate with the biomechanical properties of the tissue[8,9]. T2 values increase with tissue degeneration and the method is capable of revealing subtle macromolecular alterations invisible to knee X-rays, computer tomography (CT) or conventional MRI[10]. Several clinical studies have demonstrated the ability of T2 mapping to identify patients with OA and to predict early knee OA onset[11]. Furthermore, increased T2 values following ACL trauma or ACL-surgery have been postulated to be linked with later cartilage degradation.

Several studies have examined the relationship between ACL rupture and subsequent cartilage damage by T2 relaxation time[12–16]. However, only a few of them have reported these parameters before reconstruction surgery. Those studies typically involved relatively small cohorts ranging from 11 to 64 patients[14,15,17–19]. Further, comparisons with findings from the contralateral uninjured knee are rare[19]. Ideally pre-injury images should have been obtained in proximity before the knee trauma in order to better be able to evaluate the acute cartilage changes. However, this is virtually unfeasible to accomplish in clinical study. Thus, in order to get new insights into potential changes of cartilage parameters associated with an acute ACL injury, we considered the contralateral knee to serve as a proxy to the status of the injured knee[20] before the acute trauma.

Hence, the aim of this study was to describe cartilage parameters of acutely ACL-injured knees shortly after the injury as assessed by T2-mapping compared to the contralateral uninjured knee. We also evaluated cartilage thickness and spatial heterogeneity of T2 relaxation time values.

Methods

Study design and participants

This study is a cross-sectional analysis of baseline MRI data of a subset of patients included in the prospective, cohort NACOX study[21], where we consecutively included all patients seeking medical care for an acute knee injury in our region's catchment area, Linköping, Sweden (population of approximately 200,000). The recruitment took place between October 2016 and October 2018. The study has been approved by the Swedish Ethical Review Authority (Dnr 2016/44-31) and prospectively registered (NCT02931084).

In the NACOX study, patients were included according to following criteria: age 15–40 years, ACL injury no more than 6 weeks from presentation. Exclusion criteria were: 1) previous ACL injury/reconstruction to the injured knee, 2) fractures that required separate treatment, 3) inability to understand written and spoken Swedish, 4) cognitive impairments, 5) other illnesses or injuries that impaired function (e.g., fibromyalgia, rheumatic diseases and other diagnoses associated with chronic pain). For the present analysis, patients with contralateral ACL injuries were excluded. All patients received written information about the study before attendance and approved participation in written consents.

During the inclusion time, 263 patients were examined by a clinician. Each patient was assessed by an orthopedic surgeon and a physiotherapist within 2 weeks after medical contact. All patients with medical history and clinical examination suggesting acute ACL injury, were referred for bilateral knee MRI examination. The diagnosis of ACL rupture was confirmed based on the MRI findings using a standard protocol. This protocol also implied information about concurrent structural abnormalities in cartilage, bone marrow, menisci and other ligaments (Table S1). The assessment of concurrent injuries was performed by consensus agreement between a radiologist and an orthopaedic surgeon. Ligament and meniscal injuries were classified according to Roemer *et al.*, 2014[22]. Eventually, 118 patients fulfilled the inclusion criteria and were included for this analysis (Fig. 1).

MRI protocol

MRI examinations were performed on both knees using a 3 T scanner (Ingenia, Philips Healthcare, Best, the Netherlands) equipped with a 16-channel coil. The mean time from injury to MRI was 29 days (range 4–61 days). The imaging protocol included a sagittal

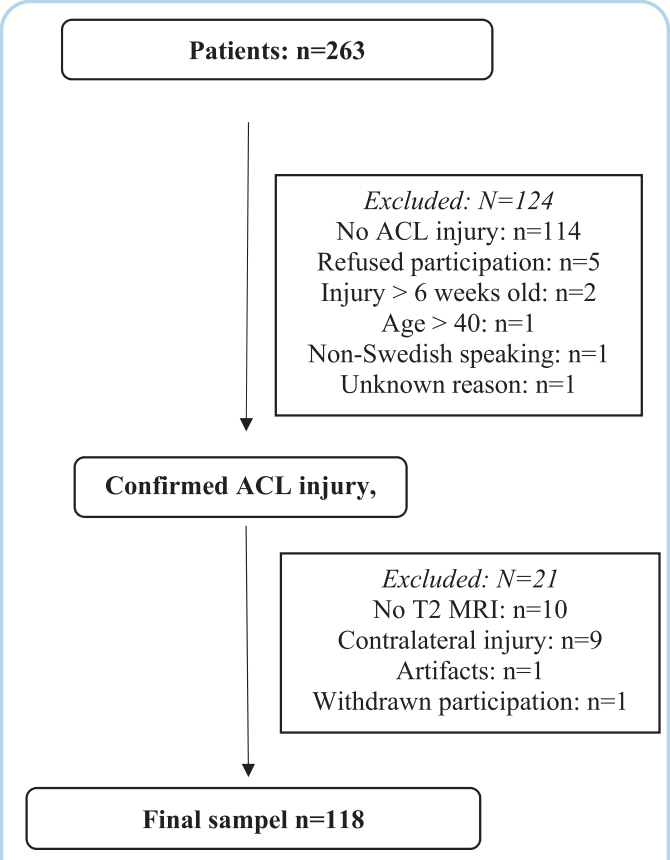

Fig. 1 Osteoarthritis and Cartilage

Flowchart of included patients.

proton density (PD) weighted sequence (TR/TE = 1800/20 ms, ETL 10, FOV 160 × 145 mm2, acquisition matrix 516 × 384, reconstructed matrix 528, spatial resolution 0.31 × 0.38 mm2, number of slices 28, slice thickness 3 mm, slice gap 0.3 mm, flip angle 40°, acquisition time 2:58 min), an axial PD FatSat sequence (TR/TE = 3981/35 ms, ETL 15; FOV 140 × 140 mm2, acquisition matrix 332 × 330, reconstructed matrix 512, spatial resolution 0.42 × 0.42 mm2, slice thickness 3 mm, slice gap 0.3 mm, acquisition time 4:15 min), a sagittal PD FatSat sequence (TR/TE = 3400/30 ms, ETL 15; FOV 160 × 145 mm2, acquisition matrix 468 × 399, reconstructed matrix 528, spatial resolution 0.31 × 0.40 mm2, slice thickness 3 mm, slice gap 0.3 mm, acquisition time 3:56 min), a coronal PD FatSat sequence (TR/TE = 3572/30 ms, ETL 16; FOV 160 × 140 mm2, acquisition matrix 516 × 332, reconstructed matrix 528, spatial resolution 0.31 × 0.42 mm2, slice thickness 3 mm, slice gap 0.3 mm, acquisition time 3:56 min), a sagittal PD FatSat 3D sequence (TR/TE = 1300/185 ms, ETL = 63, FOV = 144 × 162 mm2, acquisition matrix 228 × 226, recon matrix 448, spatial resolution 0.63 × 0.63 mm2, slice thickness 0.63 mm, acquisition time 6:31 min).

