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Review

Knee MRI biomarkers associated with structural, functional and symptomatic changes at least a year from ACL injury - A systematic review

Oliver O'Sullivan [a,b,*], Peter Ladlow [b,c], Kat Steiner [d], Dahria Kuyser [e], Omaima Ali [e], Joanne Stocks [a], Ana M. Valdes [f,g], Alexander N. Bennett [h], Stefan Kluzek [a,i]

[a] Academic Unit of Injury, Recovery and Inflammation Sciences, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, UK
[b] Academic Department of Military Rehabilitation (ADMR), Defence Medical Rehabilitation Centre (DMRC), Stanford Hall, Loughborough, UK
[c] Department of Health, University of Bath, Bath, UK
[d] Bodleian Health Care Libraries, University of Oxford, Oxford, UK
[e] University of Oxford, Oxford, UK
[f] Nottingham NIHR Biomedical Research Centre, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, UK
[g] Department of Twin Research & Genetic Epidemiology, King's College London, London, UK
[h] National Heart and Lung Institute, Imperial College London, London, UK
[i] Centre for Sport, Exercise and Osteoarthritis Research Versus Arthritis, University of Nottingham, Nottingham, UK

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ABSTRACT

Introduction: Osteoarthritis (OA) results from various aetiologies, including joint morphology, biomechanics, inflammation, and injury. The latter is implicated in post-traumatic OA, which offers a paradigm to identify potential biomarkers enabling early identification and intervention. This review aims to describe imaging features associated with structural changes or symptoms at least one year following injury.
Methodology: A systematic review was conducted using PRISMA guidance, prospectively registered on PROSPERO (CRD42022371838). Three independent reviewers screened titles and abstracts, followed by full-texts, performed data extraction, and risk of bias assessments (Newcastle-Ottawa Scale). Inclusion criteria included imaging studies involving human participants aged 18–45 who had sustained a significant knee injury at least a year previously. A narrative synthesis was performed using synthesis without meta-analysis methodology.
Results: Six electronic databases and conference proceedings were searched, identifying 11 studies involving 776 participants. All studies included participants suffering an anterior cruciate ligament (ACL) injury and utilised MRI. Different, and not directly comparable, techniques were used. MRI features could be broadly divided into structural, including joint position and morphology, and compositional. Promising biomarkers for diagnosing and predicting osteoarthritis include T1rho and T2 relaxation time techniques, bone morphology changes and radiomic modelling.
Discussion: As early as 12 months after injury, differences in tibia position, bone morphology, presence of effusion and synovitis, and cartilage/subchondral bone composition can be detected, some of which are linked with worse patient-reported or radiological progression. Standardisation, including MR strength, position, sequence, scoring and comparators, is required to utilise clinical and research OA imaging biomarkers fully.

1. Introduction

The synovial joint disease osteoarthritis (OA) causes a significant burden of morbidity, with a multifaceted pathophysiology, including joint morphology, biomechanics, genetics, previous injury, and immunology [1,2]. Initial injury and local changes influence structural abnormalities, facilitated by low-grade inflammatory mediators and reinforced by increasing joint loading with resulting pain, stiffness, and reduced function [3,4].

* Corresponding author. Academic Unit of Injury, Recovery and Inflammation Sciences, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, UK.
E-mail addresses: oliver_osullivan@hotmail.com (O. O'Sullivan), Peter.Ladlow100@mod.gov.uk (P. Ladlow), kat.steiner@bodleian.ox.ac.uk (K. Steiner), dahria.kuyser@lmh.ox.ac.uk (D. Kuyser), omaima.ali@lmh.ox.ac.uk (O. Ali), Joanne.stocks@nottingham.ac.uk (J. Stocks), Ana.valdes@nottingham.ac.uk (A.M. Valdes), alexander.bennett485@mod.gov.uk (A.N. Bennett), Stefan.kluzek@nottingham.ac.uk (S. Kluzek).
@ollieosul (O. O'Sullivan)

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Developing sensitive OA biomarkers, objective indications of biological and pathological processes, could potentially identify patients at risk of OA at a pre-radiological and pre-symptomatic stage, thereby allowing early identification and intervention [5,6]. Ongoing work is being undertaken to identify biomarkers with the highest reliability and validity. These biomarkers can be classified by role using the BIPEDS classification (Burden of Disease, Investigative, Prognostic, Efficacy of intervention, Diagnostic, Safety) [5]. In particular, these studies are being performed in the population with, or at risk for, post-traumatic osteoarthritis (PTOA) due to the well-established exposure in a younger population with fewer co-morbidities and confounders [7]. Specific injuries, such as traumatic anterior cruciate ligament (ACL) ruptures, have a significant risk of subsequent knee PTOA [7,8].

