Osteoarthritis and Cartilage 21 (2013) 1009–1024

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Review

Cartilage adaptation after anterior cruciate ligament injury and reconstruction: implications for clinical management and research? A systematic review of longitudinal MRI studies

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ARTICLE INFO

Article history:
Received 10 October 2012
Accepted 24 April 2013

Keywords:
Anterior cruciate ligament reconstruction
Cartilage
Magnetic resonance imaging
Osteoarthritis knee
Prevention

SUMMARY

Objective: To summarize the current evidence of magnetic resonance imaging (MRI)-measured cartilage adaptations following anterior cruciate ligament (ACL) reconstruction and of the potential factors that might influence these changes, including the effect of treatment on the course of cartilage change (i.e., surgical vs non-surgical treatment).
Methods: A literature search was conducted in seven electronic databases extracting 12 full-text articles. These articles reported on *in vivo* MRI-related cartilage longitudinal follow-up after ACL injury and reconstruction in "young" adults. Eligibility and methodological quality was rated by two independent reviewers. A best-evidence synthesis was performed for reported factors influencing cartilage changes.
Results: Methodological quality was heterogenous amongst articles (i.e., score range: 31.6–78.9%). Macroscopic changes were detectable as from 2 years follow-up next to or preceded by ultra-structural and functional (i.e., contact-deformation) changes, both in the lateral and medial compartment. Moderate-to-strong evidence was presented for meniscal lesion or meniscectomy, presence of bone marrow lesions (BMLs), time from injury, and persisting altered biomechanics, possibly affecting cartilage change after ACL reconstruction. First-year morphological change was more aggravated in ACL reconstruction compared to non-surgical treatment.
Conclusion: In view of osteoarthritis (OA) prevention after ACL reconstruction, careful attention should be paid to the rehabilitation process and to the decision on when to allow return to sports. These decisions should also consider cartilage fragility and functional adaptations after surgery. In this respect, the first years following surgery are of paramount importance for prevention or treatment strategies that aim at impediment of further matrix deterioration. Considering the low number of studies and the methodological caveats, more research is needed.

Introduction

Although debated[1–3], anterior cruciate ligament (ACL) reconstruction is offered to those patients actively engaged in cutting, jumping or pivoting sports and/or other functionally demanding activities. The purpose is to improve stability of a mechanically unstable knee and to reduce the risk of subsequent meniscal or chondral damage[2,4]. Long-term radiographic studies, however, suggest that ACL reconstruction may not protect against the development of post-traumatic osteoarthritis (OA)[5].

In view of OA prevention, careful attention should be paid to the rehabilitation process and to the decision on when to allow return to sports[2,6]. In view of cartilage deterioration due to (injurious or surgical) trauma and/or biomechanical disturbances

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1063-4584/$ – see front matter
http://dx.doi.org/10.1016/j.joca.2013.04.015

(e.g., excessive anterior/lateral tibial translation and rotation, decreased knee extension)[7–17], one of the key components to guide these decisions – next to graft fixation and functional improvement – should also be the course of cartilage adaptation after surgery. However, reliable and valid methods are needed to measure cartilage adaptation *in vivo*.

This systematic review pursued two main research questions. First, how does cartilage status change over time in patients who underwent ACL reconstruction? Second, if reported, which factors might affect rate of change? To understand the effect of surgery on cartilage remodeling, the effect of treatment (i.e., surgical vs non-surgical) was additionally investigated. Hence, longitudinal follow-up studies were systematically collected reporting on any magnetic resonance imaging (MRI)-measured cartilage parameter evaluated in ACL injury and reconstruction.

Methods

This systematic review was performed according to the Prisma Statement and was confined to a quality analysis[18]. Because of study heterogeneity, statistical pooling was refrained from and, as an alternative, a best-evidence synthesis was implemented[19,20].

Information sources and literature search

Boolean searches were conducted in seven electronic databases (PubMed, SportDiscus, CINAHL, Biomedical reference collection: comprehensive, Biomed Central, Science Direct via Scirus, Web of Science) using search strategies in accordance with the semantics of each database (Appendix 1). Key – if applicable MeSH – search terms and synonyms were entered separately in two main filters which were ultimately combined. The two filters focused on:

1. *Assessed outcome*: OA, knee OR knee OA OR knee osteoarthritides OR chronic disease(s) OR disease progression(s) OR cartilage OR cartilage, articular OR joint disease(s) OR cartilage disease(s)
2. *Patients/intervention*: ACL reconstruction OR ACL/surgery OR ACL/injuries

Study selection process and eligibility criteria

Figure 1 displays the flow diagram of the study selection process. An initial search (on March 22nd, 2012) identified 5.338 records. After removal of duplicates and irrelevant titles, the remaining abstracts ($n = 506$) were rated for eligibility according to seven inclusion criteria:

1. Published in an Institute of Science Index (ISI)-indexed journal
2. Original research report with retrievable abstract and full-text
3. Human *in vivo* study
4. Cartilage-related follow-up after ACL injury and/or reconstruction
5. Should include "young adults", excluding studies specifically focusing on skeletally immature or middle-aged patients
6. Should include at least two consecutive MRI readings within ACL-injured and/or reconstructed knees
7. Published in English, French, German

Two independent readers (AVG, EW) screened abstracts both blinded for author names. To be included, all eligibility

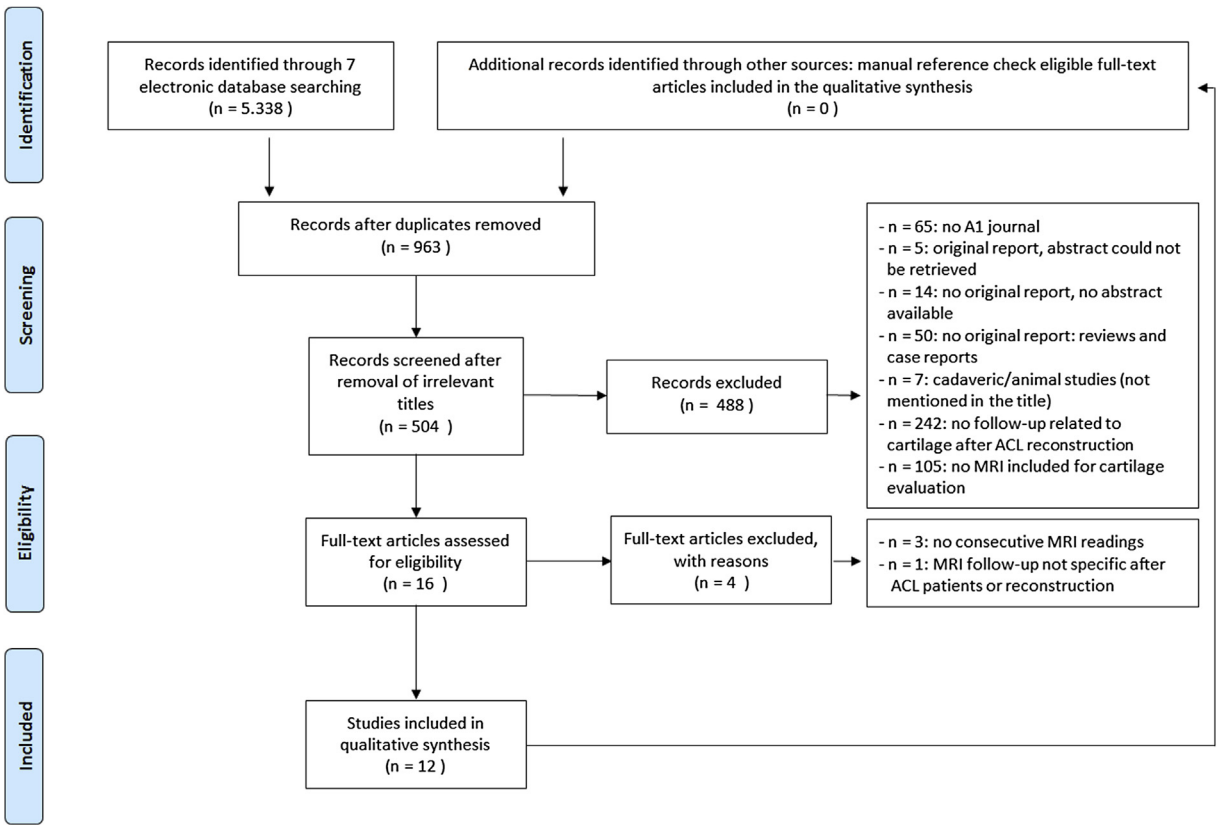

Fig. 1. Flow diagram of the study selection process adapted from Moher *et al.*[18].

criteria should be met. In case of disagreement or doubt, records were discussed and consensus was reached. Additionally, newly on-line published and potentially eligible articles were considered up until September 1st, 2012 ($n = 2$). As such, 16 full-text articles were assessed, excluding another four at this stage because of incompliance with criterion 4 and 6. Subsequently, targeted hand-searches in the reference lists of included articles were also performed. Finally, 12 studies were included in the qualitative analysis.

