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Authors

Gersing, AS
Schwaiger, BJ
Nevitt, MC
et al.

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Anterior cruciate ligament abnormalities are associated with accelerated progression of knee joint degeneration in knees with and without structural knee joint abnormalities: 96-Month Data from the Osteoarthritis Initiative

Alexandra S. Gersing, M.D.[1,3,6], **Benedikt J. Schwaiger, M.D.**[4], **Michael C. Nevitt, Ph.D.**[2], **Gabby B. Joseph, Ph.D.**[1], **Georg Feuerriegel**[3], **Pia M. Jungmann, M.D.**[5], **Julio B. Guimaraes, M.D.**[1], **Luca Facchetti, M.D.**[1], **Charles E. McCulloch, Ph.D.**[2], **Marcus R. Makowski, M.D.**[3], **Thomas M. Link, M.D., Ph.D.**[1]

[1]Department of Radiology and Biomedical Imaging, University of California, San Francisco

[2]Department of Epidemiology and Biostatistics, University of California, San Francisco

[3]Department of Radiology, School of Medicine, Technical University of Munich, Munich, Germany

[4]Department of Neuroradiology, School of Medicine, Technical University of Munich, Munich, Germany

[5]Department of Diagnostic and Interventional Radiology, Medical Center - University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[6]Department of Neuroradiology, University Hospital, LMU Munich, Munich, Germany

Abstract

OBJECTIVE—To compare progression over 8 years in knee compositional cartilage degeneration and structural joint abnormalities in knees with different types of ACL abnormalities over 8 years.

Corresponding author address: Alexandra S. Gersing, MD, Department of Radiology, Technical University of Munich, Ismaninger Strasse 22, 81675 Munich, Germany, alexandra.gersing@tum.de.

Author contributions

Alexandra Gersing, M.D. (alexandra.gersing@ucsf.edu) and Thomas Link, Ph.D., M.D. (thomas.link@ucsf.edu) take responsibility for the integrity of the work as a whole, from inception to finished article.

Conception and design of the study: Gersing, Schwaiger, Joseph, Guimaraes, Facchetti, Feuerriegel, McCulloch, Makowski, Jungmann, Nevitt, Link

Acquisition of data: Gersing, Schwaiger, Joseph, Guimaraes, Facchetti, Jungmann, Feuerriegel, McCulloch, Nevitt, Link

Analysis and interpretation of data: Gersing, Schwaiger, Joseph, Jungmann, Feuerriegel, McCulloch, Guimaraes, Facchetti, Makowski, Nevitt, Link

Drafting of article or revising it critically for important intellectual content: Gersing, Schwaiger, Joseph, Feuerriegel, Jungmann, McCulloch, Makowski, Nevitt, Link

Final approval of the version of the article to be published: Gersing, Schwaiger, Joseph, Feuerriegel, McCulloch, Guimaraes, Facchetti, Makowski, Jungmann, Nevitt, Link

Conflict of interest

None of the authors have any financial or other interests related to the manuscript submitted to Osteoarthritis and Cartilage that might constitute a potential conflict of interest.

METHOD—Baseline MR images of the right knees of 1899 individuals of the Osteoarthritis Initiative with no evidence of or mild to moderate radiographic osteoarthritis were assessed for nontraumatic ACL abnormalities. The knees of 91 individuals showed nontraumatic ACL abnormalities (age 60.6±9.8y, 46 females; mucoid degeneration (MD), *N*=37; complete tear (CT), *N*=22; partial tear (PT), *N*=32) and were frequency-matched to 91 individuals with normal ACL. MRIs were assessed for knee joint abnormalities using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) and cartilage T2 mapping at baseline, 4- and 8-year follow-up.

RESULTS—Over 8 years, cartilage T2 values of the medial tibia showed a significantly greater increase in individuals with MD, PT or CT compared to those with normal ACL (adjusted rate of change/year [95% confidence interval], normal ACL: 0.06 [0.01, 0.23], MD: 0.34 [0.07, 0.73], PT, 0.21 [0.02, 0.33], CT, 0.51 [0.16, 0.78]), indicating an association of ACL abnormalities and an increased progression rate of cartilage degeneration in subjects with and without knee joint degeneration. This effect was also seen in cartilage T2 values averaged over all compartments (normal ACL: 0.08 [0.05, 0.20] vs. abnormal ACL: 0.27 [0.06, 0.56]).

CONCLUSIONS—Over 8 years, higher progression rates of cartilage degeneration, especially in the medial tibia, were associated with ACL abnormalities compared to those with normal ACL, in subjects with and without knee joint abnormalities.

Keywords

Osteoarthritis; cartilage imaging; ACL tear; magnetic resonance imaging; T2 relaxation time

Introduction

The etiology and significance of incidental, nontraumatic anterior cruciate ligament (ACL) tears and degeneration in individuals without any history of trauma, remains elusive. It was suggested that the disruption of the ACL fibers and therefore failure of the ligament may occur due to significant degenerative changes of the ligament [1]. The intraarticular ligaments respond to inflammation associated with osteoarthritis, since they are surrounded by inflamed synovial fluid and are in contact with the joint cartilage and subchondral bone, which are gradually destructed in osteoarthritis [1–3]. These mechanisms make the ACL prone to rupture without trauma in individuals with osteoarthritis.

Various semi-quantitative Magnetic resonance imaging (MRI)-based measures have been developed to evaluate morphological knee joint abnormalities associated with osteoarthritis, e.g. the modified Whole-Organ MRI Score (WORMS)[4]. Additionally, for the detection of cartilage matrix degeneration, MRI-based compositional imaging, such as T2-relaxation time measurements, have previously shown to be a useful tool [5].

A cross-sectional study reported more prominent degenerative changes in the medial tibiofemoral compartment in individuals with nontraumatic complete ACL tear (CT) or partial ACL tear (PT) compared to individuals with normal ACL. Another longitudinal study over 48 months found that knees with mucoid degeneration of the ACL (MD) were associated with progression of degenerative changes of the medial tibiofemoral compartment [6]. In contrast, in acute traumatic ACL tears, the lateral compartment is usually more

affected due to biomechanical shear forces that occur within the knee joint and may cause accelerated cartilage deterioration [7].

However, these studies assessed either cross-sectional data or MD, CT or PT separately. Only a single previous cross-sectional study assessed differences between individuals with MD, PT and CT [8], showing no significant differences in cartilage degeneration between the fairly small groups.

Purpose of this study was therefore to analyze the associations of different types of nontraumatic ACL abnormalities (MD, PT and CT) with biochemical cartilage deterioration over 96 months, as measured with T2-relaxation time MR imaging, and with structural changes of the knee joint over time, as assessed with semi-quantitative modified WORMS subscores. We hypothesize that faster progression of knee joint degeneration is associated with nontraumatic ACL abnormalities to the progression of degeneration in knees with normal ACL over 96 months.

