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Review

The protective effect of anterior cruciate ligament reconstruction on articular cartilage: a systematic review of animal studies

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SUMMARY

Objective: It is unclear if anterior cruciate ligament (ACL) reconstruction can prevent the onset of degenerative changes in the knee. Previous studies were inconclusive on this subject. The aim of this study was to systematically review all studies on the effect of ACL reconstruction on articular cartilage in animals.
Design: Pubmed and Embase were searched to identify all original articles concerning the effect of ACL reconstruction on articular cartilage compared with both its positive (ACL transection) and negative (sham and/or non-operated) control in animals. Subsequently a Risk of bias and meta analysis was conducted based on five outcomes (gross macroscopic assessment, medical imaging, histological histochemical grading, histomophometrics and biomechanical characterization) related to articular cartilage.
Results: From the 19 included studies, 29 independent comparisons could be identified which underwent ACL reconstruction with an average timing of data collection of 23 weeks (range 1–104 weeks). Due to limited data availability meta-analysis could only be conducted for gross macroscopic damage. ACL reconstruction caused significant gross macroscopic damage compared with intact controls (SMD 2.0 [0.88; 3.13]). These findings were supported by individual studies reporting on histomorphometrics, histology and imaging. No significant gross macroscopic damage was found when ACL reconstruction was compared with ACL transection (SMD −0.64 [−1.85; 0.57]).
Conclusion: This systematic review with an average follow up of included studies of 23 weeks (range 1–104 weeks) demonstrates that, in animals, ACL reconstruction does not protect articular cartilage from degenerative changes. The consistency of the direction of effect, provides some reassurance that the direction of effect in humans might be the same.

Introduction

Many studies have shown that anterior cruciate ligament (ACL) deficient knees will deteriorate radiologically and functionally over time, due to advancing osteoarthritis (OA)[1–3]. The ACL is the most commonly injured ligament undergoing surgical intervention, aiming to return patients to their pre-injury level of activity. ACL reconstruction is primarily performed to regain stability and as a result prevent or delay OA development. However, current literature is still inconclusive on the protective effect of ACL reconstruction on OA development[4–8]. First, comparisons among studies are difficult due to a wide range of patient populations, ages, activity levels and follow-up times[9–11].

Second, long-term outcomes after ACL injury are largely influenced by the presence of associated injuries. It is well known that additional injuries (e.g., meniscus) increase the risk for OA development[12]. However, in a recently performed systematic review it was demonstrated that only a small number of high-quality studies focused on development of OA in patients with isolated ACL injury[13]. Their results showed that isolated ACL tears have a low risk of OA, but signs of degeneration are reported in different studies. Third, in humans radiographic classifications are most often used to assess the

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grade of OA development. However, there is an inability to detect early and subtle OA changes on radiography and there is a weak correlation between clinical symptoms and imaging findings[14]. Previous studies suggested that imaging methods more sensitive than knee radiography are needed to define the presence of, and estimate the severity of, OA of the tibiofemoral joint[15–17]. Magnetic resonance imaging (MRI) has been identified by the Outcome Measures in Rheumatologic Clinical Trials (OMERACT) and Osteoarthritis Research Society International (OARSI) as the most appropriate imaging modality to assess joint status in OA research[18]. Finally, in humans it is either not acceptable or very challenging to assess damage to the articular cartilage after ACL reconstruction with other methods than medical imaging[19]. Therefore, the results of animal studies are used to inform human research[20]. Over the past 50 years a large number of animal models improved our understanding of OA as well as surgical techniques used for ACL reconstruction. Despite these animal models are performed to inform human research, systematic reviews of animal research are still scarce[21].

A systematic review and meta-analysis of all animal studies results in a transparent overview of all available information. In addition, systematic reviews of animal studies have the potential to reduce some of the challenges in the translation of animal data to clinical trials (e.g., by explicitly assessing the internal validity). The aim of our study is to summarize the effect of ACL reconstruction on articular cartilage in experimental animals and discuss the translation of this effect to human research.

Methods

This systematic review investigates the effect of ACL reconstruction on articular cartilage in experimental animals. The inclusion criteria and method of analysis were specified in advance and documented in a protocol[22,23].