Quality appraisal

A customized three-composite "Total Quality Score (TQS)" was used (Table I, Appendix 2). The TQS assessed reporting adequacy, external/internal validity and power[21] and is based on general methodological requirements as put forward by the Downs and Black Quality Index[22]. Whereas the Quality Index proved reliable and valid, MRI-specific and clinical criteria were added to adjust this index to this field of study. The TQS for all included studies was determined by two readers (AVG, EW) reaching final consensus in case of disagreement or doubt. Based on two repeats performed by both readers on the included studies ($n = 12$), intra- and inter-rater reliability was evaluated for each question separately ($n = 29$). Consequently, considering the 29 separate items, intra- and inter-rater reliability was good-to-excellent (Intra-Class Correlation Coefficient (ICC) from 0.71 to 1.00) and moderate-to-excellent (ICC from 0.45 to 1.00), respectively. When compared to the Quality Index, Bland–Altman plots revealed highly correlative ($r = 0.96$, $P < 0.001$) but consistently lower TQS scores. The TQS was based on the following three components:

1. *General study quality*: 17 criteria from the Quality Index[22]
2. *Field-specific methodological features – MRI acquisition and post-processing*: eight criteria on the minimal methodological requirements of quantitative MRI studies[23]
3. *Field-specific methodological features – clinical considerations*: four criteria derived from the Coleman Methodology Score[24]

Criteria were scored ranging from 2 to 0 with (1) "yes: 1", "no: 0", or "unable to determine: 0", or (2) "yes: 2", "partially: 1", "no: 0", or "unable to determine: 0"[22], resulting into a maximum score of 38 points. If a criterion was not a requirement, the study was granted "not applicable" and the specific item was not considered in the final score. Consequently, score percentages were calculated and classified in view of the percentile-50 (P50) distribution of all scores defining "low quality" and "high quality" as "<P50" or ">P50", respectively[19].

Data extraction

Data extraction was performed by one reader (AVG) including (1) patient characteristics, (2) surgical characteristics including

Table I
TQS shortlist: Overview of the three composites with answer options

Criteria	Answer
General: reporting outcomes, external validity, internal validity*	**Max. 19 pts**
1. Hypothesis/aim/objective clearly described?	Y/N
2. Main outcomes clearly described?	Y/N
3. Main characteristics of the patients clearly described?	Y/P/N
4. Distributions of principal confounders clearly described?	Y/P/N
5. Main findings clearly described?	Y/N
6. Provision numerical estimates of random variability for the main outcomes?	Y/N
7. Characteristics of the patients lost to follow-up been described?	Y/N
8. Report of actual probability values except where probability is less than 0.001?	Y/N
9. Subjects asked to participate in the study representative?	Y/N/U
10. Analysis adjusted for different lengths of follow-up of patients?	Y/N/U
11. Statistical tests appropriate?	Y/N/U
12. Measures accurate (valid and reliable)?	Y/N/U
13. Subjects recruited from the same population?	Y/N/U
14. Subjects recruited over the same period of time?	Y/N/U
15. Adequate adjustment for confounding?	Y/N/U
16. Losses of patients to follow-up taken into account?	Y/N/U
17. Power analysis performed?	Y/N/U
Field-specific methodological features – MRI acquisition and image-analysis: reporting and internal validity†	**Max. 13 pts**
18. For quantitative imaging, loading conditions of the knee during or prior to imaging described?	Y/N
19. Magnetic field strength, scanner and coil type described/appropriate?	Y/P/N/U
20. Imaging sequence and parameters/technique described/appropriate?	Y/P/N/U
21. Anatomic regions/sub-regions clearly described?	Y/N
22. Detailed methodological description for calculation quantitative and semi-qualitative parameters described/appropriate?	Y/P/N/U
23. Longitudinal data read in pairs and blinded for sequence acquisition in view of follow-up? OR Longitudinal data read ad random and blinded to subject ID	Y/P/N/U
24. Measures of precision/reproducibility for acquisition and/or post-processing mentioned?	Y/N
25. Number of readers, level of experience and measure of reliability of reader intervention described?	Y/P/N
Field-specific methodological features – clinical considerations: reporting‡	**Max. 6 pts**
26. Rehabilitation clearly described?	Y/P/N
27. Graft use and surgical technique clearly described?	Y/P/N
28. Number of surgeons involved clearly described?	Y/N
29. Management of concomitant injuries described?	Y/N

Questions 1, 2, 5–8, 18, 21, 24, 28, 29: "Y/Yes" = score 1, "N/No" = score 0. Questions 3, 4, 25–27: "Y/Yes" = score 2, "P/Partially" = score 1, "N/No" = score 0. Questions 9–17: "Y/Yes" = score 1, "N/No" = score 0, "U/Unable to determine" = score 0. Questions 19, 20, 22, 23: "Y/Yes" = score 2, "P/Partially" = score 1, "N/No" = score 0, "U/Unable to determine" = score 0.

* Criteria and qualifications adapted from Black and Downs[22].

† Criteria based on Eckstein *et al.*[23] (2006).

‡ Criteria 26, 27, 29 derived/adapted from the Coleman *et al.* methodology[24].

outcome (Appendix 4), (3) cartilage change, (4) reference group, (5) MRI acquisition (data not shown) and post-processing, (6) baseline factors influencing the rate of cartilage change. In case of pooled cohorts, distribution of factors over individuals that underwent either operative or non-operative treatment or adjustment for treatment should be clear. Only those factors were listed that were reported to significantly influence cartilage outcomes.

The data-extraction process was performed independently of the quality appraisal. While this systematic review did not proceed to a formal meta-analysis including statistical analyses on the extracted data, consistency of the data-extraction process was not separately verified.

Best-evidence synthesis

Evidence was rated as adapted from Van Tulder *et al.*[20]: (1) strong: generally consistent findings among multiple high-quality studies, (2) moderate: generally consistent findings among multiple low-quality studies and/or one high-quality study, (3) limited: one low-quality study, (4) conflicting: inconsistent findings among multiple studies.

Results

Description of studies

All 12 studies were considered observational longitudinal studies and were published from 1999 onwards with the majority being published recently (2008–2013). Four studies included both patients that underwent surgical or non-surgical treatment[12,25–27].

One study used a 1.0 T magnet[28], five used 1.5 T[12,25–27,29], and three studies applied 3 T imaging[30–32]. Three studies reported mixed use of either 1.5 T and 0.5 T[33], 1.5 T and 3 T[34] or 1.0 T and 1.5 T magnets[35]. One study did not apply consistent sequence types between consecutive baseline and follow-up[33].

Sample sizes ranged from eight to 54 ACL-reconstructed patients with an estimated average age of 28.7 years. Apart from two studies[30,31], Body Mass Index (BMI) was not reported for ACL-reconstructed patients. Patients were predominantly male.

Hamstrings and bone-patellar tendon-bone (BPTB) autografts were each used as the only graft choice in two studies[32–35]. The other studies reported mixed graft choices entailing hamstrings and BPTB autografts[25,26], hamstrings, BPTB, and quadriceps tendon autografts[28], hamstrings autografts, tibialis posterior and Achilles tendon allografts[31], or hamstrings and BPTB autografts and Achilles tendon allografts[12].

Baseline patient and surgical characteristics are presented in Table II and Appendix 4, respectively.