Method

Study participants

The Osteoarthritis Initiative (OAI; http://www.oai.ucsf.edu) is a prospective multi-center cohort study from which participants were selected for this analysis. The OAI participants are participants with risk factor for knee OA as well as participants with symptomatic knee OA and radiographic evidence of tibiofemoral OA. This HIPAA compliant study was approved by the local institutional review board of all participating centers. Informed consent of the participants was obtained.

Of the 4796 participants, those with end-stage OA (Kellgren-Lawrence Score, KL>3), rheumatoid arthritis that developed during follow-up of the study were excluded. Moreover, previous knee surgery (history of knee surgery of the right knee, e.g. arthroscopy, ligament repair, meniscectomy), knee surgery of the right knee during follow-up of the study or prior traumatic injury (ever injured knee so badly that it was difficult to walk for at least one week) were exclusion criteria. Participant selection is shown in Fig. 1. Of the remaining study participants, the semi-quantitative modified WORMS readings for the right knees, including a grading of the ACL as modified WORMS subscore, were available for the right knee in a sample of 1899 subjects in the OAI that were preread for previous National Institutes of Health-funded studies [4, 9–16]. This modified WORMS included the subdifferentiation of the ACL status (MD, CT or PT), therefore the grading of the ACL was available in all readings of the 1899 participants. Upon assessment, 91 participants were identified with ACL abnormalities at baseline (MD, N=37; PT, N=32; CT, N=22). From the remaining participants with normal ACL, 91 participants were frequency-matched to the 91 participants with ACL abnormalities on sex (m/f), age (10 year strata from 45 to 65 and one 14 year stratum from 65 to 79), baseline BMI (BMI in 2.5 kg/m2 strata) and KL grade of the right knee (KL in strata of 0/1 and 2/3). Subjects with normal ACL were randomly selected from each stratum in the frequency matching process and matched to the respective ACL abnormality subject. None of the selected controls with normal ACL showed an ACL pathology at the 48-month or 96-month follow up.

MR Imaging

The MR images for this study were acquired using identical 3.0T scanners (Siemens Magnetom Trio; Siemens Healthineers, Erlangen, Germany) and quadrature transmit-receive coils (USA Instruments, Aurora, OH, USA) at four sites (University of Maryland, School of Medicine, Baltimore, MD; University of Pittsburgh, Pittsburgh, PA; Memorial Hospital of Rhode Island, Pawtucket, RI and The Ohio State University, Columbus, OH). The MR sequence parameters of the sequences obtained are given in Table 2 and further details about the image acquisition are available in the OAI MR protocol [17].

Image Analysis

Grading of the ACL and semi-quantitative morphological analyses of the knee joint—Morphological MR sequences were reviewed on a picture archiving communication system (PACS) workstations (Agfa, Ridgefield Park, NJ, USA), using the semi-quantitative modified WORMS grading system, as previously described [18, 19]. All of the 182 selected and preread MR images were individually and independently reviewed by two radiologists (A.S.G. and B.J.S., each with 8 years of experience) in order to confirm the pre-existing modified WORMS and to ensure that there were no other findings present than those reported with the WORMS. The radiologists were blinded to demographic parameters and follow-up imaging results before they evaluated baseline studies. After at least 4 weeks, readers evaluated the 48-month follow-up studies. After another 4 weeks, readers evaluated the 96-month follow-up studies. In cases of disagreement (N=8), a consensus reading was performed with a third, more experienced musculoskeletal radiologist (T.M.L. with 25 years of experience). None of the patients showed abnormalities other than those assessed with the modified WORMS. None of the readings had to be corrected and the grading of the ACL remained consistent at baseline, 48-month and 96-month follow-up in all subjects, none of the subjects had to be re-categorized during follow up.

Grading of the ACL abnormalities was based on MR images. Abnormalities of the ACL were graded as MD on MR imaging if the ligament was ill-defined and thickened with an increase of the signal intensity on the sagittal fat-saturated intermediate-weighted and coronal PD FSE sequences as well as a loss of the normal fibrillary pattern, as previously described (Figure 2) [8, 20]. Moreover, if the ACL was partially disrupted with some fibers remaining continuous, the ACL was defined as PT [21]. If there was a complete loss of the fibers of the ACL, the diagnosis of a CT was made [22].

Aside from the ACL, meniscal lesions, cartilage lesions and bone marrow edema pattern (BMEP) lesions were graded from 0 to 3, as described previously [18]. For each subscale (modified WORMS cartilage, meniscus, BMEP), a sum subscore was calculated for each participant by adding the scores of all subregions of each knee joint structure [18, 19].

T2 relaxation time measurements—For the T2-relaxation time analysis of the MR images an in-house, spline-based algorithm written in MATLAB (version 9.6, the Mathworks, Natick, Massachusetts) was used as previously reported [11, 23]. The cartilage of five compartments (PAT, MF, LF, MT and LT) was semi-automatically segmented by two radiologists (L.F. and G.F., with 6 years and 1 year of experience, respectively) under

supervision of an experienced radiologist (T.M.L.). The knee joints were randomly distributed to one of the radiologists for the analysis. Segmentations were performed using the first echo of the sagittal 2D MSME sequence as previously described [24]. T2 relaxation times averaged over each cartilage compartment were computed were calculated as previously described [23, 25].

Additionally, as part of the laminar analysis, algorithms subdivided each cartilage compartment automatically into a superficial layer (articular surface) and a deep layer (bone interface) of equal thickness [26] and extracted T2 values for each layer of each compartment for further more detailed analyses.

Statistical Analysis

Statistical analysis was performed with Stata/IC version 14 software (StataCorp LP, College Station, TX) by G.B.J. and C.E.M.. Mixed-effects regression models adjusting for age, sex, baseline BMI, KL score and physical activity score of the elderly (PASE), baseline BMEP, baseline lateral and medial meniscal lesions and effusion were used to assess the validity of the hypothesis that rates of change of cartilage T2 values and modified WORMS subscores over 96 months were higher in participants with compared to those without ACL abnormalities. All of our mixed models included participant as a random effect to accommodate multiple measurements per participant. $P \leq 0.017$ ($0.05 ¸ 3$ because there are three pairwise comparisons among the groups) was used to indicate significance for the analyses that compared the parameters between the three groups in order to reduce the possibility of a type I error due to multiple testing. Due to the large number of parameters, the analyses were split into the following categories (based on previously published data [8, 27–30]): primary outcomes (modified WORMS analyses sum score cartilage and medial and lateral meniscus, mean global T2 analysis of the compartments; longitudinal analysis); exploratory outcomes (modified WORMS cartilage medial tibia and femur, lateral femur and tibia, patella and trochlea as well as WORMS subscore BMEP, cartilage mean T2 analysis of the compartments: medial tibia, medial femur, patella, lateral tibia, lateral femur; imaging parameters: laminar analysis of all compartments; baseline analysis). Moreover, in order to assess the validity of our hypothesis, that individuals with MD, the group with PT and the group with CT showed differences in annual rates of change of cartilage T2 values and modified WORMS subscores over 96 months between the different groups as well as compared to the normal ACL group, further analyses mixed-effects regression models were used, adjusting for age, sex, baseline BMI, KL score and PASE, baseline BMEP, baseline lateral and medial meniscal lesions and effusion. We allowed for a non-linear change of T2 and found the quadratic relationships with time to be significant, while modified WORMS changes showed a linear relationship with time, as previously described [31]. We hypothesized that there were no significant differences in baseline T2 values and WORMS between the groups with and without ACL abnormalities. In a sensitivity analysis we performed the mixed-effects regression models analysis including random ‘slopes’ and found no substantial changes in the results. Moreover, for the assessment of associations between the overall WORMS and T2 progression rates, study subjects were distributed into two groups depending on their baseline WORMS and differences in T2 progression rates were assessed using mixed-effects regression models.