The patients were centered in the scanner, lying down with the examining knee in the channel coil during day- and evening time. The examination started when participants arrived at the radiology department without any recommendations regarding rest or physical activity before the examination.

Cartilage segmentation

Segmentation of femoral and tibial cartilage was performed manually on T2-weighted images by a single segmenter (B.T., 1 year of experience, supervised by V.C., 8 years of experience). Six slices per knee were manually selected and segmented, three slices from the central part of the lateral femur and tibia condyle and three slices from the central part of the medial femur and tibia condyle. We assessed both injured and uninjured knee. We selected the centermost slices for the lateral and the medial compartments (maximal load bearing part of the tibiofemoral joint and showing most of cartilage). This generated a total of 1416 segmented slices. Seventeen regions were defined (Fig. 2), nine in the lateral compartment and eight in medial compartment (cartilage in anterior aspect of trochlea is usually not visible in medial compartment from sagittal sles).

Image analysis

T2 relaxation time maps were generated by fitting signal intensities to a two-parameter monoexponential decay function for each pixel. For each region of interest (ROI), the average T2 of the three consecutive slices, weighted by the number of pixels, was obtained for full-thickness, superficial and deep half cartilage (Fig. 2). Additionally, for each ROI the relative spatial distribution of T2 was assessed via spatial coefficient of variation (CV-T2), calculated as the ratio of the standard deviation of T2 for the ROI to the mean T2 value of the same ROI. Overall data analysis was performed using an in-house MATLAB-based software (MathWorks Inc., Natick, MA) for segmentation and T2 calculation.

Furthermore, a thickness calculation tool based on Laplace's equation was applied to the segmented images and the mean cartilage thickness was then measured for each ROI[23].

Intrareader reliability

Intrareader agreement was assessed by re-segmenting three times five randomly selected knees and calculating the root-mean-square coefficient of variation (RMS-CV) of T2 for each region. The test was blinded with 2 weeks between the segmentations.

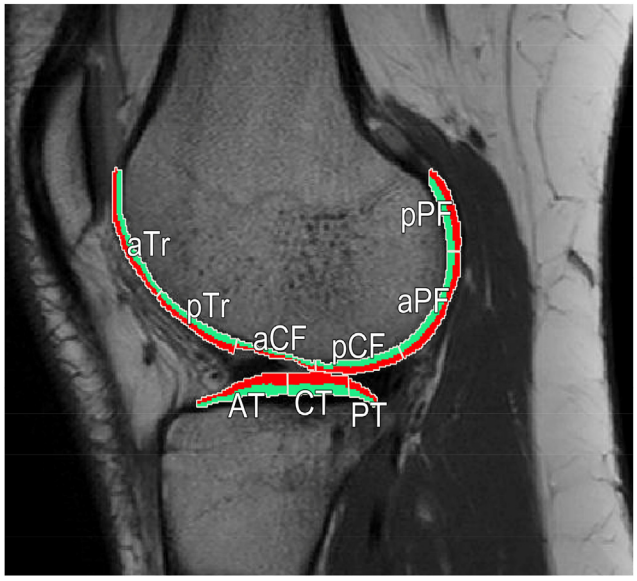

Fig. 2 Osteoarthritis and Cartilage

Illustration of the regions of interest in femoral and tibial cartilage on a sagittal slice from the center of the lateral femoral condyle. Anterior trochlea (aTr), posterior trochlea (pTr), anterior central femur (aCF), posterior central femur (pCF), anterior part of posterior femur (aPF), posterior part of posterior femur (pPF), anterior tibia (AT), central tibia (CT), posterior tibia (PT). Superficial and deep cartilage regions are marked in red and green, respectively.

Statistical analysis

Differences between the injured and contralateral control knee in cartilage T2 values, CV-T2 and thickness were assessed for each ROI using Wilcoxon signed-rank test, with Benjamini-Hochberg correction for multiple comparisons. We also did the analyses stratified by time from injury to MRI (≤21 days or >21 days) to examine whether the results would change with respect to the time

Age, years, mean (SD, range)	25 (7.0, 15–40)
Sex, female, *n* (%)	54 (46)
BMI, mean (SD, range)	24 (3.7, 18–46)
Injured knee right, *n* (%)	59 (50)
Time from injury to MRI, days median (range)	29 (4–61)
IKDC-level, *n*, (%)*	
Level I	64 (54)
Level II	18 (15)
Level III	36 (31)

* IKDC-level = sports level participation before injury. Level I, pivoting and contact sports; level II, pivoting and non-contact sports; level III, sports with no pivoting and no contact.