Quality appraisal

TQS ranged from 31.6% to 78.9%. Six studies were depicted as "low quality"[28–30,33–35], and six studies as "high" quality"[12,25–27,31,32]. Lowest scores were attained for general external and internal validity, power, and MRI-related reporting and internal validity (Appendix 3, Table III).

Cartilage changes in view of follow-up time

In Tables IV–VII, cartilage changes are listed in view of follow-up time and baseline joint status. Follow-up ranged from 2 weeks[30] to 11 years[12].

Semi-quantitative morphology

Two studies used the MRI-modified Outerbridge score[12,28], and three studies reported on Whole-Organ MRI Score (WORMS) scores[29,31,34]. Three out of five were low-quality studies[28,29,34]. At 1 year follow-up, Li *et al.*[31] reported no change. After an average follow-up of 2.2 years from surgery, Lee *et al.*[34] detected progressive cartilage degeneration in 26.7% of all investigated sites, or improvement in 5% of sites. After an average of 2.8 years from surgery, Weninger *et al.* documented[28] cartilage degeneration in 68.9% of patients. After an average of 3.7 years from surgery, Arnoldi *et al.*[29] could not detect significant changes in prevalence of cartilage defects. Potter *et al.*[12] displayed progressive cartilage loss in femoral, tibial, patellar and trochlear cartilage registered up to 11 years post-injury.

Quantitative morphology

Two studies reported on subjective thickness changes[33,35], whereas three studies applied 3D computation of cartilage volume, thickness, or area[25,26,29]. Similarly, three out of five were low-quality studies[29,33,35]. At 1 year follow-up, Frobell *et al.*[25] noted a non-significant reduction in cartilage area of the trochlear femur and an increase in cartilage volume and thickness of the central medial femur. After 2 years, cartilage thickening of the central

Table II
Characteristics of ACL-reconstructed patients in included studies ($n = 12$)

Authors	*N* subjects	Gender M/F	Age baseline average (range or SD)	BMI average (range or SD)
Faber (1999)	23	18M/5F	30 (20–49)	NR
Costa-Paz (2001)	21	15M/6F	31 (20–58)	NR
Weninger (2008)	54	31M/14F	27.6(17-48)	NR
Frobell (2009)	34	NR*	NR*	NR
Arnoldi (2011)	9	7M/2F	35 (12)	NR
Frobell (2011)	45	NR*	NR*	NR*
Li (2011)	12	7M/5F	34 (27–45)	24.1 (2.5)
Neuman (2011)	14	NR*	NR*	NR*
Potter (2012)	26 (28 knees)	NR 14M/14F	35.1 (8.2)	NR
Theologis (2011)	9	5M/4F	35.4 (6.0, 27–45)	23.1 (2.1)
Hosseini (2012)	8	5M/3F	(19–38)	NR
Lee (2013)	36	30M/6F	34.5 (19–60)	NR

"NR": Not reported, "NR*": data not separately reported for ACL-reconstructed patients in the cohort.

Table III
Extracted data on MRI-related reporting and internal validity: post-processing algorithms in quantitative imaging methods

Authors	Method	Segmentation	Processing algorithms	Registration images?	2D/3D	Laminar or zonal?	Reproducibility precision error
Faber (1999)	Subjective thickness	No	No	NA	2D/3D	No	NR
Costa-Paz (2001)	Subjective thickness	No	No	NA	2D	No	NR
Frobell (2009–2011)	Thickness, volume, surface area	3D region-growing and knowledge-based 3D deformable model, automatic feature-based atlas for ROI, piece-wise mesh based tracking, trimming*	3D surface mesh models Volume, surface area: integration polygonal surface and triangulation, Thickness: normal distance to opposite surface*	Yes	3D	Yes	NR
Arnoldi (2011)	Thickness, volume	B-spline snakes	NR	NA	3D	No	CV: 3.3–3.5%
Li (2011)	T1rho T2	Bezier splines and edge detection*	Mono-exponential two-parameter nonlinear least square fit	Yes	3D	Yes	NR
Neuman (2011)	dGEMRIC	Manual	Bi-exponential three-parameter fit pixel by pixel	NR	2D	No	RMS CV: 5–8%*
Potter (2012)	T2	Functool 3.1 GE software	Mono-exponential, two-parameter nonlinear least squares fit	NR	2D	Yes	NR
Theologis (2011)	T1rho	Bezier splines and edge detection	Mono-exponential two-parameter nonlinear least squares fit	Yes	3D	Yes	NR
Hosseini (2012)	Thickness	Rhinoceros software package	3D surface mesh models Thickness: Euclidean distance (surface to cartilage–bone interface)	Yes	3D	No	NR

(RMS) CV: (Root Mean Square) Coefficient of Variation. NR: "Not Reported". NA: "Not Applicable".
* Reported by reference.

medial femur and thinning of the trochlear femur significantly progressed accompanied by significant thinning in the posterior medial and lateral femur[26]. After an average of 2.8 years from surgery, Costa-Paz *et al.*[35] noted cartilage thinning in 23.8% of patients. After an average of 3.7 years follow-up, Arnoldi *et al.*[29] described no significant changes. After an average of 6 years from surgery, Faber *et al.*[33] described significant cartilage thinning of the lateral femur in 56.5% of patients.

Table IV
Cartilage changes relative to baseline as an assessed MRI outcome in view of average follow-up time and baseline joint status (cartilage and concomitant injuries or procedures): Semi-Quantitative morphology

Authors	FU (years)	Parameter	Reference	ROI	Change	Baseline joint status			
						Cartilage	Meniscus	BML	Other
Li (2011)	1	WORMS	Baseline	General	=	Yes, WORMS:	Yes	Yes	K/L 1
				FL	NR	1,3			Osteophytes
				FM	NR	1			
				TL	NR	1,2,3			
				TM	NR	1			
				Ftr	NR	NR			
				P	NR	NR			
Lee (2013)	2.2	WORMS	Baseline	General	–	NR	Yes	NR	NR
				P (M-L)	=,↑				
				FL (ant-post-centr)	=,↑,↓				
				FM (ant-post-centr)	=,↑,↓				
				TL (ant-post-centr)	=,↑,↓				
				TM (ant-post-centr)	=,↑,↓				
Weninger (2008)	2.8	Outerbridge	Baseline	General	↑	Yes, Outerbridge	Yes	Yes	NR
				FL	NR	–			
				FM	NR	2			
				TL	NR	3			
				TM	NR	–			
Arnoldi. (2011)	3.7	WORMS	Baseline	General	=	Yes, WORMS:	Yes	Yes	Ligament
				FL	NR	NR			Sub-articular cyst
				FM	NR	NR			
				TL	NR	NR			
				TM	NR	NR			
				P	NR	NR			
Potter (2012)	11	Outerbridge	Baseline	General	–	Yes, Outerbridge:	No	Yes	Ligament
				FL	↑	1.8			Popliteus tendon
				FM	↑	0.0–0.5			Lateral meniscal fascicle
				TL	↑	3.0			Meniscocapsular separation
				TM	↑	0.0			
				P	↑	0.5–1.0			
				Ftr	↑	0.0–0.5			

FU: Follow-Up time in average years. ROI: Region Of Interest. K/L. Kellgren/Lawrence grade. NR = "Not Reported". P (M-L):Patella (Medial-Lateral). FL/FM: Femur Lateral/Femur Medial. "=": no (significant) difference compared to reference. "↑/↓": (significant) increase (i.e., worsening)/decrease (i.e., improvement) compared to reference. Baseline joint status includes the presence of cartilage abnormalities (i.e., "Yes", indicated by parameter and/or degree; "No", indicated by parameter and/or degree; "NR"), meniscal involvement (i.e., Yes/No/NR), Presence of BML (i.e., Yes/No/NR), or Other (i.e., specified concomitant injuries).