Reproducibility

The reproducibility error for T2 measurements acquired for the present study was assessed by calculating the root mean square average of the single coefficients of variation (CV) on a percentage basis, as previously described [32]. For inter-reader reproducibility the T2 relaxation time was assessed in 10 randomly selected participants between the two readers (L.F. and G.F.) overall and for each of the five compartments segmented (PAT, MF, LF, MT, and LT).

The intra- and inter-reader reproducibility of the modified WORMS grading were performed for each of the two readers (B.J.S. and A.S.G.). Therefore, the modified WORMS grading was assessed twice by each reader independently for 10 randomly selected participants. Both readings of each reader were performed at least 14 days apart from each other. Intra-class correlation coefficients (ICCs) were calculated to compare the WORMS overall and to compare each modified WORMS subscore (meniscus, cartilage, BMEP and ligaments) separately.

Results

Subject Characteristics

Subject characteristics are presented in Table 1. When comparing participants with normal ACL to those with ACL abnormalities, no substantial differences between the groups were found regarding mean age and BMI at baseline, as well as in sex and KL score distribution.

Comparison of rates of change of cartilage T2 over 96 months between the normal ACL group and the ACL abnormality group

When assessing the differences in rates of change of the T2 values over 96 months between the group with normal ACLs and the combined group with abnormal ACLs, the rate of increase over 96 months of the T2 values in the global knee was greater in the combined group with ACL abnormalities compared to the normal ACL group, suggesting an accelerated cartilage degeneration over 96 months (Adjusted rate of change/year 95% CI, Normal ACL: 0.08 [0.05, 0.20]ms/year vs. Abnormal ACL: 0.27 [0.06, 0.56] ms/year; Table 3). In the compartmental analyses, the rate of change of T2 values in the medial tibia was greater in the group with abnormal ACL compared to those with normal ACL (normal ACL: 0.06 [0.01, 0.23]ms/year vs. Abnormal ACL: 0.45 [0.26, 0.75]ms/year). Yet this finding was not found in the medial femur (normal ACL: 0.11 [−0.03, 0.28]ms/year vs. Abnormal ACL: 0.22 [−0.10, 0.63]ms/year).

Analyses of baseline and cartilage T2 progression over 96 months in participants by ACL subtype compared to participants with normal ACL

Over 96 months, rates of increase in T2 cartilage of the medial tibia were higher in the group with MD, PT and CT group compared to the group with normal ACL (normal ACL: 0.06 [0.01, 0.23]ms/year, MD: 0.34 [0.07, 0.73]ms/year, PT: 0.21 [0.02, 0.33]ms/year, CT: 0.51 [0.16, 0.78]ms/year; Table 4), indicating an association between greater rates in change of cartilage matrix degeneration and the different groups with ACL abnormalities. This effect was also seen in the T2 values assessed and averaged over all compartments when

comparing the MD group with the normal ACL group (normal ACL: 0.08 [0.05, 0.20]ms/year, MD: 0.46 [0.23, 0.78]ms/year). Yet this effect was not detected in the medial femur (normal ACL: 0.11 [−0.03, 0.28]ms/year, MD: 0.24 [0.02, 0.84]ms/year). In a subanalysis with only participants with a KL grade of 0 and 1, the rate of change of T2 values, averaged over all compartments, was greater in the ACL abnormality group compared to the group with normal ACLs (normal ACL: 0.09 [0.01, 0.19]ms/year vs. abnormal ACL: 0.33 [0.05, 0.60]ms/year). This effect was also detected in the medial tibia (normal ACL: 0.04 [0.01, 0.15]ms/year vs. abnormal ACL: 0.22 [0.05, 0.53]ms/year). The baseline T2 values are given in Table 6.

Comparison of baseline and rates of change of modified WORMS cartilage, meniscal and BMEP over 96 months in different ACL abnormality subgroups and the normal ACL group

At baseline differences between the groups with normal and abnormal ACL were minimal (supplemental data). The PT and CT group showed a higher rate of progression of the overall modified WORMS subscore for meniscal lesions (normal ACL: 0.53 [0.24, 0.58], PT: 0.63 [0.26, 0.74], CT: 0.62 [0.28, 0.73]), which may have been caused by the overall degeneration of the knee joint, whereas no substantial difference was found in the rate of progression of the modified WORMS subscore for meniscal lesions between the MD group and the normal ACL group. Also, there was a higher increase in modified WORMS subscore for cartilage at the lateral femur in the MD ACL group compared to the normal ACL group (normal ACL: 0.18 [0.11, 0.25], MD: 0.32 [0.15, 0.48]). There were no such effects found at the medial tibia or medial femur (Table 5). In the analyses of cartilage subregions on average 1 out of 6 subregions progressed over 96 months in the MD group, whereas in the other groups (PT and CT and normal ACL group) none of the 6 subregions progressed. There were no differences between the different subgroups with ACL abnormalities and the normal ACL group in rates of change of the overall BMEP score. In the analyses of BMEP subregions on average 2 out of 6 subregions progressed significantly over 96 months in the MD and CT group, whereas in the other groups (PT and normal ACL group) only 1 out of 6 subregions progressed significantly.

In the subanalysis of subjects with KL 0 and 1, no differences were found between the ACL abnormality group and the normal ACL group regarding the WORMS subscores (data not shown).

When distributing the study participants in two groups, depending on their WORMS at baseline, the group with high WORMS showed no difference in progression of cartilage T2 over 96 months compared to the low WORMS group (global T2: low WORMS group: 0.36 [0.03, 0.68], high WORMS group: 0.37 [−0.01, 0.73]; MF: low WORMS group: 0.18 [−0.04, 0.40], high WORMS group: 0.19 [−0.07, 0.44]; MT: low WORMS group: 0.23 [−0.09, 0.61], high WORMS group: 0.32 [0.10, 0.53]).

Reproducibility

Intra-reader reproducibility CVs for mean T2 measurements were 1.52% and 1.83%, respectively. Inter-reader reproducibility is given in the supplemental data.