This study is reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Search strategy and selection of studies

The search strategy, composed of three components (ACL, graft, and animals), was developed in collaboration with information specialists from the medical library of the Radboud university medical center Nijmegen, the Netherlands, according to the step-by-step guide by Leenaars *et al.*[24]. To detect all animal studies, animal search filters for Pubmed and Embase were used[25,26]. The full search strategy is reported in Supplementary file 1. No limits (e.g., on language or publication date) were used.

The search strategy was carried out in Pubmed and Embase (last search performed, 3 October 2017). Additionally, reference lists of the included studies and of relevant reviews were screened for additional potentially relevant papers.

After removal of duplicates, all unique records were imported in Early Review Organizing Software (EROS, developed by Institute of Clinical Effectiveness and Health Policy, Buenos Aires, Argentina) to randomly allocate references to two independent reviewers responsible for screening and selection (CD, PS). Discrepancies were solved by discussion with a third investigator (GH).

During the first screening phase, primary studies evaluating ACL reconstruction in healthy animals were screened for eligibility based on title and abstract. When not enough information was provided to make a valid judgment the full-text was evaluated.

Full-text versions of all eligible studies were screened and included if they met the following pre-specified eligibility criteria[27]: (1) a controlled interventional design (ACL transection as positive control and/or sham or non operated as negative control); (2) description of (semi-) quantitative outcome measures related to articular cartilage damage (radiographic assessment, gross macroscopic assessment, histological/histochemical based grading, immunohistochemistry based grading, histomorphometry, MRI, and/or biomechanical characterization). Studies were excluded based on the following exclusion criteria (1) no original study; (2) no animal study; (3) no ACL reconstruction; (4) no isolated ACL injury or reconstruction (e.g., in combination with meniscectomy); (5) co-interventions (e.g., biological mediators).

Data extraction

Two independent reviewers (CD, PS) performed data extraction from each included study.

Information related to study design, animal model, intervention, outcome measures, and risk of bias was extracted. Outcome measures related to assessment of damage to articular cartilage were divided in five principal outcome categories[27]: (1) gross macroscopic assessment of damage (grading or determining the area of articular cartilage with gross morphological changes, International Cartilage Regeneration & Joint Preservation Society (ICRS) scores, Outerbridge scores, either with or without staining methods); (2) medical imaging of changes related to OA(plain radiographical and MRI based classifications of morphological changes); (3) histological histochemical grading of changes in articular cartilage (Mankin Grading method); (4) histomorphometrics (any kind of quantitative study on microscopic images of articular cartilage); and (5) biomechanical characterization of articular cartilage (tensile and compressive measures of stiffness).

If outcome data were presented incompletely or only graphically, we tried to contact the authors to obtain the original data. A reminder was sent to those who had not replied within 2 weeks. When attempts to obtain original data failed, the article was excluded from meta-analysis. If data were presented only graphically, they were converted to numerical data using digital ruler software (Web Plot Digitizer, version 3.12, https://automeris.io/WebPlotDigitizer).

Risk of bias assessment

Risk of bias of all included studies was assessed by two independent reviewers (CD, PS) using Systematic Review Centre for Laboratory Animal Experimentation's (SYRCLE) Risk of Bias tool[28]. This tool is based on the Cochrane risk of bias tool[29] and has been adjusted for particular aspects of bias that play a role in animal intervention studies. It contains ten items related to six types of bias (selection, performance, detection, attrition, reporting and 'other' bias). The score 'yes' indicates a low risk of bias, 'no' indicates high risk of bias, and '?' indicates an unclear risk of bias.

Previous studies have shown that in animal studies experimental details are often poorly reported, which severely hampers the assessment of risk of bias[30–32]. To determine whether this is also the case in the studies included in this review, we added two questions to assess the reporting of randomization and blinding at any level of the study: 1) Was it stated that the experiment was randomized at any level? (yes/no) and 2) Was it stated that the experiment was blinded at any level? (yes/no).

Data analysis

Data were analyzed using R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) using package "meta" version 4.9.0.

Meta-analysis was performed whenever three or more independent comparisons per outcome category could be included (provided that outcome measures were sufficiently comparable). Standardized mean differences (SMD) were calculated to allow pooling of data reported in different units of measurement. For studies which presented results separately for different anatomic regions in the knee joint, the mean and pooled SD of all regions combined was calculated. If the same control group served more than one experimental group, the number of animals in the control group was divided by the number of experimental groups served.