Non-invasive imaging techniques, such as x-ray (XR), ultrasound (USS) and magnetic resonance imaging (MRI), may provide insights into early joint changes or established disease by quantifying various features of the image intensity, texture, shape, and spatial relationships to detect pathological processes [9]. XR changes, including joint space narrowing (JSN) as a proxy for the thickness, integrity, and health of hyaline articular cartilage, are used as European Medicines Agency and Federal Drug Administration approved endpoints for disease-modifying OA drug clinical trials [10,11]. The Kellgren-Lawrence (K-L) score is used to report XR and identify the presence and severity of OA; however, it does not capture early disease progression, with subjective early changes having poor reproducibility [12].

To mitigate this, MRI has been proposed as a more sensitive and reliable marker of early OA changes, as it can visualise the whole joint and identify structural changes or the presence of effusion. In addition, advanced techniques, including contrast-enhanced (dGEMRIC), T1rho (also known as T1P and 'spin-lock'), and T2 relaxation time, can indicate macromolecular content, hydration and molecular interactions in cartilage extracellular matrix (ECM) [13,14]. For example, 50% depletion of proteoglycan from articular cartilage results in average T1rho increases by more than 50% (from 110 to 170 ms) [15]. These compositional modalities are transitioning from descriptive evaluations of calcified tissues to the identification of key changes in soft tissue composition, such as cartilage water content increases and collagen organisation or proteoglycan density decreases, indicating tissue degradation, inflammation and oedema, all of which are closely linked to early-stage cartilage degeneration and OA/PTOA.

The hypothesis for this systematic review is that some MRI features of the post-traumatic knee are linked with functional or clinical knee changes and can be used as biomarkers for PTOA. A previous review identified that adaptive cartilage morphological changes, joint fluid volumes and bone marrow lesions (BMLs) were present within the first year following ACL injury, resolving over time [16]. Therefore, this systematic review aims to describe cross-sectional knee OA imaging features present one year or more following injury and their associations with structural, functional, or symptomatic changes.

2. Methodology

2.1. Registration and searches

The systematic review protocol was registered prospectively on PROSPERO (CRD42022371838) and performed using PRISMA guidance [17]. Ovid, Medline and Embase were searched, along with Cochrane CENTRAL (via Wiley) and ClinicalTrials.gov on the 8th, WHO ICTRP 9th, and conference proceedings on the 10th of November 2022. Authors with similar systematic reviews registered on PROSPERO were contacted. A Medline and Embase human studies hedge was employed [18]. No other filters or limits were used. Topic experts recommended additional studies missed by searches. Searches utilised knee PTOA and imaging biomarkers keywords and subject headings, with the search strategy in Supplementary File 1. EndNote 20 and SR Accelerator (https://sr-accelerator.com) were used to deduplicate the results.

Table 1
Study selection inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Full text articles, in English, Polish, Danish, or Spanish	Laboratory based, in-vivo or animal studies
Participants aged between, and inclusive of, 18 and 45 years old	Participants aged under 18 or over 45 years old
Significant injury one year or more previously	Significant injury sustained less than one year ago
Study involved imaging biomarkers	

2.2. Screening

Using pre-determined criteria (Table 1), title and abstract screening was undertaken by two independent reviewers (DK and OA) before a detailed, full-text review was conducted. A third reviewer (OOS) resolved conflicts. Inclusion criteria included full-text imaging studies; involving participants aged 18–45 (to avoid any confounding with skeletal immaturity or idiopathic OA); who sustained a significant injury at least a year prior (to ensure that initial adaptive morphological changes had resolved). Screening was undertaken using Rayyan (www.rayyan.ai). Independent data extraction was undertaken with the same reviewers in the same roles, using a pre-prepared data extraction form (Excel, Microsoft, Redmond, Washington, USA).

2.3. Extraction

Extracted data included.

- First Author, Title, Journal, Year
- Population: Number (cases/control), Sex, Injury Type, Time from Injury
- Imaging Modality, Machine Settings, Sequence, Strength, Positioning, Processing
- Comparators Used

2.4. Quality control

The Newcastle-Ottawa Scale (NOS) was used to perform risk of bias (RoB) assessments by both reviewers independently (DK and OA) with OOS adjudicating, which assesses participant selection, case-control comparability, and outcome assessment. Scoring for cohort studies is 0–9, with studies scoring 0–2 rated poor, 3–5 fair, and 6–9 good/high [19].

2.5. Synthesis

Due to study heterogeneity, a meta-analysis was not possible, with the results presented in the narrative format following the Synthesis Without Meta-analysis (SWiM) guidelines (full details in Supplementary File 2) [20].