The intra-reader agreement for modified WORMS subscores ranged from 0.74 to 0.95. ICCs for inter-reader agreement for overall modified WORMS were 0.83 (0.74–0.95) and ranged from 0.74 to 0.92 for subscores meniscus, cartilage and BMEP. Intra-reader reproducibilities for the ACL were 1.00 and 0.95, respectively (inter-reader reproducibility: 0.95).

Discussion

The most important finding of this study is that rates of change of cartilage T2 values averaged over all compartments increased significantly more over 96 months in individuals with ACL abnormalities compared to those without ACL abnormalities in individuals with and without knee joint degeneration. Especially the medial tibia showed higher rates of increase in cartilage T2 values in individuals with ACL abnormality, yet this effect was not detected in the medial femur. When assessing the rates of change of structural knee joint abnormalities, individuals with MD also showed higher rates of increase of cartilage WORMS in the lateral femur compared to those with normal ACL, suggesting an association between cartilage degeneration and MD.

Previously, cartilage T2 values have shown to detect biochemical changes of cartilage as biomarker for cartilage degeneration [13]. When performing an analysis of the rates of change of T2 values averaged over all compartments and of the medial tibia over 8 years in individuals with ACL abnormalities were higher compared to those in individuals without ACL abnormalities. This effect was also seen, when comparing the ACL abnormality group with the normal ACL group in subjects with KL 0 and 1, suggesting that these effects were also detected in initially healthier knees. In a previous baseline study, there were no differences in cartilage T2 values between individuals with ACL abnormalities and individuals without ACL abnormalities found [8]. Yet, this previous study was only a cross-sectional study and only assessed 52 subjects with ACL abnormalities. When looking at the rate of change of the T2 values over 8 years, especially the T2 values of the medial tibiofemoral compartment (MTFC) showed a significantly higher T2 increase in the individuals with abnormal ACL compared to those with normal ACL, indicating an association between a higher rate of progression of cartilage degeneration and ACL abnormalities. In a study in individuals with mucoid degeneration and chronic ACL insufficiency, increased MTFC OA and MTFC cartilage damage were reported in comparison to patients with normal ACL [28] [29, 30, 33].

On the one hand, when assessing the cartilage T2 values for each ACL abnormality subtype separately, T2 values of the medial tibia were significantly increased in individuals with PD and CT compared to individuals with normal ACL. On the other hand, the group with MD showed significantly elevated T2 values in the medial tibia and in the lateral femur, as assessed in an exploratory analysis. This suggests that in subjects with MD, degenerative changes of the cartilage can be found within the knee joint. No significant associations were found between increase in T2 over 96 months and WORMS when categorizing WORMS into high and low WORMS groups.

In subjects with PT or CT, the rates of progression of morphological cartilage and meniscus lesions over all compartments, as assessed with modified WORMS, were greater in

individuals compared to individuals with a normal ACL over 8 years. These findings demonstrate an association between ACL abnormalities and knee joint degeneration. Yet, it needs to be noted, that the damage of the ACL may be a consequence of the degenerative process in individuals with knee joint degeneration, as present in the majority of the individuals included in this study. Moreover, a previous study has shown that the predominant pattern of knee joint degeneration was found in the medial tibiofemoral joint in individuals with CT or PT [33]. Change of biomechanics following an acute and chronic ACL rupture may cause altered cartilage contact, pronounced in the region of the tibia plateau, with a consequent increase of loading in areas which were not adjusted to constant loading prior to the loss of ACL integrity [34–36]. Therefore, ACL deficient knees resulting from the degenerative process of the knee joint, may be exposed to increased shear forces to the cartilage, contributing to even more severe OA, typically in the medial compartment [7, 37]. This suggests that long-term, individuals with ACL tears as part of the degenerative process, may be exposed to more severe knee OA and therefore reduced functionality and greater knee pain. In contrast acute ACL ruptures typically effect the lateral compartment with potentially subsequent degenerative changes more prominent in the lateral compartment [38].

In a previous study over 8 years in obese subjects with different weight loss regimens, differences in rates of change of T2 values per year above 0.12 ms were significantly different from each other indicating progression of cartilage matrix degenerative changes [24]. Moreover, Schneider et al. showed RMS CVs% between 1.5 to 5.3% over 8 years, assessed using a phantom [13]. Yet, the phantom was smaller than human knees, and this may have caused more severe fluctuation. The differences in change in cartilage degeneration over 8 years between subjects with and without ACL abnormalities emphasize, that especially in patients with MD, PT or CT of the ACL preventative strategies (e.g. adjustment of weight, adjustment of physical activity or reduction of further risk factors) or even therapeutic regimens need to be undertaken in order to slow the cartilage from deteriorating, regardless of the preexisting knee joint abnormalities. Overall, the limited reproducibility and intra- and inter-individual variability of T2 relaxation time mapping needs to be acknowledged.

This study has several other limitations. There are other risk factors for nontraumatic ACL abnormalities, such as anatomical, biomechanical or hormonal risk factors, that we did not adjust for in the analyses. Also, there are further potential confounders, such as morphological knee joint abnormalities that may have been present at baseline (e.g. meniscal tears) that may have substantially contributed to the progression of cartilage degeneration. In order to minimize these effects, we have adjusted for the most important morphological knee joint abnormalities at baseline (baseline BMEP, baseline lateral and medial meniscal lesions and baseline effusion) additionally to the baseline subject characteristics. Yet, it needs to be noted, that the majority of the individuals presented with a KL grade of 2 or 3. Moreover, knees with history of surgery at follow-up were excluded from our study. Although these were only nine participants, this may have caused a potential selection bias, which needs to be considered when interpreting the data. Yet, surgery may cause severe artifacts post-operatively (e.g. postoperative changes/hemorrhage, sutures or metal-artifacts), which may impair the WORMS assessment and T2 mapping significantly. We were able to adjust for

PASE in our analysis. Yet, it is known, that PASE is limited, since this is a reported assessment and further information on sports participation was missing. Moreover, 'history of knee injury' was only a reported parameter, which may be inaccurate. Nevertheless, in this study, answers such as 'unknown', 'uncertain' or 'c annot remember' were treated as 'potential history of knee injury' and were excluded from the study. A further limitation of this study was the categorization of the ACL abnormalities with MRI only without reformatted orientation. This methodology may be less accurate than using arthroscopy and especially challenging in knees with moderate to severe degeneration, since the ACL may show signal alterations in degenerated knees.