Table V
Cartilage changes relative to baseline as an assessed MRI outcome in view of average follow-up time and baseline joint status (cartilage and concomitant injuries or procedures): quantitative morphology

Authors	FU (years)	Parameter	Reference	ROI	Change	Baseline joint status			
						Cartilage	Meniscus	BML	Other
Frobell (2009)	1	Volume/thickness/ surface area	Baseline in patients treated with surgery or no surgery	General FL (total, centr, periph) FM (total, centr, periph) TL TM Ftr P	– = = = = = =	NR	Yes	Yes	Cortical depression fractures
Frobell (2011)	2	Thickness	Baseline in patients treated with surgery or no surgery	General FL (centr) FL (post) FM (cent) FM (post) TL TM Ftr P	– = ↓ ↑ ↓ = = ↓ =	No, No full-thickness lesions	Yes	Yes	Cortical depression fractures Meniscocapusular separation
Costa-Paz (2001)	2.8	Subjective thickness	Baseline	General FL FM TL TM	↓ NR NR NR NR	No, No arthroscopic lesions	NR	Yes	NR
Arnoldi (2011)	3.7	Volume/ thickness	Baseline	General FL FM TL TM P	– = = = = =	Yes, WORMS NR NR NR NR NR	Yes	Yes	Ligament Sub-articular cyst
Faber (1999)	6	Subjective thickness	Baseline	General FL TL	– ↓ =	No, No arthroscopic lesions	Yes	Yes	NR

FU: Follow-Up time in average years. ROI: Region Of Interest. NR = "Not Reported". P: Patella. FL/FM/Ftr: Femur Lateral/Femur Medial/Femoral Trochlea. Centr: central; periph: peripheral; post: posterior. "=": no (significant) difference compared to reference. "↑/↓": (significant) increase/decrease compared to reference. Both increases and decreases in quantitative morphology (i.e., thickness and volume) are associated with worsening of cartilage status. Baseline joint status includes the presence of cartilage abnormalities (i.e., "Yes", indicated by parameter and/or degree; "No", indicated by parameter and/or degree; "NR"), meniscal involvement (i.e., Yes/No/NR), Presence of BML (i.e., Yes/No/NR), or Other (i.e., specified concomitant injuries).

Estimates of collagen and water

Two high-quality studies applied T2 mapping[12,31]. After 1 year, Li *et al.*[31] did not detect significant T2 increases. From 1 up to11 years post-injury, Potter *et al.*[12] registered significant progression of T2 values in lateral femoral cartilage and superficial and deep patellar cartilage.

Estimates of proteoglycan (PG)/glycosaminoglycan (GAG) content

Two studies reported on changes in T1rho values[30,31] and one study used the delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) index[27]. Two out of three were high-quality studies[27,31]. Up to 1 year, Theologis *et al.*[30] revealed significant T1rho elevations in bone marrow lesion (BML)-overlying cartilage when compared to adjacent cartilage in the lateral tibial full-thickness and superficial layer. In contrast, significant T1rho decreases were established in full-thickness as well as superficial and deep BML-overlying cartilage of the lateral femur. At 1 year follow-up, Li *et al.*[31] monitored significantly elevated T1rho values in both full-thickness as well as superficial cartilage layers of the medial weight-bearing femur and tibia. After an average of 2 years from injury, when compared to healthy controls, Neuman *et al.*[27] reported an overall decrease in dGEMRIC indices in lateral and medial femoral cartilage in the patient group both at baseline and follow-up, despite the patients' attempts to recover.

Functional properties: deformational behavior

At 6 months post-surgery, a high-quality study by Hosseini *et al.*[32] showed, at lower knee flexion angles, a 42% and a 29% increase in contact-deformation in respectively the medial and lateral compartment in the reconstructed knee when compared to the healthy contra-lateral knee at baseline. Despite this difference, an attempt to recover was noted when comparing the reconstructed knee to the post-injury condition (i.e., cartilage contact-deformation in the medial compartment of 29 ± 9% and 27 ± 3%, and in the lateral compartment of 33 ± 6% and 31 ± 3% in the ACL-deficient and reconstructed knee, respectively).

Potential factors affecting rate of cartilage change (best-evidence synthesis)

BMLs (moderate evidence)

Four of the included studies associated initial BML (location, type, size/volume) with location and occurrence of cartilage thinning/increased cartilage loss, depression or increased T1rho values at 2 weeks up to 11 years follow-up[12,30,33,35]. In this regard, Potter *et al.*[12] established that the initial BML size was significantly associated with increased cartilage loss the first 3 years in the lateral tibia and the first 2 years in the lateral femur. In the lateral tibia, Theologis *et al.*[30] found a significant positive correlation between BML volume and percentage increase in T1rho values of the cartilage overlying the BML relative to the surrounding cartilage up to 1 year from injury ($r = 0.74$).

Meniscal injury/meniscectomy (strong evidence)

Medial meniscal lesions at baseline showed increased T1rho and T2 values in the ipsilateral femur at 1 year follow-up[31]. In support,

Table VI
Cartilage changes relative to baseline as an assessed MRI outcome in view of average follow-up time and baseline joint status (cartilage and concomitant injuries or procedures): estimates of collagen/water, and PG/GAG content

Authors	FU (years)	Parameter	Reference	ROI	Change	Baseline joint status			
						Cartilage	Meniscus	BML	Other
Li (2011)	1	T2/T1rho	Baseline in healthy controls	General	–	Yes, T2/T1rho	Yes	Yes	K/L 1
				FL (total, sup, deep)	=/=	=			Osteophytes
				FM (total, sup)	=/↑	=			
				FM (deep)	=/=	=			
				TL (total, sup)	=/=	=/↑			
				TL (deep)	=/=	↑/=			
				TM (total, sup)	=/↑	=			
				TM (deep)	=	=			
Theologis (2011)	Up to 1	T1rho in cartilage overlying BML	Surrounding cartilage	General	–	Yes, T1rho	No	Yes	No
				FL	↓	↓			
				FLsup	↓	↓			
				FLdeep	↓	↓			
				FM (total, sup, deep)	=	=			
				TL	↑	↑			
				TLsup	↑	↑			
				TLdeep	=	=			
				TM (total, sup, deep)	=	=			
Neuman (2011)	2	dGEMRIC	Baseline in patients treated with surgery or no surgery	General	–	No, No lesions in ROI	Yes	Yes	NR
				FL	↑				
				FM	=				
Potter (2012)	1–11	T2	Baseline in patients treated with surgery or no surgery	General	–	Yes, Outerbridge	No	Yes	Ligament
				FL	↑	1.8			Popliteus tendon
				TL	=	3.0			Lateral meniscal fascicle
				P (sup, deep)	↑	0.5–1.0			Meniscocapsular separation

FU: Follow-Up time in average years. ROI: Region Of Interest. K/L: Kellgren/Lawrence grade. NR = "Not Reported". P: Patella. FL/FM: Femur Lateral/Femur Medial. Sup: superficial. "=": no (significant) difference compared to reference. "↑/↓": (significant) increase (i.e., worsening in case of T2or T1rho and improvement in case of dGEMRIC index)/decrease (i.e., improvement in case of T2 or T1rho and worsening in case of dGEMRIC index) compared to reference. Baseline joint status includes the presence of cartilage abnormalities (i.e., "Yes", indicated by parameter and/or degree; "No", indicated by parameter and/or degree; "NR"), meniscal involvement (i.e., Yes/No/NR), presence of BML (i.e., Yes/No/NR), or other (i.e., specified concomitant injuries).

lateral/medial meniscal tears corresponded with lower femoral cartilage dGEMRIC indices at on average 2 years follow-up from injury[27]. Partial meniscectomy also led to lower femoral cartilage dGEMRIC indices[27].

Time from injury (moderate evidence)

Regardless of surgical intervention, Potter *et al.*[12] established that, when compared to baseline (i.e., post-injury), the risk of cartilage loss doubled from year 1 for the lateral femur, lateral tibia, and medial femur, and tripled for the patella. By years 7–11 after injury, the risk of cartilage loss for lateral femur was 50 times that of baseline, 30 times that for the patella, and 19 times for the medial femur.

Biomechanical factors (moderate evidence)

One study linked lack of biomechanics restoration after reconstruction to shifts in contact points toward regions of thinner cartilage displaying increased contact-deformation, especially at lower flexion angles[32].