Table I Osteoarthritis and Cartilage

Baseline characteristics

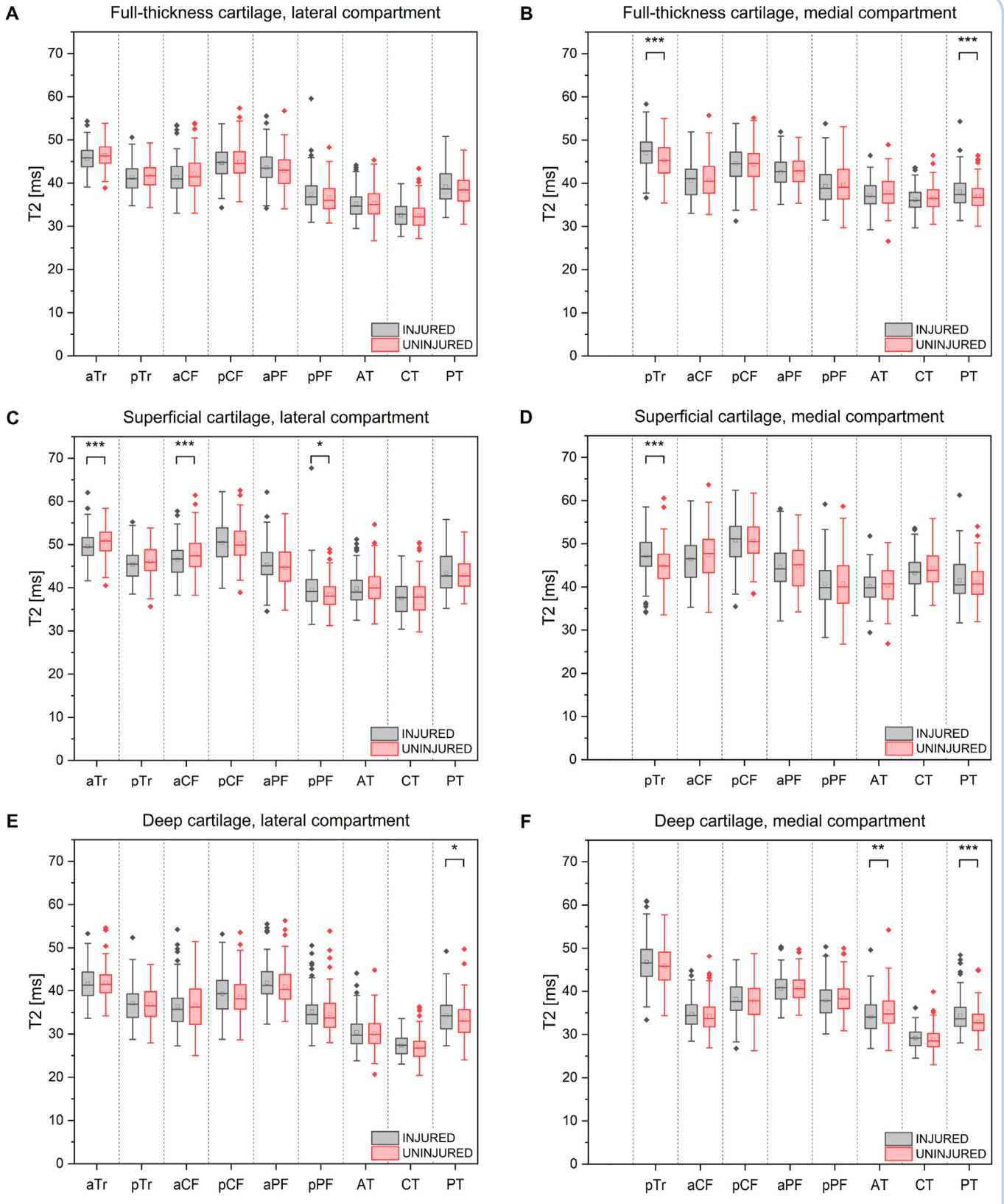
A
Full-thickness cartilage, lateral compartment
B
Full-thickness cartilage, medial compartment
C
Superficial cartilage, lateral compartment
D
Superficial cartilage, medial compartment
E
Deep cartilage, lateral compartment
F
Deep cartilage, medial compartment
T2 [ms]
0
10
20
30
40
50
60
70
aTr
pTr
aCF
pCF
aPF
pPF
AT
CT
PT
INJURED
UNINJURED
***
**
*

Fig. 3

from the initial trauma. The effect size estimates of the differences were calculated as $r = Z/\sqrt{2N}$, where Z is z-statistic of the Wilcoxon test, and N is the sample size. Finally the effect on cartilage T2 values of concomitant meniscal tear within the same compartment of the injured knee was assessed, and T2 relaxation times in patients with and without meniscal tear were compared using Mann–Whitney test, with Benjamini-Hochberg correction for multiple comparisons. The effect size estimates for the Mann–Whitney test were calculated as $r = Z/\sqrt{N}$. For all tests, statistical significance was set at a two-tailed P-value < 0.05. The effect size was considered small for $r < 0.30$, medium for $0.30 \leq r < 0.50$ and large for $r \geq 0.50$. All statistical analyses were conducted using SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Patient characteristics

The mean age of study cohort was 25 years with 46% women, and the mean time from knee injury to MRI examination was 29, standard deviation (SD 13) days, range 4–61 days (Table I). The physical activity leading to the ACL-injury was predominantly soccer (36%), downhill skiing (20%) and floorball, an indoor team sport similar to hockey (19%), which together accounted for 75% of the injuries.

Concurrent structural abnormalities on MRI

The majority of the patients (92%) presented bone marrow lesions in the injured knee. In 81% of the cases, the presence of an extensive oedema pattern consistent with pivot shift injury was confirmed. Most of the participants (85%) presented normal cartilage, and only seven subjects presented lesions in tibiofemoral joint. Twenty patients (17%) had lesions in the lateral collateral ligament (14% oedemas, 3% partial ruptures), while in 24 cases the medial collateral ligament presented either partial rupture (12%) or complete disruption (5%). Meniscal abnormalities were more frequent in the medial meniscus than in lateral meniscus. The number of knee joints affected with structural abnormalities in cartilage, menisci and collateral ligaments in different compartments is presented in Table S1.

Intrareader reliability

The intrareader reliability was excellent (RMS-CV < 5%) for all ROIs, except for superficial anterior central femur (aCF) in the lateral compartment (RMS-CV = 5.0%). The RMS-CVs were below 2% in over 50% of the ROIs, and the average for femoral and tibial ROIs were 2.0% (range 0.59–5.0%) and 2.4% (1.1–4.7%), respectively.

Cartilage T2 relaxation time

Statistically significant differences in T2 relaxation times between injured and uninjured knees were observed in both medial and lateral compartments [Fig. 3 and Fig. 4(A)–(B)], although mostly with small effect sizes. Overall median differences were relatively small (below 1–2 ms), and the only difference greater than 2 ms observed in medial trochlea (pTr, Fig. 4). As compared with uninjured knees, increased T2 relaxation times with moderate effect sizes were observed only in two sites of the medial compartment of injured knees, namely in superficial posterior trochlea (pTr, effect size $r = 0.36$, P-value < 0.001) and in deep posterior tibia (PT, $r = 0.33$, P-value < 0.001). The differences remained significant in the same sites when full-thickness regions were considered, however the effect sizes became small ($r = 0.28$ and $r = 0.22$, respectively). In the lateral compartment, only small effect sizes were observed in several regions, also including superficial aCF and deep posterior tibia (PT). Median T2 values and interquartile ranges for each ROI in injured and uninjured knee are reported in Supplemental Table S2.

In the stratified analysis (by time from injury to MRI), differences with moderate effect sizes were seen in the lateral compartment in superficial posterior femur (pPT) and deep central tibia (CT) of subjects imaged within 21 days, however they disappeared for subjects imaged after 21 days. On the contrary, the difference in superficial lateral trochlea (aTr) was significant with moderate effect sizes only after 21 days. The differences between injured and uninjured knees observed in medial superficial trochlea (pTr) and deep PT were confirmed in both strata, although the median differences (Fig. 4) and effect sizes became smaller in patients imaged after 21 days (full data available in Supplemental Tables S3 and S4).

Cartilage T2 spatial coefficient of variation

The spatial coefficients of variation calculated from T2 maps presented statistically significant decreased values with moderate effect size only in lateral trochlea in injured knees (aTr, $r = 0.31$, P-value < 0.001) as compared to the contralateral uninjured knees (Fig. 5, Supplemental Table S5). This difference was confirmed both strata in the stratified analysis. Differences with moderate effect sizes in anterior and central tibia (AT, CT) were observed only in patients imaged within 21 days (full data available in Supplemental Tables S6 and S7).