In summary, our study showed higher biochemical cartilage degeneration assessed using cartilage T2 averaged over all compartments and in the medial tibia in subjects with ACL abnormalities compared to those with normal ACL with the majority of the subjects showing moderate degenerative findings of the knee joint.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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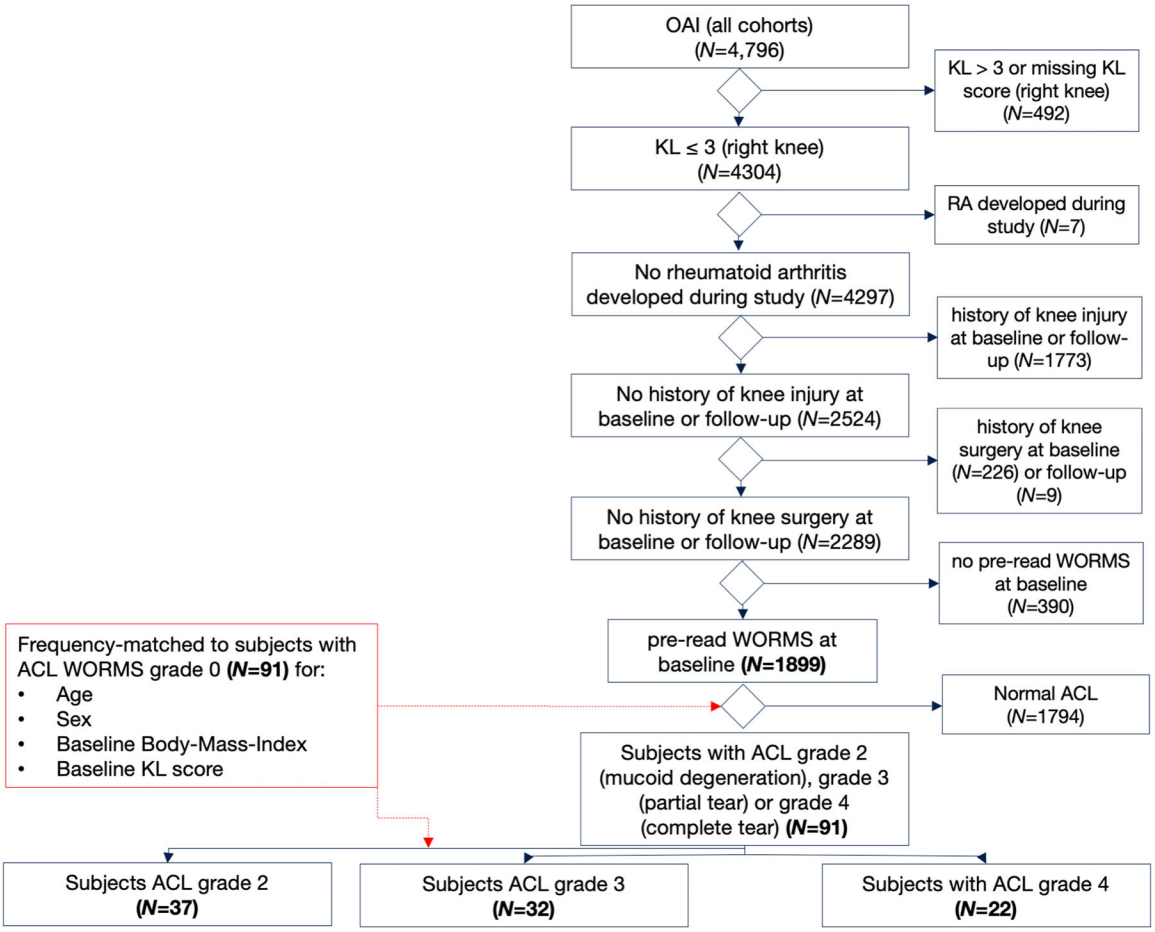

Figure 1.

Participant selection from OAI database for the subgroups with the ACL abnormalities and the control group with a normal ACL.

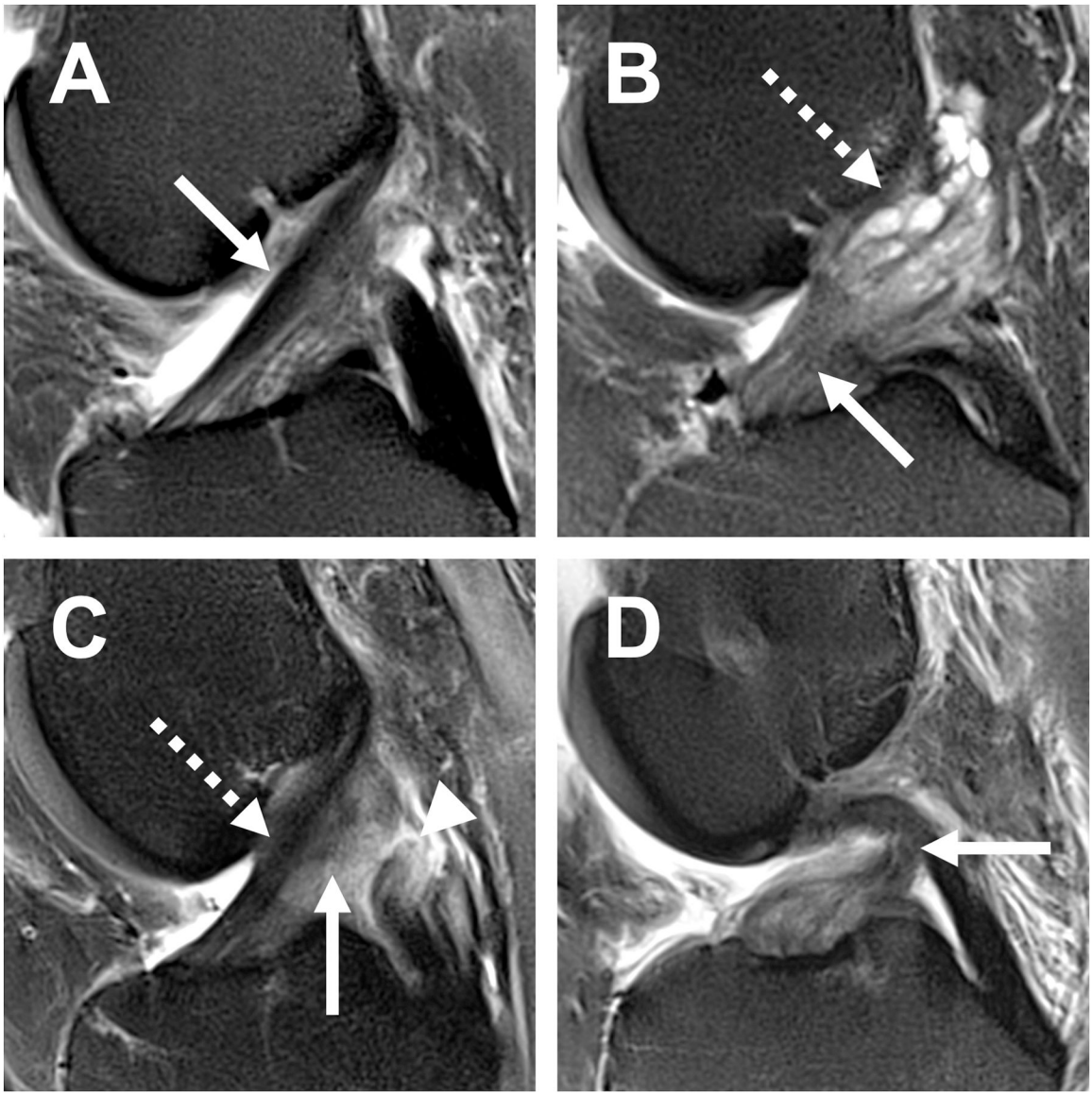

Figure 2.

depicting normal appearance and different pathologies of the ACL on sagittal intermediate-weighted fat-saturated sequences: A—normal ACL with taut appearance, uniformly low signal intensity and continuous fibres (arrow); B—mucoid degeneration of the ACL with an overall signal increase as well as lines of signal hyperintensities (arrow) as well as ganglion cysts (dashed arrow); C—partial tear of both ACL bundles with swelling and linear signal hyperintensities as well as several fiber discontinuities (arrow); D—complete tear of the ACL with proximal discontinuity of all fibres (arrow), distal retraction and heterogeneous signal increase.