Surgical vs non-surgical treatment

At 1 year after injury, ACL reconstruction was directly and significantly related to a reduction in cartilage area of the trochlear femur and to an increase in cartilage volume and thickness of the central medial femur[25]. After 2 years, treatment was no longer related to any of the changes in cartilage morphology[26]. Similarly, Neuman *et al.*[27] reported a similar course in dGEMRIC index changes in both patients that underwent surgical or non-surgical treatment after an average of 2 years from injury. Based on 11 years follow-up, Potter *et al.*[12] established higher Odd's ratios for cartilage loss in the medial tibia in non-surgical compared to surgical treatment.

Discussion

Next to baseline influencing factors, the main goal of this systematic review was to summarize the MRI-detected evidence of cartilage adaptation after ACL reconstruction. To understand the effect of surgery on the course of cartilage adaptation, this systematic review additionally investigated the effect of treatment (i.e., operative vs non-operative). The main conclusions regarding clinical management and research directions are tabulated in Table VIII.

While MRI evaluation is the measure of interest, several methodological issues require consideration. Next to insufficient field strength (<1.0 T) in one study, three studies implemented mixed

Table VII
Cartilage changes relative to baseline as an assessed MRI outcome in view of average follow-up time and baseline joint status (cartilage and concomitant injuries or procedures): functional properties – deformational behavior

Authors	FU (years)	Parameter	Reference	ROI	Change	Baseline joint status			
						Cartilage	Meniscus	BML	Other
Hosseini (2012)	0.5	Contact deformation	Baseline contra-lateral intact knee	General	–	No, No visible lesions	No	No	No
				Lateral compartment	↑				
				Medial compartment	↑				

FU: Follow-up time in average years. ROI: Region Of Interest. "=": no (significant) difference compared to reference. "↑/↓": (significant) increase (i.e., worsening)/decrease (i.e., improvement) compared to reference. Baseline joint status includes the presence of cartilage abnormalities (i.e., "Yes", indicated by parameter and/or degree; "No", indicated by parameter and/or degree; "NR"), meniscal involvement (i.e., Yes/No/NR), Presence of BML (i.e., Yes/No/NR), or Other (i.e., specified concomitant injuries).

Table VIII
Take Home Messages for clinical management and future research directions

Clinical management	Future research directions
• Chondral defects are commonly detected in ACL-injured and reconstructed knees • Gross MRI-detected morphological change requires approximately 2 years • Prevention should focus on ultra-structural deterioration accelerating cartilage loss • In the lateral compartment, morphological and/or ultra-structural damage most likely progresses from blunt trauma onwards. Medially, changes presumably start during the first year, hitherto recorded the soonest at 3 weeks follow-up • Moderate-to-strong evidence exist for baseline factors meniscal lesion/meniscectomy, BML, time from injury and persistent altered biomechanics as influencing rate of cartilage change after ACL reconstruction • (Late) post-operative rehabilitation should also consider cartilage status in return to play decisions • ACL-reconstructed knees may benefit from longer recovery than non-surgically treated knees. After 1 year, treatment effects disappear and, so far, no treatment option appears convincingly superior in view of structural longevity of the knee	• Longitudinal follow-up studies of cartilage ultra-structural changes during the first year(s) following injury or reconstruction. UTE and UTE-T2* and T1rho imaging may be more sensitive than standard T2 mapping in this respect • Validation of MRI biomarkers in long-term studies in view of the prediction of future radiographic and/or symptomatic OA • Prospective risk factor studies to support identification of patients treated with ACL reconstruction at risk for accelerated cartilage degeneration • High quality (multi-center) Randomized Controlled Trials (RCT's) on the efficacy and safety of biological, surgical, and rehabilitation techniques in mediating cartilage morphological and ultra-structural deterioration following ACL injury and reconstruction both in the short- and long-term

field strengths and/or sequence types throughout consecutive baseline and follow-up[33–35]. These inconsistencies jeopardize longitudinal morphological assessment[36–41]. Quantitative morphology was rated on 2D[33,35] or 3D image stacks[25,26,29,33]. As opposed to 2D (Fast) Spin Echo ((F)SE) imaging, 3D Spoiled Gradient echo Recalled acquisition (SPGR)/Fast Low Angle Shot (FLASH) or Dual Echo in the Steady State (DESS) sequences allow thinner sections with near-isotropic high-resolution that avoid partial volume averaging and allow analysis independent of slice orientation or localization[36–38,41]. Hence, computerized 3D quantification is superior over 2D or subjective evaluation. Although the reported 3D techniques are appropriate, measures of reproducibility were hardly described (Table III). A recent systematic review by Hunter *et al.*[42] confirmed that both semi-quantitative and quantitative morphological methods perform with moderate-to-excellent intra- and inter-reader consistency and good responsiveness to longitudinal change. However, present variability of quantitative techniques attained up to a coefficient of variation (CV) of 3.5% (Table III), limiting detection of significant change within the first year (i.e., expected mean relative changes: −2.2% to +3.3%[25,26]). Despite the majority of low-quality studies, the course of morphological adaptation described below is supported by the few high-quality trials[12,25,26,31].

Apart from morphology, compositional imaging techniques such as T2, T1rho mapping and dGEMRIC imaging were appraised. T2 mapping is sensitive to changes in hydration (or, nearly equivalently collagen concentration) as well as to organization of the anisotropic arrangement of the collagen fibrils in the extra-cellular matrix. Early cartilage degeneration, reflected by increased matrix permeability, appears as an increase in T2[36–38,41,43]. T1rho mapping is suggested to provide superior sensitivity to early deterioration compared to standard T2 mapping, especially when applying laminar analyses[31]. While reported non-specific, T1rho relaxation times inversely relate to PG depletion[36–38,41,43]. dGEMRIC, T1 imaging in the presence of $GdDTPA^{2-}$ (i.e., T1Gd or dGEMRIC index), reflects cartilage $GdDTPA^{2-}$concentration, and, hence indirectly, GAG concentration. Low dGEMRIC indices are commonly observed in areas of cartilage degeneration[36–38,41,43,44].

Whereas both T2 and T1rho analyses may have benefited from a multi-exponential decay model[43,45,46], Ultra-short TE (UTE) and UTE-T2* imaging techniques may have been more sensitive than standard T2 mapping in detecting early matrix changes (toward the cartilage–bone interface)[47]. An increased sensitivity for change of T2* compared to standard T2 has already been shown in ACL-reconstructed knees as soon as 6 months post-surgery[6]. Whereas T1rho quantification may have been less orientation-dependent[44,46–48], magic angle effects may have affected T2 outcomes[44]. Despite all influencing factors, relative changes were interpreted instead of actual values to allow for comparison between studies. As dGEMRIC index quantification depends, next to GAG content, on contrast supply and distribution within the tissue, matrix permeability may have gradually changed during follow-up warranting circumspection in the interpretation of index change[49]. Apart from Neuman *et al.*[27], no compositional imaging study reported measures of reproducibility (Table III). Variability (i.e., CV) in T2, T1rho and dGEMRIC indices is documented to range from 1 to 9%[6,50,51], 3.3–8.5%[51,52], and 5–8%[27], respectively, appropriate in view of the expected differences during the first years (i.e., −3.4% to +17.6%[27,31]).

This review determined that MRI-detectable progressive macroscopic change after ACL reconstruction requires on average 2 years. The absence of substantial baseline cartilaginous injury did not seem protective against progressive degeneration when time reaches or elapses 2-year follow-up[26,33,35]. Noted both medially and laterally, macroscopic changes appeared more evident in the femur than in the tibia[25,26,33,34]. In support, animal models documented that ACL transection resulted in higher thickness increases in femoral than tibial cartilage[53,54]. The corresponding decrease in compressive stiffness might render femoral cartilage more susceptible to surface fibrillation[55] possibly explaining the location of most evident morphological change[53–57].