3. Results

The searches identified 959 studies, with 670 remaining after deduplication. Initial title/abstract screen identified 70 papers meeting the criteria. All full-text manuscripts were retrieved and screened, with 11 studies meeting the inclusion criteria [21–31]. Twenty conference abstracts also met the criteria and, as per Cochrane recommendations [32,33], can be found in Supplementary File 3 [34–53]. Excluded studies can be found in Supplementary File 4, with the two most common reasons for exclusion being participant age outside the specified range and time to follow-up within a year from injury. Fig. 1 displays the PRISMA diagram.

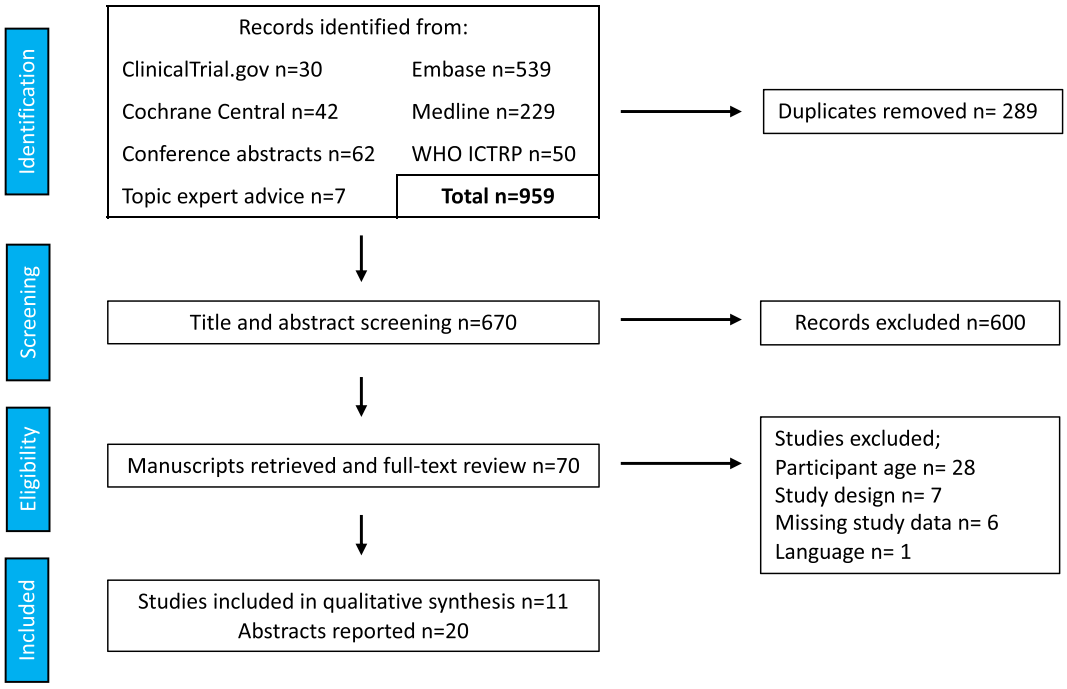

Fig. 1.

Table 2
Summary of included study characteristics.

Author, year	Exposed	Controls	Age (yrs)[a]	Study period[b]	Strength	Scoring	Comparators
Van Meer, 2016	n = 143 94 M:49F	No	25.2 (21.4–32.6)	B/L: <6mo FU: 2 yrs	1T, 1.5T, 3T	MOAKS	TAS, clinical exam, B/L MRI
Wang, 2017	n = 28 17 M:11F	n = 9 4 M:5F	29.8 (SD 6.3)	B/L: 2–3yrs FU: 2 yrs	3T	T2	ICRS, B/L MRI
Lansdown, 2017	n = 38 21 M:17F	Contra-lateral knee	29.0 (SD 8.0)	B/L: <6mo FU: 1yr	3T	SSM	SSD, B/L MRI
Pietrosimone, 2018	n = 18 8 M:10F	Contra-lateral knee	22.4 (SD 4.2)	B/L: <2wks FU: 1yr	3T	T1rho	KOOS
Zhong, 2019	n = 30 15 M:15F	n = 13 5 M:8F	32.0 (SD 8)	B/L: NS FU: 6mo, 1,2,3yrs	3T	SSM, WORMS	T1rho, T2, KOOS, previous MRI
Culvenor, 2019	n = 117 85 M:32F	No	28.2 (SD 4.9)	B/L: <4wks FU: 2,5yrs	1.5T	Cartilage thickness (PF)	Previous MRI
Struglics, 2020	n = 116 86 M:30F	No	28.2 (SD 4.9)	B/L: <4wks FU: 2,5yrs	1.5T	ACLOAS	KOOS, SF-36, molecular biomarkers
Li, 2020	n = 34 17 M:17F	Yes	30.7 (SD 8)	B/L: <3mo FU: 6mo, 1,2,3yrs	3T	TT, TR	T1rho, T2, WORMS, previous MRI
Friedman, 2021	n = 35 19 M:16F	No	31.0 (SD 7.6)	B/L: NS FU: 6mo, 1,2,3yr	3T	T1rho, WORMS	MARS, KOOS, previous MRI
Xie, 2021	n = 114 108 M:6F	n = 43 38 M:5F	26.2 (SD 3.8)	2yrs (retrospective)	3T	Radiomics modelling	T2
Wirth, 2021	n = 117 85 M:32F	No	28.2 (SD 4.9)	B/L: <4wks FU: 2,5yrs	1.5T	Cartilage thickness (FT)	Previous MRI