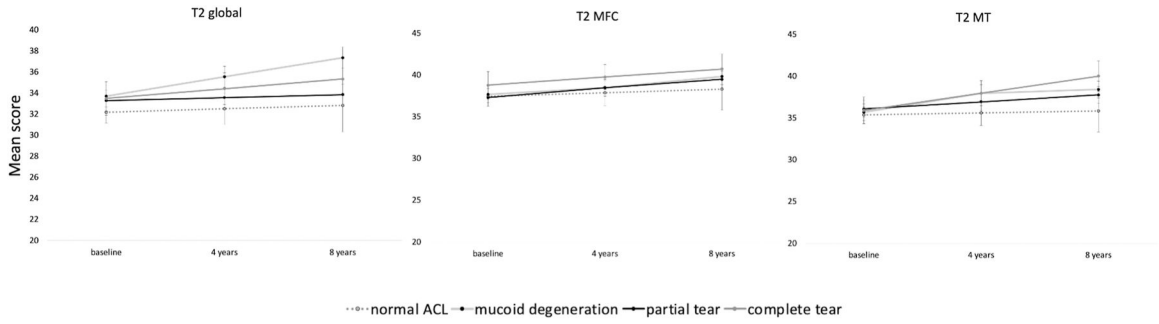

Figure 3.

Mean Cartilage T2 over 8 years. The associations between different ACL abnormality groups and rate of change in cartilage T2 over 96 months were assessed using mixed random effects models adjusting for age, sex, baseline BMI, baseline KL score, baseline physical activity survey for the elderly (PASE), baseline bone marrow edema pattern (BMEP), baseline lateral and medial meniscal lesions and effusion. Error bars indicate standard deviation. MFC = medial femur condyle, MT = medial tibia, global = mean of all compatments.

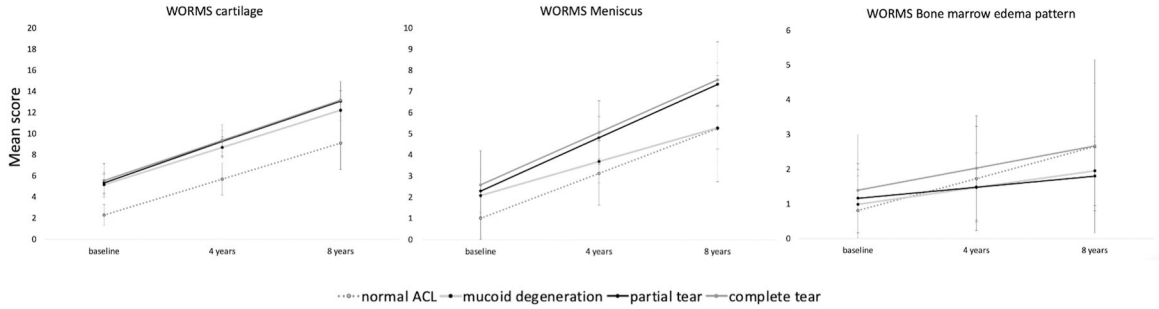

Figure 4.

Mean WORMS over 8 years. The associations between different ACL abnormality groups and rate of change in WORMS subcsore cartilage, meniscus and Bone marrow edema pattern over 96 months were assessed using mixed random effects models adjusting for age, sex, baseline BMI, baseline KL score, baseline physical activity survey for the elderly (PASE), baseline bone marrow edema pattern (BMEP), baseline lateral and medial meniscal lesions and effusion. Error bars indicate standard deviation.

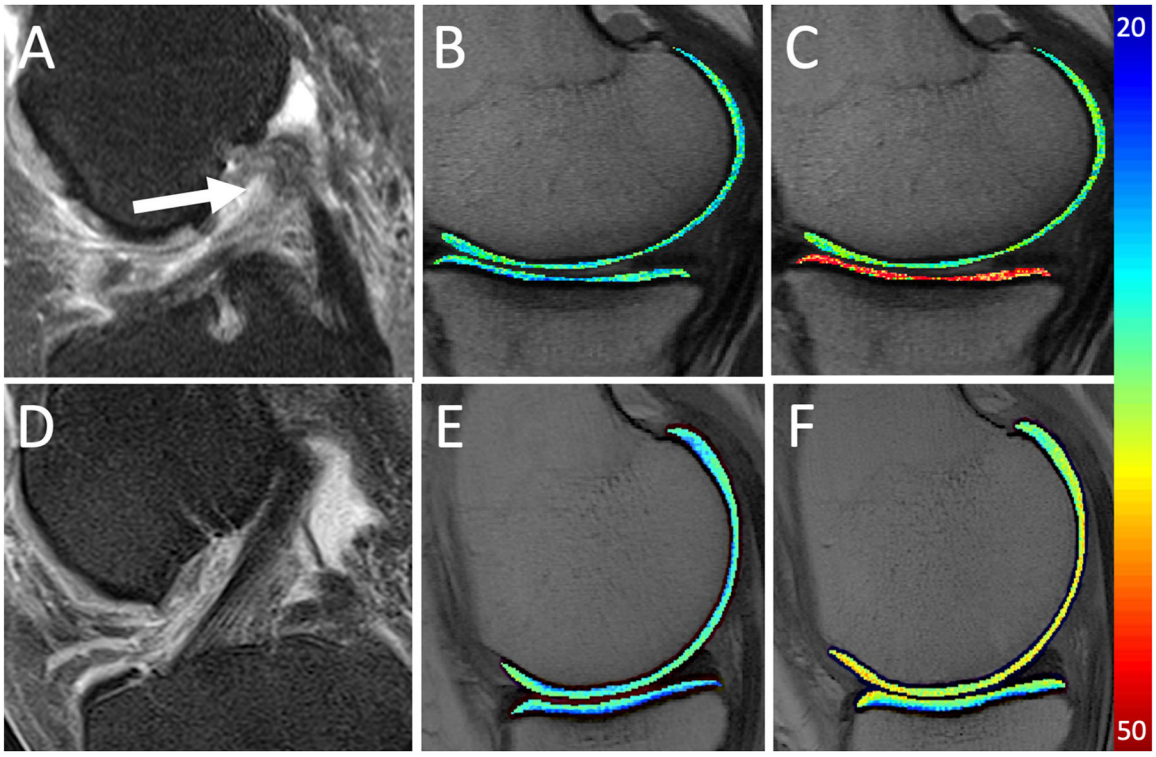

Figure 5.