Cartilage thickness

As shown in Fig. 6, lower cartilage thickness with moderate effect size was observed in injured knee as compared with contralateral knee only on the medial compartment in trochlea (pTr, $r = 0.34$, P-value < 0.001). Median thickness values and interquartile ranges for each ROI are reported in Supplemental Table S8. Thickness and mean T2 values were not related in almost all of the regions. A significantly weak negative correlation was found only in lateral aCF of injured knees ($r = -0.34$, P-value < 0.01) and uninjured knee ($r = -0.23$, P-value = 0.01), in medial aCF of injured knees ($r = -0.19$, P-value = 0.04), in lateral aPF of injured knees ($r = -0.21$, P-value = 0.02) and in lateral AT of uninjured knees ($r = -0.34$, P-value < 0.01). The stratified analysis confirmed the significant difference in medial pTr for both strata, however the

T2 values for injured and uninjured contralateral leg in lateral and medial full-thickness cartilage regions (A,B), superficial cartilage regions (C,D) and deep cartilage regions (E,F). Squares and lines inside the boxes indicate means and medians, respectively. Asterisks indicate statistical significance after correction for multiple testing (*P-value < 0.05, **P-value < 0.01, ***P-value < 0.001). aTr = anterior trochlea, pTr = posterior trochlea, aCF = anterior central femur, pCF = posterior central femur, aPF = anterior part of posterior femur, pPF = posterior part of posterior femur, AT = anterior tibia, CT = central tibia, PT = posterior tibia.

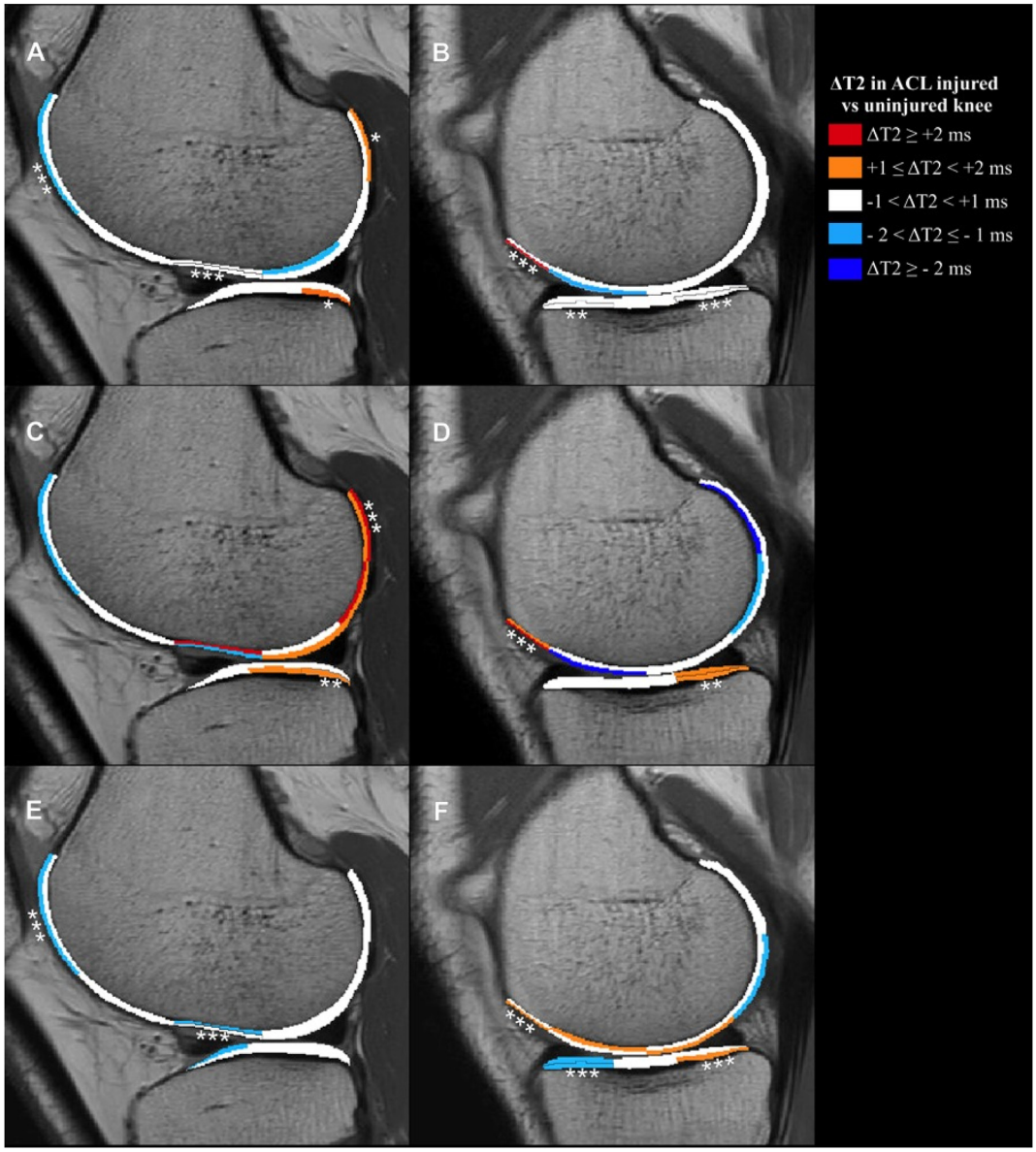

Fig. 4

Osteoarthritis and Cartilage

Median differences in T2 relaxation time values (ΔT2) between ACL injured and uninjured knee for superficial and deep cartilage regions of interest of the lateral (left column) and medial compartment (right column). ΔT2 for all patients (A,B), and stratified by the time to MRI from the injury: within 21 days (C,D) and after 21 days (E,F). Asterisks indicate statistically significant differences (*P-value < 0.05, **P-value < 0.01, ***P-value < 0.001).

effect size became small in subjects imaged after 21 days from injury. (full data provided in Supplemental Tables S9 and S10).

Effect of meniscal status

T2 were longer in ACL injured knees with associated meniscal tear vs no tear, mostly in medial compartment with small effect sizes. However, all significance differences disappeared after correction for multiple comparisons (Supplemental Table S11).