To account for anticipated heterogeneity, a random effects model was used to pool individual effect sizes and obtain an overall standardized mean difference (SMD) and 95% confidence interval[33]. Heterogeneity was addressed by I^2 which is the proportion of total variance explained by between-study heterogeneity.

Subgroup analysis was performed for variables of which at least one of the strata contained a minimum of 3 independent comparisons. Subgroups were planned for animal species, type of reconstruction (autograft/allograft), and duration of follow-up (<3 months/≥3 months). The subgroup analysis on follow-up duration was based on the assumption that damage to the articular cartilage is observed 3 months after ACL reconstruction[34].

Publication bias was addressed by means of a funnel plot, if at least 15 studies could be included. Sensitivity analysis was performed by changing the time point for outcome assessment to ≥3 months after ACL reconstruction instead of ≥1 week after ACL reconstruction.

Results

Search and study selection

Conducting our search in PubMed and Embase retrieved 1898 unique records. After screening of abstracts and full texts, 1879 articles were excluded because they did not meet our eligibility criteria. A flow chart of the study selection process is presented in Fig. 1.

Nineteen articles were included in our systematic review[35–53].

Study characteristics

Study characteristics of all included studies are reported in Table I. Five different animal species were used: seven studies used sheep, four pigs, three dogs, three goats and two studies used rabbits. Different types of ACL reconstruction were performed: seven studies used a bone-patellar tendon-bone (BPTB) reconstruction, seven studies used grafts other than BTPB and five studies performed an ACL reconstruction using the original ACL for reconstruction purposes (Table I). Of these five studies, three used an ACL core surgery method[38,39,48]. They detached the femoral bone core and ACL insertion before fixing it with two crossed Kirschner wires[38]. The remaining two studies used repetitive in situ freeze–thaw of the original ACL[35] or suturing of the original ACL along with tunnel fixation[50]. Included studies had an average timing of data collection of 23 weeks (range 1–104 weeks).

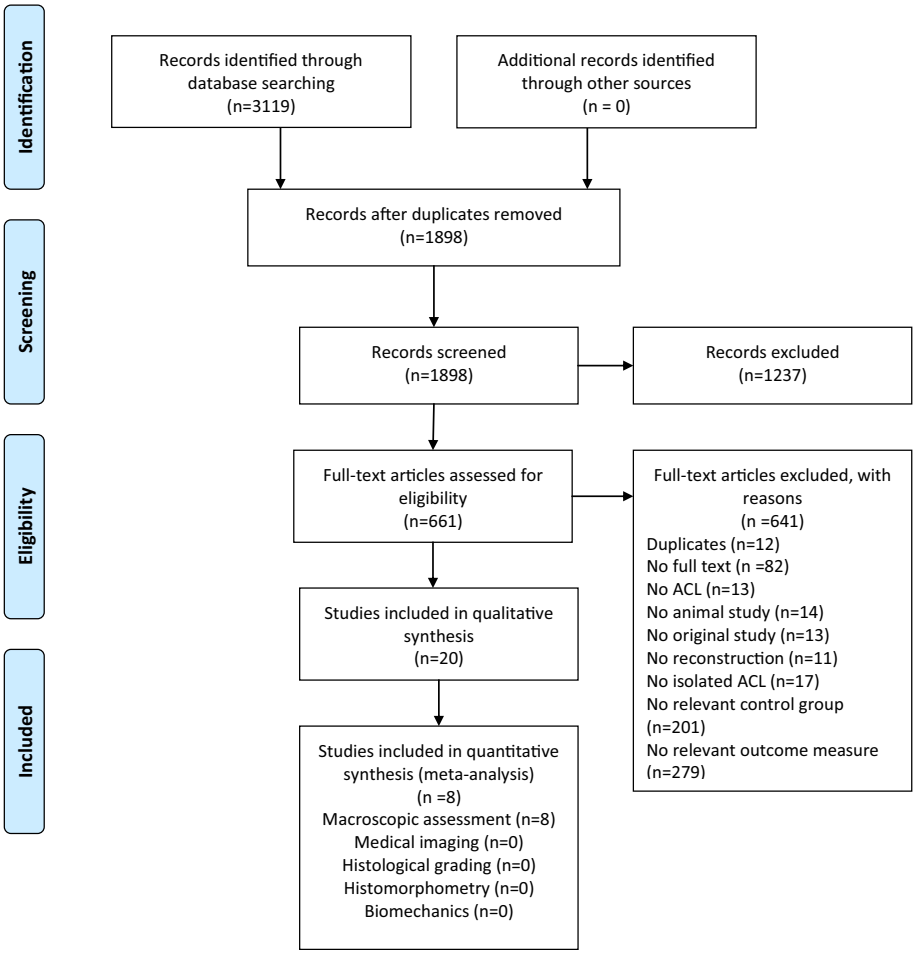

Fig. 1. Flow diagram of the systematic review and meta-analysis literature search results.