M: Male, F: Female, Mo: Month, yrs: Years, wks: Weeks, T: Telsa, B/L: Baseline, FU: Follow up, MRI: Magnetic Resonance Imaging, OA: Osteoarthritis, MOAKS: MRI OA Score, TAS: Tegner Activity Scale, ICRS: International Cartilage Repair Society, SSM: Statistical Shape Modelling, SSD: Side-to-Side Difference, T2: Transverse relaxation time, T1rho: spin-lattice relaxation time constant in rotating frame, WORMS: Whole-Organ MRI Score, PF: Patellofemoral, ACLOAS: Anterior Cruciate Ligament OA Score, KOOS: Knee OA Outcome Score, SF-:36: Short Form 36 questions, TT: Tibial translation, TR: Tibial Rotation, MARS: Marx Activity Rating Scale, FT: Femorotibial.

[a] Age of injured participants only, reported in Mean (SD) with exception of Van Meer 2016 which is reported as Median (Range).

[b] Baseline signifies time from injury to recruitment, follow-up reports time from recruitment.

3.1. Study characteristics

The 11 included studies had a total population of 768, with 612 injured and 78 control participants. All included studies utilised MRI; no other imaging modalities were found. The characteristics of the studies are found in Table 2, including participant numbers and ages, time to follow-up, MRI details, and comparators. Due to significant similarities in studies, the participants in Lansdown and Friedman [22,29], and Zhong and Li [25,28], are likely to be the same, with three studies analysing the KANON cohort [26,27,31,54], so there are 391 individuals involved in this review. All studies, bar one retrospective [30], were prospective and utilised observational study designs, with four adopting a case-control methodology [23,25,28,30]. Four studies used different treatment methods (surgical vs non-surgical) to define their exposure and risk of PTOA [21,26,27,31].

All injured participants sustained an ACL injury, and subsequent reconstruction (ACL-R), except for four studies comparing operative and non-operative management of ACL injuries [21,26,27,31]. After ACL

injury, 78% (n = 475) underwent ACLR. Most studies excluded concurrent joint pathology, including known OA [21–24,28-30] or meniscal and multi-ligamental injury [22,24,28–30]. Two studies reported meniscal interventions [21,25].

Some studies had equal or relatively equal numbers of males and females [24,25,28,29]; however, overall, there were more males (67% of all participants). The mean or median age of all study participants was in the early-mid 20's [21,24,30] and late 20's-early 30's [22,23,25–29, 31](Table 2).

Post-injury study observation periods varied, ranging from >1 to 5 years, as indicated in Table 2. Furthermore, the time interval from injury to ACL-R varied, with nearly all performed within six months, aside from the four studies with a late ACL-R arm [21,26,27,31]. Time to follow-up post-surgery ranged from one [22,24], two [21,26–28,30,31], three [25, 29], four [23] or five years [26,27,31].

3.2. Techniques

MR systems with different magnetic field strengths (measured in Tesla, T) and imaging sequences were employed. Seven studies utilised 3T machines, representing 65% of all study participants (n = 297). However, the KANON studies [26,27,31] used 1.5T, and Van Meer [21] utilised a combination of 1T, 1.5T, and 3T machines.

Six studies reported the use of specific knee coils, including 93% of participants (n = 422) [21–23,25,28–30], one a four-channel large flex coil [24], and three circular polarised surface coil [26,27,31]. Five studies reported participant position during MRI acquisition (57% of exposed participants, n = 261), either neural [21], sitting and supine [23], only seated [24], or partial weight-bearing extended and flexed [22,28]. 81% of studies reported detailed sequencing information, and 63% reported post-imaging processing methods (Table 2, Supplementary File 5). 54% of studies reported the reliability of their scoring methodology [21–24,28,30], and 36% reported the experience of their reporting radiologists, either fellowship trained [24] or with 8-ten years' experience [21,30,31]. Two studies, with 7% of participants (n = 56), also imaged the contralateral knee [22,24].