Exemplary MR images and T2-maps of a 52-year old female participant with chronic complete anterior cruciate ligament (ACL) tear at baseline (A, white arrow). T2 maps at baseline (B) and after 8 years (C) showing increase of cartilage T2 values in the medial tibiofemoral compartment (orange and red regions), indicating progression of biochemical cartilage degradation. A 58-year old female with normal ACL (D). T2 maps at baseline (E) and after 8 years (F) showing only a subtle increase of T2-relaxation times in the medial tibiofemoral compartment (yellow regions), suggesting less cartilage progression compared to the participant with chronic ACL tear.

Table 1:

Subject demographics for ACL normal group and the ACL abnormality subgroups

	Normal ACL	Mucoid degeneration	Partial tear	Complete tear
	***N*=91**	***N*=37**	***N*=32**	***N*=22**
Baseline				
Age [years ± SD]	60.32 ± 8.27	60.15 ± 9.31	62.56 ± 9.59	58.23 ± 8.87
Females [n (%)]	46 (50.55%)	25 (67.57%)	16 (50.00%)	8 (36.36%)
BMI [kg/m^2 ± SD]	28.74 ± 4.07	26.96 ± 4.18	29.23 ± 4.74	29.16 ± 4.49
Physical activity	164.44 ± 77.64	168.65 ± 82.18	179.50 ± 91.29	171.73 ± 74.60
KL scores				
K/L score 0 [n (%)]	34 (27.36%)	9 (24.32%)	5 (15.63%)	5 (22.73%)
K/L score 1 [n (%)]	5 (5.49%)	2 (5.41%)	2 (6.25%)	1 (4.55%)
K/L score 2 [n (%)]	22 (24.18%)	14 (37.84%)	7 (21.88%)	7 (31.82%)
K/L score 3 [n (%)]	30 (32.97%)	12 (32.43%)	18 (56.25%)	9 (40.91%)

Table 2.

MR sequence parameters

Sequence	PD-w FSE	DESS	T1-w FLASH	IM-w FS FSE	T2 MSME SE
Additional features	2D	3D	§D	2D	2D
Plane	Coronal	Sagittal	Coronal	Sagittal	Sagittal
Echo time/step (TE; ms)	29	4.7	7.6	30	10,20,30,40,50,60,70
Repetition time (TR; ms)	3700	16.3	20	2700	3200
Field of view (FOV; mm)	140	140	160	160	120
Matrix	128×256	307×384	512×512	313×448	269×384
Slice thickness (mm)	3	0.7	1.5	3	3
Flip angle (°)	180	25	12	180	n/a
Number of slices	35	160	80	37	21
Echo Train Length	7	1	1	5	1
Bandwidth per pixel (Hz)	352	185	130	248	250
Acquisition time (min)	3.4	10.6	8.6	4.7	10.6

PD-w, proton density-weighted; IM-w, intermediate-weighted; FSE, fast spin echo; DESS, dual-echo steady-state; FLASH, fast low-angle shot; 3D, three-dimensional; 2D, two-dimensional; FS, fat saturated; MSME, multislice-multiecho; SE, spin echo.

Table 3:

Comparison of rate of change of global and laminar T2 over 96-months*

T2 Parameters 96 months	Normal ACL	Abnormal ACL	*P*-value
	Adjusted rate of change/year 95% CI	Adjusted rate of change/year 95% CI	
Cartilage T2			
Global knee	0.08 [0.05, 0.20]	0.27 [0.06, 0.56]	**0.008**
PAT	0.03 [−0.09, 0.25]	0.20 [0.05, 0.60]	0.77
MT	0.06 [0.01, 0.23]	0.45 [0.26, 0.75]	**0.001**
LT	0.10 [−0.12, 0.31]	0.31 [0.01, 0.39]	0.38
MF	0.11 [−0.03, 0.28]	0.22 [−0.10, 0.63]	0.22
LF	0.13 [−0.02, 0.50]	0.23 [0.02, 0.59]	0.04
Deep layer T2			
Global knee	0.07 [0.05, 0.20]	0.27 [0.11, 0.46]	**0.006**
PAT	0.05 [−0.10, 0.30]	0.13 [−0.03, 0.30]	0.60
MT	0.05 [0.01, 0.13]	0.52 [0.07, 0.74]	**0.009**
LT	0.06 [−0.09, 0.21]	0.25 [−0.08, 0.41]	0.05
MF	0.12 [−0.12, 0.24]	0.17 [0.02, 0.60]	0.39
LF	0.15 [0.00, 0.33]	0.21 [−0.09, 0.67]	0.25
Superficial layer T2			
Global knee	0.09 [0.01, 0.33]	0.28 [0.09, 0.50]	**0.009**
PAT	0.01 [−0.05, 0.07]	0.25 [−0.15, 0.44]	0.68
MT	0.10 [−0.10, 0.32]	0.35 [0.09, 0.51]	0.09
LT	0.12 [0.03, 0.58]	0.53 [0.18, 0.65]	0.03
MF	0.07 [0.02, 0.23]	0.27 [0.18, 0.41]	**0.008**
LF	0.07 [0.02, 0.11]	0.29 [0.03, 0.43]	**0.002**

LF, lateral femur; LT, lateral tibia; MF, medial femur; MT, medial tibia; PAT, patella

*The differences between the rates of change of T2 relaxation times over 96 months between the ACL abnormality group and normal ACL group were assessed using multivariable regression models adjusting for age, sex, baseline BMI, baseline KL score, baseline physical activity survey for the elderly (PASE), baseline bone marrow edema pattern (BMEP), baseline lateral and medial meniscal lesions and effusion. Significant results (**P < 0.017**) are bolded.