Before or simultaneous with macroscopic change, cartilage in ACL-reconstructed knees suffers from compositional adaptations. Changes in matrix constituents may present as remnants of blunt trauma and afterward as maintained by the biochemical environment within the knee, co-existing injuries, surgical procedures and persistent biomechanical alterations. Baseline elevated T2, T1rho values and decreased dGEMRIC indices in the lateral tibia or femur are presumably resulting from blunt trauma and tissue edema[7,27,31]. In this regard, impact traumata cause ultra-structural and morphological changes (i.e., surface fraying and delamination, tidemark disruption, accumulation of unbound water, PG loss)[7,58] and are likely accompanied by BML or cortical depression fractures on MRI[59]. These concomitant baseline injuries were frequently reported and, hence, support that blunt trauma led to the ultra-structural baseline changes captured by MRI. Interestingly, in the lateral femur, Theologis *et al.*[30] reported decreased T1rho values in BML-overlying cartilage suggestive of increased relative PG contents. This study mainly compared weight-bearing to non-weight-bearing regions within the same knee with the latter possibly presenting with higher T1rho values because of the natural topographical variation in GAG contents[48,60].

During the first year(s), healing attempts in the lateral compartment are noted (i.e., increase in dGEMRIC index, decrease

in T2 and contact-deformation)[7,27,31,32], however based on limited follow-up (i.e., up to an average of 2 years from injury) as deterioration appears to progress nonetheless. In this regard, signs of incomplete recovery are pronounced by progressive cartilage defects accompanied by T2 prolongation in the lateral femur and patella from the first year onwards[12] and by maintenance or development of ultra-structural, morphological, and functional changes medially recorded the soonest at 3 weeks after injury[7,12,25–27,31,32,34]. Early medial deterioration presumably results from net GAG loss rather than trauma-induced tissue edema suggesting global biochemical disturbance in the ACL-injured joint[7]. Although the medial compartment is not likely involved in blunt trauma, it often develops OA in the long-term[61–64].

The prevalence of radiographic patella-femoral (PF) OA is reported to range from 11 to 90% following 2–15 years after ACL surgery[65–67]. In this study, six articles[12,25,26,29,31,34] included investigation of the patella and/or femoral trochlea, four of those revealing considerable PF involvement in morphological[25,26,34] and ultra-structural changes[12]. PF cartilage damage might result from impaction of joint surfaces and/or from inflammatory responses upon injury or surgery[66]. Additionally, insufficient restoration of knee biomechanics or patellar orientation, accompanied by possible extension Range Of Motion (ROM) or quadriceps strength deficits, may affect PF joint contact areas and loading patterns increasing its vulnerability toward degeneration[66–69].

Moderate-to-strong evidence was provided for meniscal lesions/meniscectomy, time from injury, BML and altered biomechanics as potentially influencing cartilage change following reconstruction. Association sizes (e.g., Odd's Ratio) were not consistently presented but were rather reported by *P*-values and/or averages. Nonetheless, in long-term studies of ACL reconstruction or OA, meniscal involvement[5,62–64,70–73], BML[74] and length of follow-up[63,75] persist as risk factors for MRI-detected cartilage degeneration or radiographic OA. As reconstruction (combined with partial medial meniscectomy) only partially restores knee biomechanics[13–17,76,77], cartilage–cartilage contact points may shift toward regions of thinner cartilage not sufficiently adapted to cope with impact or shear stresses[32,78]. Next to shifts in contact area, MRI cartilage T2 and thickness analyses in animal models additionally proposed that medial meniscectomy resulted in increased contact stress[79,80]. As revealed by finite element modeling, altered contact stresses may impair cartilage fluid pressurization, dissipation and load-transferring properties[81]. Finally, BMLs are hypothesized to reduce the stress-dissipating capacities of the cartilage-subchondral bone unit and to impede nutritional flow toward the cartilage tissue potentially contributing to quality degradation[82]. Four of the presently evaluated studies investigated cohorts that included both individuals that underwent operative and non-operative treatment[12,25–27]. With respect to these studies, caution may be warranted when directly applying factors potentially influencing rate of cartilage change onto ACL reconstruction alone because of the suggested treatment effects on cartilage status in the early years of follow-up. In this regard, despite protection against subsequent meniscal procedures, ACL reconstruction presented with pronounced morphological changes during the first year when compared to non-surgical treatment[25]. When time progressed, treatment effects disappeared or even displayed protective effects against cartilage loss in cases treated with isolated reconstruction[12,26,27]. Supplementary BML and/or prolonged inflammatory cascades caused by surgery might cause slower resolution of BML and joint fluid volumes during the first year[25] inviting speculation on the need for extended recovery in ACL reconstruction[6,25,26]. Nonetheless, cartilage in both patients that underwent surgical or non-surgical treatment evolves toward early arthritic changes[26] and neither of both treatment options convincingly safeguards structural longevity of the knee so far[83]. Therefore, in view of these treatment effects during the early years of follow-up, this systematic review only considered those risk factors in the best-evidence synthesis for which distribution over operated and non-operated patients could be clearly discerned or for which adjustment for treatment was made clear. Hence, risk factors are not limited to those presented here and more research is needed identifying patients at risk for accelerated cartilage disease after ACL reconstruction.

MRI-measured morphological changes, low dGEMRIC indices, and increased T2 are associated with accelerated cartilage degeneration, radiographic OA or total knee arthroplasty[84–87]. Although confirmation in future long-term studies on radiographic and/or symptomatic OA following ACL injury remains warranted, the present early arthritic changes are considered important in view of future joint deterioration. As during the early phase cartilage might be more susceptible to treatment and prevention strategies[88], speculation on biological, surgical and rehabilitation interventions effecting chondroprotection is tempting. One needs to stress that these interventions require well-designed short- and long-term clinical trials to confirm efficacy and safety in (ACL-injured) patients. Proposed biological treatments may include symptomatic slow acting drugs, biophysical stimulation modalities, viscosupplementation, blood derivates, mesenchymal cell based therapies, and stimulation or inhibition of respectively anabolic and catabolic pathways[89]. Whereas in view of restoring joint kinematics anatomic double-bundle reconstruction may be preferred, surgical interventions may also involve cartilage repair or meniscal preservation or restoration procedures (i.e., meniscus repair or replacement)[90–92]. Altered biomechanics including gait, affects both limbs and is – of the identified influencing factors – the only potentially modifiable post-surgery[93–95]. Apart from graft positioning[14,90], neuromuscular and/or quadriceps (eccentric) strength training may remedy altered gait while potentially positively influencing GAG content[95,96]. Additionally, specific gait retraining focusing on cadence and stride frequency preferably directed by a metronome[97] could be useful next to the potential use of insole or shoe modification[98]. Furthermore, joint and cartilage vulnerability, especially in case of BML or meniscal involvement, should be considered in return to sports approvals. In this regard, depending upon the athlete's profile and type of sports, return to play takes place at on average 6 months from surgery. At this point in time, diminished cartilage quality and *in vivo* resiliency was revealed in ACL-reconstructed patients especially in those resuming sports before 5 months after surgery[6]. Hence, one might argue that cartilage may be at risk for further deterioration when imposed with high(er) impact loads that typically occur during sports. Ideally, adding a feasible MRI protocol to functional tests may support return to play decisions. As a weak correlation exists between symptoms and joint health[99], in this review, no baseline clinical factors (Appendix 4) related to cartilage status. Interestingly, although cause-effect interpretation remains unclear, Potter *et al.*[12] linked increased cartilage loss to decreased patient-reported activity-related scores at follow-up.

Conclusion

In ACL reconstruction, cartilage macroscopic changes were detectable after approximately 2 years follow-up. In view of OA prevention, braking (early) deterioration of matrix constituents is key. In the lateral compartment, ultra-structural and morphological damage most likely progresses from blunt trauma onwards. Medially, changes presumably start during the first year, hitherto recorded the soonest at 3 weeks follow-up. These results may have implications on future research directions, prevention and treatment including return to play decisions. Important factors are meniscal lesions/meniscectomy, BML, time from injury, persistent

altered biomechanics. First-year morphological changes were more pronounced in knees that underwent reconstruction compared to non-surgical treatment.

Author contribution

Van Ginckel, Ans: conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, collection and assembly of data.

Verdonk, Peter: conception and design, critical revision of the article for important intellectual content, final approval of the article.

Witvrouw, Erik: conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article.

Conflicts of interest

Peter Verdonk receives consultancy and lecture fees, payment for development of educational presentations and travel expenses/accommodation/meeting expenses and owns stock/stock options from Smith and Nephew. The other authors did not declare any conflict of interest.