3.3. MRI features

3.3.1. Structural tissue features

90% of studies divided the knee into different regions, between three [21] and 20 (29), with most adopting variations of anatomical location (medial, lateral femur and tibia, and patella) [21,23–26,28–31](Table 2, Supplementary File 5), with different scoring methods used, including semi-quantitative and quantitative.

Semi-quantitative scoring systems employed included the Whole-Organ MRI score (WORMS), MRI Osteoarthritis Knee Score (MOAKS), and ACL OA Score (ACLOAS) (Table 2, Supplementary File 5). WORMS is a composite score of 14 features, including cartilage morphology, subarticular and articular bone, ligaments, meniscus and synovitis [55]. MOAKS is a further iteration of this, refining the meniscus, cartilage and BML component scoring [56]. ACLOAS is a system specifically developed following ACL injury and includes baseline joint damage, ligament and graft characteristics and other incident features [57].

18% of studies performed quantitative analysis of cartilage thickness in different regions (patellofemoral and femorotibial) two and five years after ACL injury [26,31]. Lansdown [22] reported bone morphology, including of the contralateral knee, to determine the position of the tibia to the femur (side-to-side difference, SSD), semiautomatic segmentation and shape of bony features (statistical shape modelling, SSM) and kinematics using multiple weight-bearing positions. Zhong [25] also used SSM to compare the bone shape and Li [28] bone position. Xie [30] developed quantitative radiomics models to describe cartilage and subchondral bone characteristics.

3.3.2. Compositional tissue features

Quantitative cartilage composition measurements were employed in 55% of studies, with two studies using T1rho values [24,29], two T2 values [23,30], and two both [25,28].

3.4. Comparators

45% of studies evaluated and compared MRI findings to patient-reported outcome measures (PROMs), clinical assessments, or molecular biomarkers. PROMs included activity scores in 36% [21,23–25], including the Marx activity rating scale [58] and Tegner activity score and sports activity level [59,60], the Knee Osteoarthritis Outcome Score (KOOS) [61] in 27% [24,25,27], and the short-form 36 ([62]) by 9% [27]. Van Meer [21] also recorded clinical and functional assessments, and Struglics [27] measured concurrent inflammation-associated serum and synovial fluid molecular biomarkers (Table 2).

4. Findings

4.1. Structural features

4.1.1. Bone related

4.1.1.1. Position of the tibia Using the anatomical position of the tibia (translation, TT, and rotation, TR), T1rho & T2 and WORMS, Li [28] demonstrated that ACL-R is unable to fully restore joint position, with significantly increased anterior TT and internal TR in the injured knee. TT and TR changes were also seen in the contralateral knee throughout the study period, suggesting significant biomechanical adaption. TT and internal TR increased from 1 to 2 years and were associated with significantly longer T1rho/T2 relaxation time at one year in the medial tibial (MT) region, and MT and medial femoral condyle (MFC) region at two years, suggesting a relationship between tibiofemoral position and cartilage composition. There was no cross-sectional correlation seen between TT/TR and WORMS. This study had a 33% attrition rate in the injured group, and the follow-up period varied for injured (2 years) and control participants (3 years), implicating potential selection bias.

4.1.1.2. Bone shape Using side-to-side difference (SSD) to compare the injured to the non-injured knee, Lansdown [22] demonstrated that SSM bone shape changes were associated with abnormal knee kinematics a year after ACL-R. These included increased sphericity and height of the MFC in extension and MFC height in flexion, and the lateral tibial plateau (LTP) length, medial tibial plateau (MTP) height and MTP slope. They suggest that bone shape and altered biomechanics could contribute to OA development. There were multiple significant confounders (including age, muscle function, rehabilitation, and surgical techniques) and a 30% attrition rate, potentially representing bias. Lansdown suggests their findings are correlation, not causation, and also demonstrate that ACL-R does not fully restore pre-injury joint anatomy.

Zhong [25] also employed SSM alongside T1rho, T2 relaxation, and WORMS 1, 2 and 3 years after ACL-R. The tibial plateau area and posterior tibial slope increased between injured and controls by one year, with the former increasing by three years, possibly representing early joint degeneration. There was a significant correlation between trochlear inclination and MFC height to the KOOS pain subscale at three years, and early bone changes correlated to T1rho and T2 relaxation times. This study had significant variation in time between ACL injury and ACL-R and contained no details on recruitment or attrition.

4.1.2. Cartilage morphology

Culvenor [26] demonstrated significantly greater loss of patellofemoral cartilage in the early ACLR-R after five years, most prominent in the trochlear region, compared to the other two groups, with the majority

of this occurring in the first two years. Wirth [31] did not find a significant difference in the femorotibial cartilage at five years but noted thickening of this region in the first two years. This suggests that the patellofemoral region may be more susceptive to cartilage loss. Neither study analysed features on the two-year MRI for their predictive value nor compared them to other measures, such as function or symptoms.