Table I
Study characteristics of the included studies

Study ID	Animal Characteristics				Study Characteristics						Graft Characteristics		
Reference	Species	Sex	Age	Weight (kg)	Experimental groups¤ (*n* per time of data collection)	Control groups ¤ (*n* per time of data collection)	Paired controls (control lateral)	Surgery uni/bi	Timing data collection	Early postoperative rehabilitation	Type of reconstruction	Graft sizing	Graft fixation
Asahina *et al.*, 2000£	Rabbits (JAP)	M	Mature	3.0–3.5	Au − Au (12), Au − S (6) Au − C (6), Au − N (6)		Yes	Uni (18) Bi (18)	Au: 4 weeks (n = 12), 12 weeks (n = 12), 24 weeks (12) Sham = *	Not immobilized	Freeze thaw of original ACL	N.A.	N.A.
Drez *et al.*, 1991	Goats (Angora)	*	2–3 yr	22–32	All (6 + 6)	None	Yes	Uni	26 and 52 weeks	Free cage activity	BPTB	No	Bone block, staple
Fleming *et al.*, 2015	Pigs (YM)	*	15.4 ± 1.3 mo	48 ± 9	All (14)	ACL-T (10)	Yes	Uni	15 weeks	Free cage activity	BPTB	Age, weight, sex matched	Interference screw
Heard *et al.*, 2011	Sheep (SC)	F	3–4 yr	*	Au (9)	C (6); S(3)	Yes	Uni	2 weeks	*	Anatomical fixation of original ACL	N.A.	Kirschner wires
Heard *et al.*, 2013	Sheep (SC)	F	3–4 yr	*	Au (7)	C (8); S(7)	Yes	Uni	20 weeks	*	Anatomical fixation of original ACL	N.A.	Kirschner wires
Jackson *et al.*, 1987	Goats (Spanish)	F	Mature	35–50	All (7)	None	Yes	Uni	1 yr	No restrictions	Bone–ACL–bone graft	Species matched	Bone block
Jackson *et al.*, 1993	Goats (Spanish)	F	4–5 yr	>25	Au (6 + 6) All (6 + 6)	ACL-T (6)	Yes	Uni	6 weeks and 6 mo	No restrictions	BPTB	Age, weight, height sex matched	Bone block
Johnson *et al.*, 2001[29]	Hounds	M/F	Mature	23–32	Au (5) 4 weeks after ACL-T	S (3) 4 weeks after ACL-T	Yes	Uni	0, 1,3,5 mo After 5 mo sacrificed	Free cage activity	Distal fascia lata and patella tendon; intracapsular graft	N.A.	Tunnel, suture
Johnson *et al.*, 2001 [30]	Hounds (pure bred)	M/F	Mature	23–32	Au (5) 4 weeks after ACL-T	S (3) 4 weeks after ACL-T	Yes	Uni	0, 1,3,5 mo After 5 mo sacrificed	Free cage activity	Distal fascia lata and patella tendon; intracapsular graft	N.A.	Tunnel, suture
Kiapour *et al.*, 2017	Pigs (YM)	*	15 ± 1 mo	61 ± 7 kg	All (8)	None	Yes	Uni	1 yr	No restrictions	BPTB	Age, weight, sex, matched	Interference screw
Lopez *et al.*, 2003	Hounds (CB)	F	Mature	23.5–29	Au (4)	None	Yes	Uni	52 weeks	Free cage activity	Hamstring graft in bone tunnel	N.A.	Bone staples
Mahalingam *et al.*, 2016	Sheep (BS)	F	Adult	*	All (4)	None	Yes	Uni	2 years	No restrictions	Tissue engineered bone–ligament-bone	60 mm long	Tunnel, suture
Murray *et al.*, 2013	Pigs (YM)	*	15 ± 0.95 mo	58.6 ± 7.9	All (7 + 8)	ACL-T (7 + 7)	Yes	Uni	6 and 12 mo	No restrictions	BPTB	Age, weight, sex matched	Interference screw
O'Brien *et al.*, 2012	Sheep (SC)	F	3–4 yr	*	Au (5)	C (17); S(7)	Yes	Uni	20 weeks	*	Anatomical fixation of original ACL	N.A.	Kirschner wires
Radford *et al.* 1994	Sheep (SB)	F	Mature	*	All (12)	None	Yes	Uni	6 mo	No restrictions	TTC (4), OTT (4), DB (4), graft is polyester fiber	130 mm long (parallel structure)	Screw
Richter *et al.* 1997	Sheep	F	Mature	72.5 ± 6.7	Au (16)	ACL-T (8)	Yes	Uni	13 weeks	No restrictions	Suture of original ACL (8), suture of original ACL + parallel augmentation(8)	N.A.	Resorbable 2.0 sutures (16), resorbable 2 mm PDS II cord (8)
Sieker *et al.*, 2017	Pigs (YM)	*	Mature	*	All (6 + 6)	C (6) ACL-T (6 + 6)	No	Uni	1 and 4 weeks	Free cage activity	BPTB	Age, weight, sex matched	Interference screw
Wang *et al.*, 2017	Rabbits (NZW)	*	*	2.3–3.1	Au (6 + 6+6); All (6 + 6+6)	S (6 + 6+6); C (6 + 6+6)	No	Uni	2, 4, 8 weeks	*	Semitendinosus tendon	*	Tunnel, Traction suture
Zimmerman *et al.*, 1994	Sheep (ROM)	F	Mature	*	All (5)	None	Yes	Uni	6 mo	No restrictions	BPTB	Age, size matched	Interference screw