Table 4:

Comparison of rate of change of T2 parameters for each ACL abnormality group compared to the normal ACL group over 96 months *

	Normal ACL *N*=91	Mucoid degeneration *N*=37	*P*-value	Partial tear *N*=32	*P*-value	Complete tear *N*=22	*P*-value
T2 Parameters	**Rate/year 95% CI**		**Mucoid degeneration vs. normal ACL**	**Rate/year 95% CI**	**Partial tear vs. normal ACL**	**Rate/year 95% CI**	**Complete tear vs. normal ACL**
Cartilage T2							
Global knee	0.08 [0.05, 0.20]	0.46 [0.23, 0.78]	**<0.001**	0.07 [−0.17, 0.42]	0.95	0.23 [−0.02, 0.29]	0.81
PAT	0.03 [−0.09, 0.25]	0.09 [−0.04, 0.55]	0.64	0.15 [−0.05, 0.44]	0.38	0.24 [−0.19, 0.59]	0.17
MT	0.06 [0.01, 0.23]	0.34 [0.07, 0.73]	**0.012**	0.21 [0.02, 0.33]	**0.012**	0.51 [0.16, 0.78]	**0.005**
LT	0.10 [−0.12, 0.31]	0.38 [0.03, 0.83]	0.03	0.22 [−0.21, 047]	0.48	0.22 [−0.21, 0.45]	0.23
MF	0.11 [−0.03, 0.28]	0.24 [0.02, 0.84]	0.10	0.25 [−0.06, 63]	0.85	0.24 [−0.14, 0.68]	0.13
LF	0.13 [0.02, 0.40]	0.33 [0.07, 0.97]	**0.014**	0.18 [−0.02, 0.61]	0.22	0.22 [−0.10, 0.94]	0.81
Deep layer T2							
Global knee	0.06 [0.05, 0.20]	0.47 [0.14, 0.92]	**<0.001**	0.07 [0.05, 0.24]	0.79	0.15 [−0.12, 0.34]	0.09
PAT	0.06 [−0.10, 0.30]	0.10 [−0.12, 0.40]	0.40	0.01 [−0.14, 0.25]	0.48	0.21 [−0.18, 0.50]	0.36
MT	0.05 [0.01, 0.13]	0.36 [0.08, 0.67]	**0.010**	0.25 [0.02, 0.23]	**0.017**	0.55 [0.24, 0.85]	**<0.001**
LT	0.06 [−0.09, 0.21]	0.52 [0.12, 0.95]	**<0.001**	0.07 [−0.40, 0.33]	0.96	0.11 [0.02, 0.88]	**0.011**
MF	0.12 [−0.12, 0.24]	0.22 [−0.21, 0.77]	0.17	0.03 [−0.17, 0.54]	0.65	0.08 [−0.18, 0.27]	0.37
LF	0.17 [0.00, 0.33]	0.47 [0.05, 0.90]	0.02	0.18 [−0.35, 0.38]	0.96	0.19 [−0.30, 0.68]	0.88
Superficial layer T2							
Global knee	0.08 [0.01, 0.33]	0.52 [0.26, 0.79]	**<0.001**	0.10 [−0.13, 0.69]	0.82	0.32 [0.03, 0.62]	0.40
PAT	0.01 [−0.05, 0.07]	0.23 [−0.17, 0.64]	0.20	0.04 [−0.07, 0.15]	0.25	0.31 [−0.17, 0.78]	0.22
MT	0.10 [−0.10, 0.32]	0.43 [0.01, 0.94]	0.04	0.13 [−0.32, 0.59]	0.56	0.32 [−0.15, 0.78]	0.18
LT	0.12 [0.03, 0.58]	0.17 [0.01, 0.69]	0.18	0.25 [−0.21, 0.71]	0.28	0.22 [−0.17, 0.53]	0.67
MF	0.07 [0.02, 0.23]	0.25 [0.03, 0.37]	0.02	0.18 [−0.22, 0.59]	0.37	0.31 [0.00, 0.69]	**0.007**
LF	0.07 [0.02, 0.11]	0.18 [0.05, 0.69]	0.03	0.14 [0.03, 0.24]	0.04	0.33 [0.03, 0.48]	**0.001**

LF, lateral femur; LT, lateral tibia; MF, medial femur; MT, medial tibia; PAT, patella

[*] The associations between different ACL abnormality groups and rate of change in cartilage T2 over 96 months were assessed using mixed random effects models adjusting for age, sex, baseline BMI, baseline KL score, baseline physical activity survey for the elderly (PASE), baseline bone marrow edema pattern (BMEP), baseline lateral and medial meniscal lesions and effusion. Significant results (**P < 0.017**) are bolded.

Table 5:

Comparison of rate of change of modified WORMS for each ACL abnormality group compared to the normal ACL group over 96 months

	Normal ACL *N*=91	Mucoid degeneration *N*=37	*P*-value	Partial tear *N*=32	*P*-value	Complete tear *N*=22	*P*-value
WORMS Parameters	**Rate/year 95% CI**			**Rate/year 95% CI**		**Rate/year 95% CI**	
Cartilage lesions							
PAT	0.14 [0.03, 0.23]	0.28 [0.05, 0.51]	0.03	0.32 [0.05, 0.58]	0.04	0.18 [0.04, 0.30]	0.02
TRO	0.13 [0.04, 0.22]	0.18 [0.03, 0.40]	0.37	0.25 [0.02, 0.55]	0.10	0.19 [0.00, 0.48]	0.06
MT	0.11 [0.04, 0.18]	0.07 [−0.08, 0.23]	0.39	0.21 [0.05, 0.40]	0.08	0.13 [0.04, 0.22]	0.10
LT	0.17 [0.09, 0.25]	0.09 [−0.09, 0.28]	0.15	0.18 [0.07, 0.29]	0.44	0.17 [−0.04, 0.37]	0.95
MF	0.04 [0.00, 0.06]	0.12 [0.04, 0.48]	0.04	0.20 [0.08, 0.33]	0.03	0.27 [0.11, 0.37]	0.04
LF	0.18 [0.11, 0.25]	0.32 [0.15, 0.48]	**0.005**	0.01 [−0.08, 0.30]	0.27	0.14 [0.03, 0.32]	0.48
Cartilage lesions overall	0.85 [0.52, 1.18]	0.88 [0.06, 1.59]	0.91	0.98 [0.55, 1.42]	0.02	0.95 [0.54, 1.36]	0.02
Meniscus lesions overall	0.53 [0.24, 0.58]	0.40 [−0.29, 0.83]	0.48	0.63 [0.26, 0.74]	**0.01**	0.62 [0.28, 0.73]	**0.003**
Meniscus lesions medial	0.26 [0.08, 0.45]	0.17 [−0.24, 0.59]	0.44	0.40 [−0.03, 0.84]	0.26	0.31 [0.14, 0.53]	0.02
Meniscus lesions lateral	0.27 [0.08, 0.46]	0.23 [−0.21, 0.65]	0.70	0.31 [0.08, 0.55]	0.07	0.18 [0.18, 0.59]	0.40
Bone marrow edema pattern overall	0.23 [0.04, 0.39]	0.12 [−0.27, 0.49]	0.29	0.08 [−0.31, 0.47]	0.20	0.16 [−0.20, 0.49]	0.44

LF, lateral femur; LT, lateral tibia; MF, medial femur; MT, medial tibia; PAT, patella

*The associations between different ACL abnormality groups and rate of change in cartilage T2 over 96 months were assessed using mixed random effects models adjusting for age, sex, baseline BMI, baseline KL score, baseline physical activity survey for the elderly (PASE), baseline bone marrow edema pattern (BMEP), baseline lateral and medial meniscal lesions and effusion. Significant results (**P < 0.017**) are bolded.