Discussion

The presence of knee cartilage lesions in ACL-deficient knees has been suggested to be a risk factor for PTOA[24,25]. Early subtle cartilage changes secondary to the trauma could play a role in the development of OA after ACL injury. In this study, T2 mapping was used to assess the state of both superficial and deep zones of cartilage matrix about 4 weeks after acute ACL injury. In brief, we found tibiofemoral cartilage of injured and contralateral uninjured

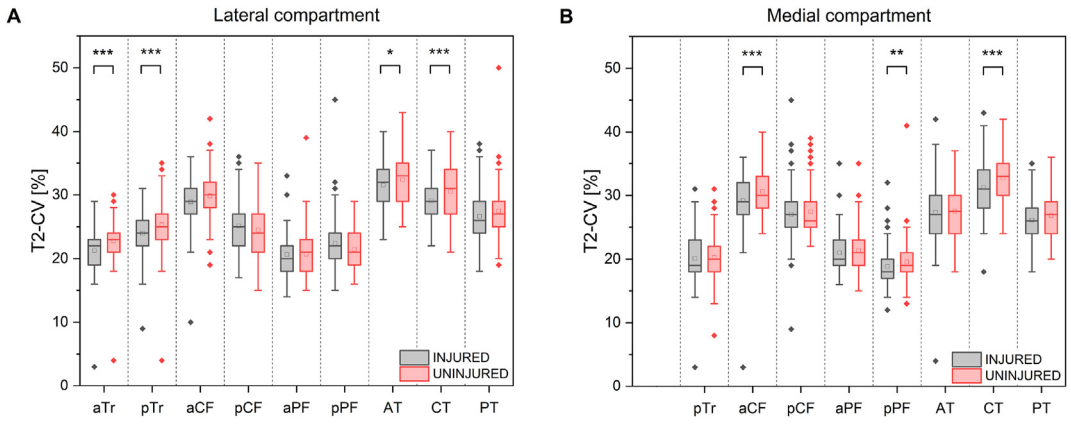

Fig. 5 Osteoarthritis and Cartilage

Coefficients of variation (CV) of T2 in lateral and medial cartilage regions (A,B) for injured and uninjured contralateral leg. Squares and lines inside the boxes indicate means and medians, respectively. Asterisks indicate statistical significance after correction for multiple testing (*P-value < 0.05, **P-value < 0.01, ***P-value < 0.001). aTr = anterior trochlea, pTr = posterior trochlea, aCF = anterior central femur, pCF = posterior central femur, aPF = anterior part of posterior femur, pPF = posterior part of posterior femur, AT = anterior tibia, CT = central tibia, PT = posterior tibia.

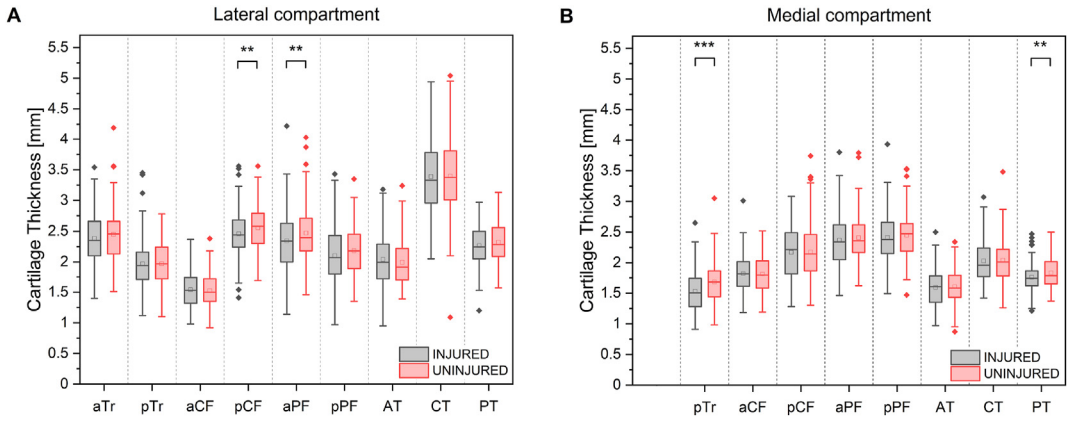

Fig. 6 Osteoarthritis and Cartilage

Cartilage thicknesses of lateral and medial regions (A, B) for injured and uninjured contralateral leg. Squares and lines inside the boxes indicate means and medians, respectively. Asterisks indicate statistical significance after correction for multiple testing (*P-value < 0.05, **P-value < 0.01, ***P-value < 0.001). aTr = anterior trochlea, pTr = posterior trochlea, aCF = anterior central femur, pCF = posterior central femur, aPF = anterior part of posterior femur, pPF = posterior part of posterior femur, AT = anterior tibia, CT = central tibia, PT = posterior tibia.

knee to exhibit small differences in T2 relaxation time at multiple joint sites. The largest differences were seen in the medial compartment, where of ACL-injured knees displayed increased T2 relaxation times, in trochlea and PT. Moreover, the same regions exhibited thinner cartilage in the injured joint as compared to the contralateral. Those findings, higher T2 and lower thickness, might suggest early pathological changes of the articular cartilage in the injured knee[26,27].

Particularly, increased T2 has been reported to correlate with high water content and deterioration of collagen matrix structure, which are considered to be early signs of knee OA[9,28]. In this study, T2 relaxation times were mostly longer in the injured knee than in the non-injured contralateral knee, in both central part on medial and lateral maximal weight-bearing areas and anterior/posterior regions of femur and tibia. These findings are consistent with previous studies using quantitative MRI techniques for assessing cartilage prior to ACL reconstruction, which have observed increased relaxation time values in injured knees as compared to healthy controls or healthy contralateral knees[14,15,17–19,29]. The relative differences observed in our cohort are rather small, mostly

below clinical significance, and due to the cross-sectional nature of the study, the true nature and causes to the observed differences remains to be determined. Hypothetically, they can be interpreted as a result of relative unloading of the injured (painful) knee in the immediate post injury period, or early changes consequential to altered mechanics due to the ACL deficiency. The differences may hypothetically also be influenced by acute inflammation induced by the ACL injury that may affect cartilage metabolism[30]. The acute impact of pivot-shift trauma, the most frequent cause to ACL injury, is typically contusion to the posterior part of the lateral tibia plateau and to the central part of the lateral femoral condyle[31,32]. Most of the patients presented on MRI bone oedema pattern typically associated with the pivot shift injury. However, we observed only small T2 differences in these regions in injured vs contralateral non-injured knee.

The medial compartment is the most affected by primary knee OA[33], and several cohort studies on subjects with ACL injury reported osteochondral lesions on arthroscopy in both compartments but predominantly in the medial side of the tibiofemoral joint[34–36]. A recent MRI study on the progression sub-cohort of the Osteoarthritis Initiative has reported higher prevalence of cartilage damage in the medial tibiofemoral for patients with ACL tear as compared to the lateral side[37]. Furthermore, individuals with complete ACL tears were more likely to display cartilage lesions in lateral PT and medial anterior femur, two sites that both showed increased cartilage T2 in the injured knees of our cohort compared to the respective regions in contralateral uninjured knees, suggesting alteration of cartilage matrix. The relatively high frequency of associated injuries to medial meniscus reported in our cohort could partially explain the larger T2 differences found in the medial compartment as compared to the lateral compartment. Meniscal lesions are frequently found in knee with acute ACL tears[38,39] and are associated with increased probability of damaging the articular cartilage in the same compartment[40]. However, in the present study it does not seem to be a strong association between meniscal tear and longer T2 at baseline.