4.1.3. Meniscal features

Post-hoc analysis to identify the impact of chondral and meniscal injury was conducted in one study [24]. In participants with a lateral meniscal injury (the most common subset), there were associations seen with increased T1rho relaxation time in lateral femoral condyle (LFC) cartilage and worse KOOS outcomes, although as a sub-analysis in an exploratory study, this was not powered.

4.2. Compositional

Using T1rho relaxation times between the injured and contralateral knees and their relationship to KOOS, Pietrosimone [24] demonstrated that indicators of reduction in articular cartilage proteoglycan density were associated with worse patient outcomes a year from injury. The increase in interlimb T1rho mean relaxation time was correlated with worse KOOS subscores on the LFC and the medial femoral condyle (MFC). Specifically, the Posterior-LFC correlated with KOOS-Pain, and KOOS-ADL, while the Central-LFC, Posterior-LFC and Medial-MFC correlated with KOOS-Sport and KOOS-QoL. They suggest that this shows a link between decreased proteoglycan density and patient-reported knee symptoms in patients after ACL-R. This study did not fully address confounders and, being a cross-sectional study, couldn't assess progression.

Friedman [29] reported WORMS, T1rho and PROMS over three years, demonstrating that 46% (16/35) participants had cartilage degeneration, most frequently in the medial compartment (12/16), but also lateral (7/16) and patella (7/16) regions by the end of the study period. 3-year activity Marx scores positively correlated with medial femoral (MF) and MT cartilage changes, and KOOS QoL scores were inversely correlated with MT changes at three years. No relationship was seen between WORMS to T1rho or PROMs at three years, with the authors suggesting that semi-quantitative scoring alone may not be a good predictive tool. The definition of cartilage degeneration was a 14.3% change in T1rho score, based on a population with more advanced OA (n = 10) [63]. This might not apply to a post-traumatic study population, nor were different surgical procedures or injuries controlled for, with no details on attrition.

Wang [23] compared longitudinal T2 values at 2-3- and 4-5-years post ACL-R across six sub-regions to a control population. They demonstrated higher T2 values in the deep layer of the MFC region at the first time point, followed by lower T2 values in the deep layer of the lateral tibia (LT) two years later in their ACL-R group compared to their control group. They concluded that the MFC results were due to early degenerative cartilage changes post-injury, and the LT values suggested ineffective cartilage repair with poor mechanical properties. In the control group, no follow-up MRI scans were conducted, limiting relative comparisons over time, and no comparisons were made to patient-related or functional outcomes.

4.3. MRI features of inflammation

Struglics [27] was the only study to measure MRI markers of inflammation using ACLOAS. At two years, 43% of individuals had MRI-defined inflammation, of which 8% was moderate/severe effusion-synovitis, and those with effusion-synovitis present had worse KOOS subscale and SF-36 PCS scores. No longitudinal comparisons were performed, nor were correlations to cartilage composition evaluated.

4.4. Combined MRI features

Using MOAKS, Van Meer [21] showed that 40% of participants had cartilage defects and osteophytes progression over two years. BMLs were positively associated with the progression of osteophytes and cartilage defect a year later, with an odds ratio (OR) of 5.19 (95% confidence interval, 95%CI; 1.56–17.25). On the other hand, joint effusion was associated with a progression of osteophytes alone (OR 4.19; 95%CI 1.05–16.72). The authors state that their findings are hindered by the variety of MRI equipment used and MOAKS's inability to detect subtle joint abnormalities [21].

Xie [30] developed a radiomics model for distinguishing individuals at risk of PTOA two years from injury using 13 of 1116 features of cartilage and subchondral bone from T2 mapping imaging with a training (n = 110, n = 80 injured, n = 30 control) and testing cohort (n = 47, n = 34 injured n = 13 control). The model utilising 13 features based on compositional cartilage and subchondral bone markers was able to differentiate well between post-ACL-R knees and controls. This cross-sectional study had one of the largest study populations (n = 114); however, it consisted predominantly of males (92%) and did not control for other injuries.

Table 3
Risk of bias assessment using Newcastle-Ottawa Scale for cohort studies.

Author, Date	Selection	Comparability	Outcome	Overall	Rating
Van Meer, 2016	***	–	**	5	Fair
Wang, 2017	***	**	***	8	Good
Lansdown, 2017	**	–	**	4	Fair
Pietrosimone, 2018	***	–	**	5	Fair
Zhong, 2019	*	**	**	5	Fair
Culvenor, 2019	***	–	***	6	Good
Struglics, 2020	*	–	***	4	Fair
Li, 2020	**	**	**	6	Good
Wirth, 2021	***	–	***	6	Good
Friedman, 2021	**	–	**	4	Fair
Xie, 2021[a]	***	**	***	8	Good

[a] NOS adapted for cross-sectional studies used.