Abbreviations: ¤ = only groups noted relevant for our systematic review; experimental groups with added biological mediators were excluded as were groups in which no relevant outcome was assessed. £ = exception made; n per time data collection not mentioned under groups but can be found in column timing data collection.* = not mentioned/unknown. ¥ = ACL-R, 3 weeks after ACL-T, JAP = Japanese, SC = Suffolk-cross, YM = Yucatan minipigs, CB = cross breed, ROM = Rombolette, SB = Scottish blackface, NZW = New Zealand White, BS = black Suffolk, Yr = year, mo = months, ACL-R = reconstruction Au = autograft reconstruction, All = allograft reconstruction, ACL-T = transection, N = normal knee not used in study, C = intact control, S = sham, BPTB: bone patellar tendon bone, OTT = over the top technique, TTC = through the condyle technique, DB = double bundle

Johnson *et al.*[43] and Kiapour *et al.*[44] presented results of the same animal cohort in more than one article. Both confirmed that results of one single animal cohort were presented in more than one article. This was taken into account, by presenting results of the same animal cohort only once in our meta-analysis.

Risk of bias and quality of reporting

The risk of bias assessment is summarized in Fig. 2 and the individual scores of each study are presented in Supplementary file 2. Our assessment of the reporting quality shows that eight out the 19 papers reported blinding at some level and that 10 of the 19 papers reported randomization at some level. However, only Sieker *et al.*[51] mentioned details of the randomization process. The insufficient reporting of these measures to reduce bias reflected in our risk of bias assessment: many items were scored as unclear risk of bias, because either no measures to reduce bias were reported, or the procedure was unclear.

Data synthesis: effect of ACL reconstruction on articular cartilage

From the 19 included studies, 29 independent experimental groups could be identified which underwent ACL reconstruction. Fleming *et al.*[37], Murray *et al.*[47] and Sieker *et al.*[51] provided additional data upon request.

Meta-analysis

Meta-analysis could only be performed for gross macroscopic assessment, because of insufficient data for the other outcomes.

We separated comparisons into three groups, depending on the control used, and performed a separate meta-analysis for each: ACL reconstruction compared to ACL transection (nine comparisons), ACL reconstruction compared to sham control (three comparisons), and ACL reconstruction compared to intact ACL control (14 comparisons). The average follow-up duration in studies included in the meta-analyses was 25 weeks (range [2–52 weeks]).