In the lateral compartment, the largest differences were observed in anterior trochlea, where superficial T2 of injured knees was surprisingly found to be shorter than in corresponding regions of the contralateral knee. This is unlikely a result of concomitant or pre-existing occult cartilage lesions in contralateral joint, as the stratified analysis seems to suggest. One explanation for the decreased T2 values in the injured knee lateral trochlea may be a possible initial physiologic response of the tissue in attempt to repair or adapt to the abnormal mechanical demands. This relaxation time shortening has been rarely observed and reported only in few early degeneration studies[41–43], although the underlying mechanism has never been investigated. Furthermore, our analysis revealed decreased spatial coefficient of variation of T2 in several areas of the injured knees, and particularly in lateral trochlea. The spatial coefficient of variation of T2 has never been investigated before in cartilage and therefore is not possible to provide a clear physical interpretation of our results. Nonetheless, as cartilage T2 values reflect differences between the histological zones[28,44], one possible explanation for the decreased spatial variance in T2 could be the loss of tissue organization as a result of degradation in the injured joint. Finally, differences in regional median and spatial coefficient variation of T2 values may be partially explained by the relatively high rate of collateral ligaments injuries. Particularly medial ligament injuries results in increased lateral cartilage compression and posterolateral corner injuries[45].

Previous studies using quantitative MRI techniques for assessing cartilage prior to ACL reconstruction have reported heterogeneous findings with respect to the specific regions affected[14,15,17–19]. Tao *et al.*[15] reported prolonged T2 and T2* in ACL-ruptured patients in full-thickness and superficial layers of medial and lateral tibiofemoral joint. The most affected region was lateral tibia and no changes were reported in trochlea, or in deep cartilage layer. However, the generalizability of their findings might be limited by the low number of subjects included (23 patients), the lack of subregional analysis (the whole lateral and medial femur and tibia compartments were considered) and the delayed imaging time for some cases (up to 6 months from injury). In a case-control study Palmieri-Smith *et al.*[17] reported increased T2-relaxation time in superficial central lateral tibia and deep medial tibia in ACL injured knees. Furthermore, they found no difference in cartilage thickness in injured knees as compared to control group. It is again challenging to make any comparisons with our study as this study included only 11 patients with confirmed bone marrow lesions. Finally, three studies reported differences in posterior lateral tibia[14,18,19]. Li *et al.*[14] found prolonged T1ρ values in posterior lateral tibia cartilage of 12 patients with ACL-injury as compared to a control group of healthy knees. No statistically significant differences were found in T2, probably due to low statistical power. Su *et al.*[18] reported both T1ρ and T2 elevated in the superficial posterolateral tibia in a group of 15 patients with acute ACL injuries as compared to healthy volunteers. A recent multi-center study used voxel-based relaxometry to investigate the differences in cartilage relaxation times in a cohort of 64 patients with ACL tears. Shortly after the injury, elevated T1ρ and T2 were reported in injured knee as compared to uninjured contralateral knee, particularly in the posterolateral tibia[19]. Although drawing specific conclusions is not possible on the basis of a small number of studies with relatively low sample size and lacking uniform definitions for regional subdivision of cartilage, the heterogeneous findings reported in literature, together with our observations suggesting involvement of multiple cartilage sites, might suggest the existence of different patterns for different sites. Furthermore, our laminar analysis of T2 suggested that differences between injured and contralateral knees were seen only in superficial cartilage for femur and only in deep cartilage in tibia. This might indicate different tissue-specific physiological and pathological processes occurring in femur and tibia and a more active role played in tibia by crosstalk at bone-cartilage interface in the acute ACL injured knee[46].

Future longitudinal research might help clarifying this hypothesis as well as the clinical significance of the observed differences between ACL injured and contralateral healthy knee and their impact to future development of osteoarthritis. Despite several studies have shown worsening of cartilage degeneration even after ACL reconstruction[47,48], the relationship between site specific changes and development of PTOA is still unclear. There was a trend towards prolonged T2 with meniscal tear vs no tear in the present study, yet not significant, but it could have an impact of the cartilage later on.

These research questions will be investigated in a future prospective study on the NACOX cohort.

In the analysis stratified by time from injury to MRI, we could not detect any strong evidence in support that the initial trauma event, or the resulting unloading/altered biomechanics after the knee trauma, affects the cartilage parameters in an early time-dependent global manner although certain specific sub regional effects cannot be excluded. On the other hand, as the majority of the patients were active in cutting and pivoting sports, regional variations in T2 relaxation might as well caused by cartilage alterations resulting from minor traumas occurred in either knee before the injury.

To the best of our knowledge, this study has the largest sample size on evaluating differences in tibiofemoral cartilage using T2 relaxation time. The assembled material is relatively close to the time for the ACL injury, and we evaluated both the injured and the

contralateral non injured knee. To obtain a more precise status of the joint, we further subdivided the cartilage in different regions of interests, ROIs and layers of depth. Furthermore, there is a relatively large age range between participants in a young population (15–40 years). This increases the generalizability of overall population-based changes over time on PTOA development. Eventually, the methodological approach in current study can also act as a tool to validate the T2 relaxation time as a radiological method on studying cartilage changes related to OA development since no universal methodological radiologic classification method exists right now. Nevertheless, the findings of this study have to be seen in light of several limitations. Importantly, the data is cross sectional, which prevents us from making conclusions of the true nature of the differences that we report. Changes over time are though also expected in the contralateral healthy joint due to potential weight transfer from the ACL-injured knee to the healthy contralateral knee. This may induce changes in the cartilage matrix of contralateral knee as well[49,50]. A second potential limitation is the presence of previous cartilage affection for this active population in the contralateral knee, which cannot be excluded despite no ACL-injury. Another possible limitation is the lack of specific recommendations for the patients regarding rest or physical activity before the MRI examination, which may have small impacts on T2 measurement. Another aspect to consider is the manual segmentation. Individual knowledge and experiences in a segmenter may influence the results. Although our intrareader analysis suggested a very low error, automatic segmentation when possible, is preferred.

In conclusion, several statistically significant but modest differences in cartilage compositional parameters as evaluated by T2 relaxation time and cartilage thickness were observed in knee joints shortly after ACL acute injury vs the non-injured contralateral knee. The differences (longer T2 relaxation times) were mainly seen in the medial compartment. These cartilage parameters will be further monitored over time in this cohort using knee MRI with planned follow-up at 24 months after injury. These future longitudinal analyses will hopefully allow for new insights to early PTOA development.

Author contributions

VC, BET, JK, RF, MN, HG were responsible for the study design and protocol. BET and HG recruited patients. VC, MH were responsible for the statistical analyses. All authors were involved in interpreting the data and wrote the manuscript and all authors commented and approved the final version. All authors had also full access to all data.