4.5. Risk of bias assessment

RoB assessments were performed using the NOS tool [19]. All studies, bar one [30], used the cohort study version, with one more suitable for the cross-sectional version. NOS uses a point system to determine the overall risk of bias in a study, with six studies scoring 'fair' [21,22,24,25,27,29] and five studies scoring 'good' [23,26,28,30,31] (Table 3).

5. Discussion

This systematic review, involving 11 studies and 391 individual participants, summarises the evidence regarding MRI-associated features at least one year following a significant knee injury. These features demonstrate significant structural differences in terms of tibial position post-ACL-R and MFC bone shape, plus bone and cartilage compositional changes as early as 12 months after injury and their associations with pain and function., Other features, such as BML and effusion, were associated with worse patient-reported and radiological outcomes. These features, potentially the first signals of PTOA development, could represent a panel of future MRI-related biomarkers.

Several studies in this review demonstrated widespread structural joint changes from a year post-injury [21,22,25,28,30]. These bone features, identified with SSM and radiomics, including position, shape, and BMLs, have been previously associated with early PTOA ([64–66]). Significantly, these features were associated with abnormal knee biomechanics [22], pain [25], radiological changes [21] and cartilage degeneration [28]. The medial femoral region appears to be particularly susceptible to early changes in our review [22–25,28,29], also seen elsewhere [63], and could potentially act as a sentinel region in early OA. In addition, changes in cartilage morphology, examined in two studies, were consistent with rates of radiographic OA seen in the main KANON analysis (patellofemoral 19%, femorotibial 12%) [26,31,67].

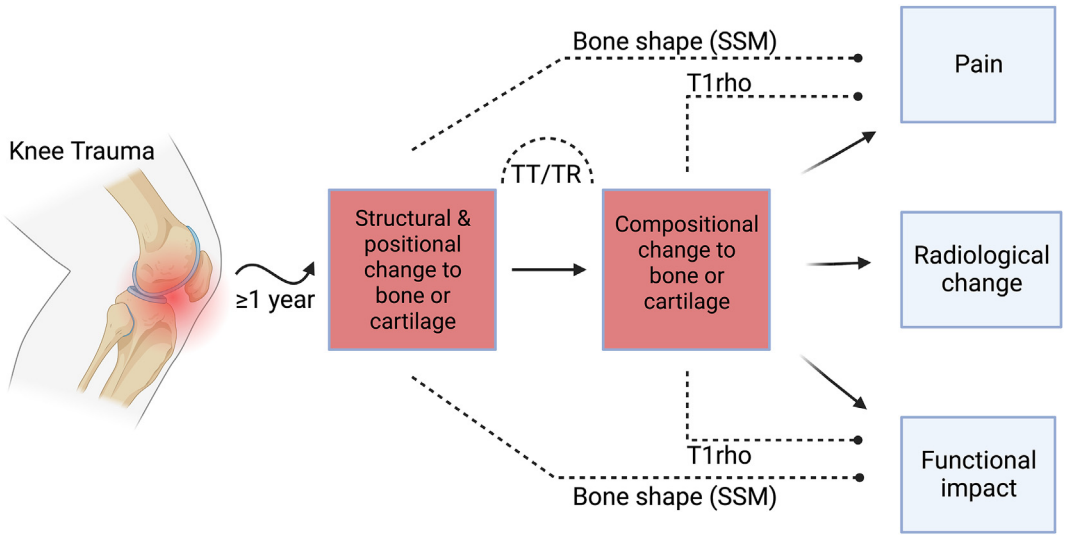

Fig. 2. The proposed pathophysiological mechanism of post-traumatic osteoarthritis with key MRI features and their associations a year or more after a significant injury. MRI: Magnetic Resonance Imaging, SSM: Statistical Shape Modelling, TT: Tibial translation, TR: Tibial rotation. Created in BioRender.

Changes to joint position post-ACL-R suggest that surgery does not seem to restore anatomical position [25,28], and bone shape, such as condylar height and length, can influence the integrity and quality of local articular cartilage [65]. Cartilage ECM degeneration with decreased proteoglycan density is linked to the subsequent development of OA/PTOA and can be investigated using advanced techniques, including T1rho and T2 [23–25,28,29]. Significant compositional changes were seen adjacent to the femoral and tibial condyles [24,29] and also at different depths of cartilage [23]. Three studies demonstrated a relationship between joint structure and cartilage composition [23,25,28], with cartilage degeneration associated with worsening pain and function [24,25,29], as seen elsewhere [68].