Role of the funding source

Ans Van Ginckel is supported by the Research Foundation – Flanders (FWO Aspirant). The funding source had no involvement in the study design, collection, analysis and interpretation of the data; in writing of the manuscript; and in the submission to submit the manuscript for publication.

Acknowledgments

The authors gratefully acknowledge the department of radiology of Ghent University Hospital, Greta Vandemaele, PhD Siemens MRI application specialist, ir Pieter Vandemaele, for sharing their expertise with our department regarding MRI sequence implementation and curve-fit analysis.

Appendix 1

Table AI
Search strategies

Pubmed All terms were searched in [All Fields], next to – if applicable – [MeSh] **MeSH terms**	(**OA**, **knee** OR **knee OA** OR **knee osteoarthritides** OR **chronic disease** OR **chronic diseases** OR **disease progression** OR **disease progressions** OR gonarthrosis OR osteoarthrosis OR degenerative arthrosis OR post-traumatic OA OR secondary OA OR **cartilage** OR **cartilage**, **articular** OR cartilage degeneration OR cartilage deterioration OR cartilage defect OR cartilage defects OR **joint disease** OR **joint diseases** OR **cartilage disease** OR **cartilage diseases**) AND (**ACL reconstruction** OR **ACL/surgery** OR ACL repair OR ACL operation OR ACL plasty OR **ACL/injuries** OR ACL injury OR ACL injuries OR ACL reconstruction OR ACL repair OR ACL surgery OR ACL operation OR ACL plasty)
SportDiscus – CINAHL – Biomedical Reference Collection: comprehensive (EbscoHost-version) Biomed Central Scirus	(Osteoarthr* knee OR knee osteoarthr* OR chronic disease* OR disease progression* OR gonarthr* OR osteoarthr* OR degenerative arthr* OR post-traumatic osteoarthr* OR secondary osteoarthr* OR cartilage OR cartilage, articular OR cartilage degeneration OR cartilage deterioration OR cartilage defect* OR joint disease* OR cartilage disease*) AND (ACL reconstruction OR ACL surgery OR ACL repair OR ACL operation OR ACL plasty OR ACL injur* OR ACL injur* OR ACL reconstruction OR ACL repair OR ACL surgery OR ACL operation OR ACL plasty)
Web of Science	1. Focus on cartilage quality TS = (Osteoarthr* knee OR "knee osteoarthr*" OR "chronic disease*" OR "disease progression*" OR gonarthr* OR osteoarthr* OR "degenerative arthr*" OR "post-traumatic osteoarthr*" OR "secondary osteoarthr*" OR cartilage OR cartilage, articular OR "cartilage degeneration" OR "cartilage deterioration" OR "cartilage defect* "OR "joint disease*" OR "cartilage disease*") AND TI = (osteoarthr* knee OR "knee osteoarthr*" OR gonarthr* OR "degenerative arthr*" OR "post-traumatic osteoarthr*" OR "secondary osteoarthr*" OR cartilage OR cartilage, articular OR "cartilage degeneration" OR "cartilage deterioration" OR "cartilage defect* "OR "joint disease*" OR "cartilage disease*") 2. Focus on ACL reconstruction TS = ("ACL reconstruction" OR "ACL surgery" OR "ACL repair" OR "ACL operation" OR " ACL plasty" OR "ACL injur*" OR "ACL injur*" OR "ACL reconstruction" OR "ACL repair" OR "ACL surgery" OR "ACL operation" OR "ACL plasty") AND TI = ("ACL reconstruction" OR "ACL surgery" OR "ACL repair" OR "ACL operation" OR " ACL plasty" OR "ACL injur*" OR "ACL injur*" OR "ACL reconstruction" OR "ACL repair" OR "ACL surgery" OR "ACL operation" OR "ACL plasty")

Appendix 2

Table AII
Criteria quality appraisal: three composites of TQS

Criteria	Answer	Remarks criteria qualifications
General: Reporting outcomes, external validity, internal validity*		
Reporting		
1. Is the hypothesis/aim/objective clearly described?	Y/N	
2. Are the main outcomes to be measured clearly described in the introduction or methods section?	Y/N	
3. Are the main characteristics of the patients included in the study clearly described?	Y/P/N	Should at least include: number of patients, gender, age, BMI. If *all* are described "Yes", if *none* are described "No", if *some but not all* are described "Partially"

Table AII (*continued*)

Criteria	Answer	Remarks criteria qualifications
4. Are the distributions of principal confounders clearly described?	Y/P/N	Age, gender, BMI, physical activity level, concomitant injuries (if applicable), different grafts used (if applicable)
5. Are the main findings of the study clearly described?	Y/N	
6. Does the study provide numerical estimates of random variability in the data for the main outcomes?	Y/N	E.g., inter-quartile range, standard error, standard deviation, confidence interval
7. Have the characteristics of the patients lost to follow-up been described?	Y/N	Should be answered "Yes" where there were no losses to follow-up or losses to follow-up were so small findings would be unaffected by their inclusion (i.e., response rate ≥80%). Should be answered "No" where study did not report losses to follow-up
8. Have actual probability values been reported for the main outcomes except where probability is less than 0.001?	Y/N	
External validity		
9. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Y/N/U	Must identify source of patient population and describe how patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample
Internal validity		
10. Do the analysis adjust for different lengths of follow-up of patients?	Y/N/U	When follow-up was the same for all study patients, or different lengths were adjusted for, answer "Yes". Studies where differences in follow-up are ignored should be answered "No"
11. Were the statistical tests used to assess the main outcomes appropriate?	Y/N/U	
12. Were main outcome measures used accurate (valid and reliable)?	Y/N/U	
13. Were all study subjects recruited from the same population?	Y/N/U	E.g., comparison of groups recruited from the same hospital
14. Were study subjects recruited over the same period of time?	Y/N/U	
15. Was there adequate adjustment for confounding in the analysis from which main findings were drawn?	Y/N/U	If the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses, the question should be answered as "No"
16. Were losses of patients to follow-up taken into account?	Y/N/U	If no loss to follow-up reported, the question should be answered as "Unable to determine". If the proportion loss to follow up was too small to affect the main findings, the question should be answered as "Yes"
Power		
17. Did the study perform a power analysis to have sufficient power to detect a clinically important effect where the probability value for a difference being due to change is less than 5%?	Y/N/U	
Field-specific methodological features – MRI acquisition and image-analysis: reporting and internal validity†		
Reporting		
18. In case of quantitative morphological or compositional imaging, were loading conditions of the knee during or prior to imaging described?	Y/N	e.g., period of rest or unloading, traction
19. Were magnetic field strength, scanner and coil type clearly described and appropriate?	Y/P/N	If adequately described and appropriate, the questions should be answered "Yes", if partially described, answer "Partially", if not reported or inadequate, answer "No". Appropriate = at least 1.0 T with consistent use of field strength at follow-up
20. Were imaging sequence and parameters/technique clearly described and appropriate?	Y/P/N	Appropriate = appropriate choice of sequence and consistent between consecutive evaluation time points
21. Were anatomic regions/sub-regions clearly described?	Y/N	
22. Was a detailed, clear and appropriate description provided on how quantitative parameters were calculated? In case of semi-qualitative scoring systems, were different grades clearly reported?	Y/P/N	In case of adequate referral, the question should also be answered "Yes"
Internal validity		
23. Were longitudinal data read in pairs and were readers blinded to sequence acquisition in view of follow-up? OR Were longitudinal data read ad random and blinded to subject ID?	Y/P/N/U	If the article does not provide information to answer, choose "unable to determine"
24. Were measures of precision or reproducibility for image acquisition and/or post-processing analysis mentioned?	Y/N	E.g., CV or RMS CV
25. Was number of readers, level of experience and measure of reliability of reader intervention described?	Y/P/N	
Field-specific methodological features – clinical considerations: reporting‡		
Reporting		
26. Was rehabilitation clearly described?	Y/P/N	"Partially" means that rehabilitation is only mentioned without time-bound and/or exercise prescription mentioned nor referred to
27. Was graft use and surgical technique clearly described?	Y/P/N	"Partially" means that only graft use or name of technique is mentioned without more detailed description of surgical description
28. Was number of surgeons involved clearly described?	Y/N	
29. Was management of concomitant injuries described?	Y/N	

Questions 1, 2, 5–8, 18, 21, 24, 28, 29: "Y/Yes" = score 1, "N/No" = score 0. Questions 3, 4,25–27: "Y/Yes" = score 2, "P/Partially" = score 1, "N/No" = score 0. Questions 9–17: "Y/Yes" = score 1, "N/No" = score 0, "U/Unable to determine" = score 0. Questions 19, 20, 22, 23: "Y/Yes" = score 2, "P/Partially" = score 1, "N/No" = score 0, "U/Unable to determine" = score 0.