Conflict of interest

ME declares serving on an advisory board for Pfizer (Tanezumab, November 2019). The other authors declare no conflict of interest.

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Supplementary data

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References

1. Lohmander LS, Ostenberg A, Englund M, Roos H. High prevalence of knee osteoarthritis, pain, and functional limitations in female soccer players twelve years after anterior cruciate ligament injury. Arthritis Rheum 2004;50:3145–52.
2. Lie MM, Risberg MA, Storheim K, Engebretsen L, Oiestad BE. What's the rate of knee osteoarthritis 10 years after anterior cruciate ligament injury? An updated systematic review. Br J Sports Med 2019;53:1162–7.
3. Watt FE, Corp N, Kingsbury SR, Frobell R, Englund M, Felson DT, *et al.* Towards prevention of post-traumatic osteoarthritis: report from an international expert working group on considerations for the design and conduct of interventional studies following acute knee injury. Osteoarthritis Cartilage 2019;27:23–33.
4. Anderson DD, Chubinskaya S, Guilak F, Martin JA, Oegema TR, Olson SA, *et al.* Post-traumatic osteoarthritis: improved understanding and opportunities for early intervention. J Orthop Res 2011;29:802–9.
5. Struglics A, Larsson S, Pramhed A, Frobell R, Sward P. Changes in synovial fluid and serum concentrations of cartilage oligomeric matrix protein over 5 years after anterior cruciate ligament rupture: an exploratory analysis in the KANON trial. Osteoarthritis Cartilage 2018;26:1351–8.
6. Chaudhari AM, Briant PL, Bevill SL, Koo S, Andriacchi TP. Knee kinematics, cartilage morphology, and osteoarthritis after ACL injury. Med Sci Sports Exerc 2008;40:215–22.
7. Faltstrom A, Kvist J, Gauffin H, Hagglund M. Female soccer players with anterior cruciate ligament reconstruction have a higher risk of new knee injuries and quit soccer to a higher degree than knee-healthy controls. Am J Sports Med 2019;47:31–40.
8. Lammentausta E, Kiviranta P, Nissi MJ, Laasanen MS, Kiviranta I, Nieminen MT, *et al.* T2 relaxation time and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) of human patellar cartilage at 1.5 T and 9.4 T: Relationships with tissue mechanical properties. J Orthop Res 2006;24:366–74.
9. Nieminen MT, Rieppo J, Toyras J, Hakumaki JM, Silvennoinen J, Hyttinen MM, *et al.* T2 relaxation reveals spatial collagen architecture in articular cartilage: a comparative quantitative MRI and polarized light microscopic study. Magn Reson Med 2001;46:487–93.
10. Liebl H, Joseph G, Nevitt MC, Singh N, Heilmeier U, Subburaj K, *et al.* Early T2 changes predict onset of radiographic knee osteoarthritis: data from the osteoarthritis initiative. Ann Rheum Dis 2015;74:1353–9.
11. MacKay JW, Low SBL, Smith TO, Toms AP, McCaskie AW, Gilbert FJ. Systematic review and meta-analysis of the reliability and discriminative validity of cartilage compositional MRI in knee osteoarthritis. Osteoarthritis Cartilage 2018;26:1140–52.
12. Klocke NF, Amendola A, Thedens DR, Williams GN, Luty CM, Martin JA, *et al.* Comparison of T1rho, dGEMRIC, and quantitative T2 MRI in preoperative ACL rupture patients. Acad Radiol 2013;20:99–107.