Based on these results, it is plausible to argue that PTOA and idiopathic OA have distinct pathophysiological mechanisms. Initial structural changes likely influence cartilage and subchondral compositions during the development of PTOA (Fig. 2), as opposed to progressive deterioration and loss of articular cartilage contributing to structural changes in the latter [1]. This mechanism has been proposed previously [63,65] and may influence tissue-specific biomarker detection in early PTOA compared to idiopathic OA.

It is believed that inflammation plays a significant role in the development of OA and PTOA, with the initial acute inflammation developing into low-grade chronic inflammation [1], affecting tribology of the joint [69], and potentially exacerbating biomechanical changes [70]; this is a focus (alongside cartilage and bone catabolism and anabolism) for molecular biomarkers [71–73]. The presence of effusion was seen to increase osteophyte progression [21] and decline in PROM scores [27], in support of previous findings describing the long-term impact of effusion, especially when associated with hemarthrosis, in the acute phase [71]. There was, however, poor concordance between imaging and molecular inflammatory biomarkers—further work is required to understand the value of imaging to identify and classify inflammation [27].

These findings suggest that timely and prospective whole-joint assessment may lead to advancements in diagnostic and prognostic tools and, consequently, the advantages of MRI over radiography. Whole-joint assessment offers the potential to identify radiographically occult injuries that may contribute to ongoing symptoms or functional impairment and provide the possibility of improved phenotyping, leading to disease stratification and personalised interventions. Another modality which provides comprehensive joint assessment is ultrasound, and it was surprising not to find any ultrasound-related studies, given evidence demonstrating its reliability and validity [9,74].

However, standardisation of MR techniques is required, including strength and reporting. Most, but not all, studies used 3T machines, which offer better image quality, higher scan efficiency and the ability to detect small lesions for musculoskeletal imaging than 1.5T ([75]). However, multiple semi-quantitative systems were in use, including MOAKS, ACLOAS and WORMS, preventing direct comparisons, and consensus should be drawn regarding this, especially in relation to time from injury, as WORMS has limitations in the acute setting, and in the assessment of bony changes, given the risk of MRI underreporting them [9,76,77].

Although all injured participants sustained an ACL injury and the majority received ACL-R, studies did not account for confounding ailments, surgical techniques, and rehabilitation programmes, all of which could have affected the variability of the findings. Current evidence suggests that concurrent meniscal injury can significantly worsen outcomes and increase the development of PTOA [78,79]. However, only two studies noted this, one of which demonstrated worse KOOS outcomes and increased T1rho relaxation time in the presence of meniscal pathology [24]. Five studies did not include concomitant meniscal injury, which, given the high prevalence of combined injuries, reduces the relevance of the results to the real world [78]. To further grasp aetiology, additional research is necessary to investigate the various injury types, single versus multi- structure injuries, and the mechanistic pathways.

There are further limitations to this review. Although RoB scores were all 'fair' or above, each study had limitations; most notably, studies were exploratory, without set hypotheses or powered sample sizes, and did not all control for confounders such as injury type or treatment, with high attrition rates. There was insufficient homogeneity to permit direct comparison and meta-analysis, which is a significant limitation. Still, SWiM guidance should provide a reliable and comparable method to report findings. Overall, the number of studies and participants was low, and despite sporting injuries being more common in females [80], the literature reviewed was heavily biased toward males. There was also a considerable variation in time from injury to surgery and follow-up, likely influencing outcomes. MRI methods varied significantly, and these should be standardised to improve data synthesis and the strength of findings. Strengths of this review include the range of sources utilised and the inclusion of conference abstracts to minimise publication bias.

In conclusion, this review has synthesised the current findings of MRI assessments a year or more following ACL injury and signposted the potential biomarkers for early OA detection in the future using structural and compositional features. The importance of whole-joint assessment

has been highlighted, given the interaction of different joint components, especially when developing diagnostic, prognostic, and predictive tools. Further evidence is required with validation in other populations, especially since it is not certain if these findings relate to PTOA or merely morphological changes following ACL-R. Until then, no definitive conclusions can be drawn regarding the utility of OA-specific MRI-based structural and compositional imaging biomarkers. During this further work, standardisation in MRI methodology and scoring is critical.

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Author contributions

OOS conceived the study. KS and OOS performed the searches. OOS, OA and DK performed the screening, data extraction and risk of bias assessments. OOS drafted the manuscript's first and subsequent versions with all authors' feedback. SK, ANB and AV provided expert guidance throughout. OOS acts as a guarantor for the study.

Data availability

Data, including data extraction forms and assessment tools, will be made available upon reasonable request to the corresponding author.

Declaration of competing interest

There are no conflicts of interest for any authors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2023.100385.

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