* Criteria and qualifications adapted from Black and Downs[22].

† Criteria based on Eckstein *et al.*[23] (2006).

‡ Criteria 26, 27, 29 derived/adapted from the Coleman methodology[24].

Appendix 3

Table AIII
Quality appraisal of included eligible studies ($n = 12$)

Criteria	Weninger (2008)	Li (2011)	Lee (2013)	Costa-Paz (2001)	Faber (1999)	Frobell (2009)	Frobell (2011)	Potter (2012)	Neuman (2011)	Hosseini (2012)	Theologis (2011)	Arnoldi (2011)
Aim/hypothesis/objective	1	1	1	1	1	1	1	1	1	1	1	1
Main outcomes	1	1	1	1	1	1	1	1	1	1	1	1
Patient characteristics	1	1	1	1	1	1	2	1	2	1	2	1
Distribution principal confounders	1	2	1	1	1	1	2	1	2	1	1	0
Main findings	1	1	1	1	1	1	1	1	1	1	1	1
Numerical estimates random variability	1	1	0	0	1	1	1	1	1	1	0	1
Patient characteristics lost to follow-up	1	1	1	1	1	1	1	1	1	1	1	1
Actual *P*-values	0	1	0	0	1	1	1	1	1	1	0	0
Representative subjects	1	0	0	0	0	0	1	0	0	0	0	0
Adjusted analysis for length follow-up	0	1	0	0	0	1	1	1	1	1	1	0
Appropriate statistics	0	1	0	0	1	1	1	1	1	1	1	0
Accuracy methods	1	1	0	0	0	1	1	1	1	1	1	1
Recruited from same population	1	0	1	0	0	0	0	0	0	1	1	0
Recruited within Same time period	1	1	1	0	0	1	1	1	1	0	0	0
Confounder-adjusted analysis	0	1	0	0	0	0	1	1	1	0	0	0
Loss to follow-up accounted for	1	1	1	1	1	1	1	1	1	1	1	1
Power analysis	0	0	1	0	0	0	0	0	0	0	0	0
Sub-score general (%)	*63.2*	*78.9*	*52.6*	*36.8*	*52.6*	*68.4*	*89.5*	*73.7*	*84.2*	*68.4*	*63.2*	*42.1*
Pre-imaging loading conditions	NA	0	NA	0	0	0	0	0	0	0	0	1
MRI equipment	1	2	0	0	0	2	2	2	2	2	2	2
Imaging acquisition/technique	1	2	1	1	0	2	2	2	2	1	2	2
Anatomic regions	0	1	1	1	1	1	1	1	1	1	1	1
Methodology derivation of MRI parameters	2	2	2	0	0	2	2	2	2	2	2	1
Blinding	0	0	0	0	0	0	0	1	0	0	0	0
Precision MRI measures	0	0	1	0	0	0	0	0	1	0	0	1
Reader number, experience, consistency	0	2	1	1	1	1	1	1	0	0	0	1
Sub-score MRI (%)	*33.3*	*69.2*	*50*	*23.1*	*15.4*	*61.5*	*61.5*	*69.2*	*61.5*	*46.2*	*53.8*	*69.2*
Rehabilitation	2	2	0	0	2	2	2	1	1	0	1	0
Graft use/surgical technique	1	1	2	1	1	1	1	1	0	2	0	0
Number surgeons	0	1	0	0	0	1	1	0	0	1	1	0
Management concomitant injury	1	1	1	1	1	1	1	1	1	1	1	0
Sub-score clinical (%)	*66.7*	*83.3*	*50*	*33.3*	*66.7*	*83.3*	*83.3*	*50*	*33.3*	*66.7*	*50*	*0*
Relative TQS (%)	***54***	***76.3***	***51.3***	***31.6***	***44.7***	***68.4***	***78.9***	***68.4***	***68.4***	***61.5***	***57.9***	***44.7***

Low quality (score < P50), high quality (score > P50), P50 = 59.7%.

Appendix 4

Table AIV
Extracted data surgical characteristics and outcome

Authors	Average surgical delay (days)	Graft use (% reconstructions)	Single/multiple surgeon	Surgical technique
Faber (1999)	12	H (100)	NR	NR
Costa-Paz (2001)	60	BPTB (100)	NR	NR
Weninger (2008)	57.4	H (84.4) BPTB (13.3) Q (2.2)	NR	NR
Frobell (2009)	43	BPTB (44) H (56)	Multiple	NR
Arnoldi (2011)	NR	NR	NR	NR
Frobell (2011)	Early: 44.5 Late: 408	BPTB (50) H (50)	Multiple	NR
Li (2011)	NR	H (50) TP (33.3) A (16.7)	NR	NR
Neuman (2011)	144	NR	NR	NR
Potter (2012)	NR	BPTB (71.4) H (17.9) A (10.7)	NR	NR
Theologis (2011)	56	NR	Single	NR
Hosseini (2012)	135	BPTB (100)	Single	Trans-tibial
Lee (2013)	39	H (100)	NR	Anatomic double bundle

Table AIV (*continued*)

Authors	Laxity		Patient-reported		Performance-based function		Rate return to sports	Comparison to controls
	B	FU	B	FU	B	FU		
Faber (1999)	–	KT-1000	–	Mohtadi quality of life measure	NR	NR	NR	ACL reconstructed un-injured cartilage KT-1000: = Mothadi quality of life: =
Costa-Paz (2001)	– –	KT-1000 Pivot shift	–	IKDC	NR	NR	NR	–
Weninger (2008)	–	Radiographic Lachman	– –	Lysholm IKDC	–	One-legged hop	62% pre-injury level 16% restricted 4% no return	Contra-lateral intact knee Lachman: = Lysholm: = 1-legged hop: =
Frobell (2009)	NR	NR	Tegner	–	NR	NR	NR	Non-surgical patients*
Arnoldi (2011)	–	KT-1000	–	Lysholm Tegner OAK	NR	NR	56%: light labour/recreational sports	Contra-lateral intact knee KT-1000: ↑
Frobell (2011)	NR	NR	Tegner	Tegner ↓	NR	NR	NR	Non-surgical patients*
Li (2011)	NR	NR	NR	NR	NR	NR	NR	Healthy control subjects
Neuman (2011)	NR	NR	Activity level –	Activity level = Lysholm	NR	NR	NR	Non-surgical patients Activity level: =
Potter (2012)	NR	NR	IKDC ADL SF-36 ARS	IKDC↑ ADL= SF-36= ARS↓	NR	NR	NR	Non-surgical patients ARS: =
Theologis (2011)	NR	NR	NR	NR	NR	NR	NR	–
Hosseini (2012)	KT-1000	KT-1000↓	NR	NR	NR	NR	NR	Contra-lateral intact knee KT-1000: =
Lee (2013)	NR	NR	NR	NR	NR	NR	NR	–

Surgical characteristics reported in the included studies ($n = 12$).
NR: Not Reported. H: Hamstrings; Q: Quadriceps tendon; TP: Tibialis Posterior; A: Achilles tendon.
Surgical outcomes after ACL reconstruction reported in the included studies at baseline and follow-up compared to controls ($n = 12$).
B: Baseline. FU: Follow-up. IKDC: International Knee Documentation Committee; OAK: Orthopädische Arbeitsgruppe Knie; ARS: Activity Rating Scale; ADL: knee outcome score Activities of Daily Living; SF-36: Short Form 36-Item (RAND) questionnaire. NR: "Not Reported". "=" no (significant) difference when compared to baseline or controls. "↑/↓": (significant) increase/decrease when compared to baseline or controls.
* Outcome not separately reported for ACL-reconstructed patients in this cohort.

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