13. Knox J, Pedoia V, Wang A, Tanaka M, Joseph GB, Neumann J, *et al*. Longitudinal changes in MR T1rho/T2 signal of meniscus and its association with cartilage T1p/T2 in ACL-injured patients. Osteoarthritis Cartilage 2018;26:689–96.
14. Li X, Kuo D, Theologis A, Carballido-Gamio J, Stehling C, Link TM, *et al*. Cartilage in anterior cruciate ligament-reconstructed knees: MR imaging T1{rho} and T2–initial experience with 1-year follow-up. Radiology 2011;258:505–14.
15. Tao H, Qiao Y, Hu Y, Xie Y, Lu R, Yan X, *et al*. Quantitative T2-mapping and T2*-mapping evaluation of changes in cartilage matrix after acute anterior cruciate ligament rupture and the correlation between the results of both methods. BioMed Res Int 2018;2018:7985672.
16. Williams A, Winalski CS, Chu CR. Early articular cartilage MRI T2 changes after anterior cruciate ligament reconstruction correlate with later changes in T2 and cartilage thickness. J Orthop Res 2017;35:699–706.
17. Palmieri-Smith RM, Wojtys EM, Potter HG. Early cartilage changes after anterior cruciate ligament injury: evaluation with imaging and serum biomarkers-A pilot study. Arthroscopy 2016;32:1309–18.
18. Su F, Hilton JF, Nardo L, Wu S, Liang F, Link TM, *et al*. Cartilage morphology and T1rho and T2 quantification in ACL-reconstructed knees: a 2-year follow-up. Osteoarthritis Cartilage 2013;21:1058–67.
19. Russell C, Pedoia V, Amano K, Potter H, Majumdar S, Consortium A-A. Baseline cartilage quality is associated with voxel-based T1rho and T2 following ACL reconstruction: a multicenter pilot study. J Orthop Res 2017;35:688–98.
20. Kozanek M, Van de Velde SK, Gill TJ, Li G. The contralateral knee joint in cruciate ligament deficiency. Am J Sports Med 2008;36:2151–7.
21. Kvist J, Gauffin H, Tigerstrand Grevnerts H, Ardern C, Hagglund M, Stalman A, *et al*. Natural corollaries and recovery after acute ACL injury: the NACOX cohort study protocol. BMJ Open 2018;8, e020543.
22. Roemer FW, Frobell R, Lohmander LS, Niu J, Guermazi A. Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS): longitudinal MRI-based whole joint assessment of anterior cruciate ligament injury. Osteoarthritis Cartilage 2014;22:668–82.
23. Jones SE, Buchbinder BR, Aharon I. Three-dimensional mapping of cortical thickness using Laplace's equation. Hum Brain Mapp 2000;11:12–32.
24. van Meer BL, Oei EH, Meuffels DE, van Arkel ER, Verhaar JA, Bierma-Zeinstra SM, *et al*. Degenerative changes in the knee 2 Years after anterior cruciate ligament rupture and related risk factors: a prospective observational follow-up study. Am J Sports Med 2016;44:1524–33.
25. Ichiba A, Kishimoto I. Effects of articular cartilage and meniscus injuries at the time of surgery on osteoarthritic changes after anterior cruciate ligament reconstruction in patients under 40 years old. Arch Orthop Trauma Surg 2009;129:409–15.
26. Potter HG, Jain SK, Ma Y, Black BR, Fung S, Lyman S. Cartilage injury after acute, isolated anterior cruciate ligament tear: immediate and longitudinal effect with clinical/MRI follow-up. Am J Sports Med 2012;40:276–85.
27. Li X, Benjamin Ma C, Link TM, Castillo DD, Blumenkrantz G, Lozano J, *et al*. In vivo T(1rho) and T(2) mapping of articular cartilage in osteoarthritis of the knee using 3 T MRI. Osteoarthritis Cartilage 2007;15:789–97.
28. Mosher TJ, Dardzinski BJ, Smith MB. Human articular cartilage: influence of aging and early symptomatic degeneration on the spatial variation of T2–preliminary findings at 3 T. Radiology 2000;214:259–66.
29. Pedoia V, Su F, Amano K, Li Q, McCulloch CE, Souza RB, *et al*. Analysis of the articular cartilage T1rho and T2 relaxation times changes after ACL reconstruction in injured and contralateral knees and relationships with bone shape. J Orthop Res 2017;35:707–17.
30. Thompson WO, Thaete FL, Fu FH, Dye SF. Tibial meniscal dynamics using three-dimensional reconstruction of magnetic resonance images. Am J Sports Med 1991;19:210–5. ; discussion 215-216.
31. Mair SD, Schlegel TF, Gill TJ, Hawkins RJ, Steadman JR. Incidence and location of bone bruises after acute posterior cruciate ligament injury. Am J Sports Med 2004;32:1681–7.
32. Nishimori M, Deie M, Adachi N, Kanaya A, Nakamae A, Motoyama M, *et al*. Articular cartilage injury of the posterior lateral tibial plateau associated with acute anterior cruciate ligament injury. Knee Surg Sports Traumatol Arthrosc 2008;16:270–4.
33. Wise BL, Niu J, Yang M, Lane NE, Harvey W, Felson DT, *et al*. Patterns of compartment involvement in tibiofemoral osteoarthritis in men and women and in whites and African Americans. Arthritis Care Res 2012;64:847–52.
34. Chavez A, Jimenez AE, Riepen D, Schell B, Khazzam M, Coyner KJ. Anterior cruciate ligament tears: the impact of increased time from injury to surgery on intra-articular lesions. Orthop J Sports Med 2020;8. 2325967120967120.
35. Unay K, Akcal MA, Gokcen B, Akan K, Esenkaya I, Poyanli O. The relationship between intra-articular meniscal, chondral, and ACL lesions: finding from 1,774 knee arthroscopy patients and evaluation by gender. Eur J Orthop Surg Traumatol 2014;24:1255–62.
36. Cox CL, Huston LJ, Dunn WR, Reinke EK, Nwosu SK, Parker RD, *et al*. Are articular cartilage lesions and meniscus tears predictive of IKDC, KOOS, and Marx activity level outcomes after anterior cruciate ligament reconstruction? A 6-year multicenter cohort study. Am J Sports Med 2014;42:1058–67.
37. Slauterbeck JR, Kousa P, Clifton BC, Naud S, Tourville TW, Johnson RJ, *et al*. Geographic mapping of meniscus and cartilage lesions associated with anterior cruciate ligament injuries. J Bone Joint Surg Am 2009;91:2094–103.
38. Tandogan RN, Taser O, Kayaalp A, Taskiran E, Pinar H, Alparslan B, *et al*. Analysis of meniscal and chondral lesions accompanying anterior cruciate ligament tears: relationship with age, time from injury, and level of sport. Knee Surg Sports Traumatol Arthrosc 2004;12:262–70.
39. Wyatt RW, Inacio MC, Liddle KD, Maletis GB. Prevalence and incidence of cartilage injuries and meniscus tears in patients who underwent both primary and revision anterior cruciate ligament reconstructions. Am J Sports Med 2014;42:1841–6.
40. Hunter DJ, Zhang YQ, Niu JB, Tu X, Amin S, Clancy M, *et al*. The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. Arthritis Rheum 2006;54:795–801.
41. Chu CR, Williams A, Tolliver D, Kwoh CK, Bruno 3rd S, Irrgang JJ. Clinical optical coherence tomography of early articular cartilage degeneration in patients with degenerative meniscal tears. Arthritis Rheum 2010;62:1412–20.
42. Nissi MJ, Toyras J, Laasanen MS, Rieppo J, Saarakkala S, Lappalainen R, *et al*. Proteoglycan and collagen sensitive MRI evaluation of normal and degenerated articular cartilage. J Orthop Res 2004;22:557–64.
43. Casula V, Hirvasniemi J, Lehenkari P, Ojala R, Haapea M, Saarakkala S, *et al*. Association between quantitative MRI and

ICRS arthroscopic grading of articular cartilage. Knee Surg Sports Traumatol Arthrosc 2016;24:2046–54.
44. Mlynarik V, Degrassi A, Toffanin R, Vittur F, Cova M, Pozzi-Mucelli RS. Investigation of laminar appearance of articular cartilage by means of magnetic resonance microscopy. Magn Reson Imaging 1996;14:435–42.
45. McDonald LS, Boorman-Padgett J, Kent R, Stone K, Wickiewicz TL, Pearle AD, *et al*. ACL deficiency increases forces on the medial femoral condyle and the lateral meniscus with applied rotatory loads. J Bone Joint Surg Am 2016;98:1713–21.
46. Kogan F, Fan AP, Monu U, Iagaru A, Hargreaves BA, Gold GE. Quantitative imaging of bone-cartilage interactions in ACL-injured patients with PET-MRI. Osteoarthritis Cartilage 2018;26:790–6.
47. Mehl J, Otto A, Baldino JB, Achtnich A, Akoto R, Imhoff AB, *et al*. The ACL-deficient knee and the prevalence of meniscus and cartilage lesions: a systematic review and meta-analysis (CRD42017076897). Arch Orthop Trauma Surg 2019;139:819–41.
48. Patterson BE, Culvenor AG, Barton CJ, Guermazi A, Stefanik JJ, Morris HG, *et al*. Worsening knee osteoarthritis features on magnetic resonance imaging 1 to 5 Years after anterior cruciate ligament reconstruction. Am J Sports Med 2018;46:2873–83.
49. Ajuied A, Wong F, Smith C, Norris M, Earnshaw P, Back D, *et al*. Anterior cruciate ligament injury and radiologic progression of knee osteoarthritis: a systematic review and meta-analysis. Am J Sports Med 2014;42:2242–52.
50. Mihelic R, Jurdana H, Jotanovic Z, Madjarevic T, Tudor A. Long-term results of anterior cruciate ligament reconstruction: a comparison with non-operative treatment with a follow-up of 17-20 years. Int Orthop 2011;35:1093–7.