ACL reconstruction showed more gross macroscopic damage when compared to intact ACL control (SMD 2.0 [0.88; 3.13], $I^2 = 88\%$, Fig. 3). However, ACL reconstruction did not prevent gross macroscopic damage when compared to ACL transection (SMD −0.64 [−1.85; 0.57], $I^2 = 83\%$, Fig. 4). When compared to sham, ACL reconstruction increased gross macroscopic damage (SMD 1.23 [0.05; 2.41], $I^2 = 58\%$, Fig. 5).

Subgroup analysis

Subgroup analysis for species, type of reconstruction and follow-up duration are presented in Table II. ACL reconstruction significantly increases gross macroscopic damage in both sheep and pigs compared to intact controls. In goats no effect of ACL reconstruction on gross macroscopic damage could be observed compared to intact controls. Both types of reconstruction used (either autograft or allograft) increased gross macroscopic damage. Last but not least, ACL reconstruction only caused increased gross macroscopic damage compared to controls after 3 months.

Due to poor reporting of measures to reduce bias, no subgroup analysis could be conducted for any of the risk of bias items.

Publication bias

Due to the low number of studies that were included in the meta-analyses the possible presence of publication bias could not reliably be assessed.

Sensitivity analyses

We performed a prespecified sensitivity analysis to assess the robustness of our findings under a change in the cut-off for follow-up duration. Changing the time point for outcome assessment to ≥3 months after ACL reconstruction instead of ≥1 week after ACL reconstruction showed similar results: ACL reconstruction compared with intact control (SMD 2.57 [1.31; 3.82], $I^2 = 86\%$), ACL reconstruction compared with ACL transection (SMD −0.84 [−2.47; 0.78], $I^2 = 86\%$). The comparison ACL reconstruction and sham was no longer possible, only two independent comparisons could be made.

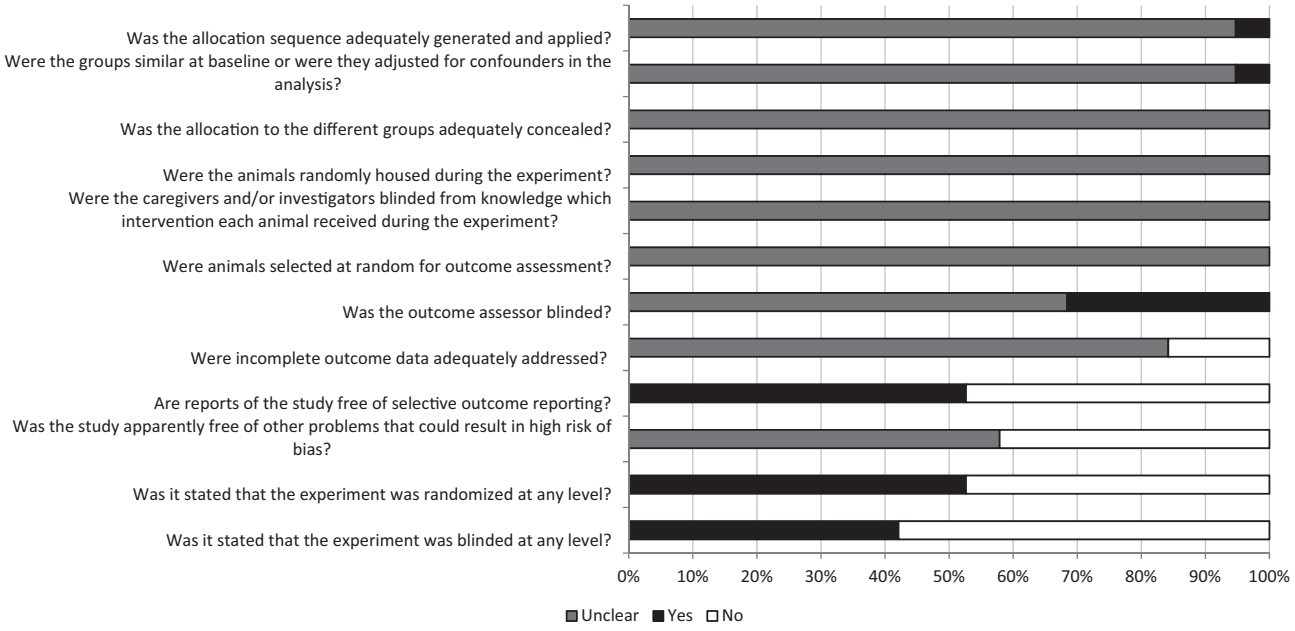

Fig. 2. Risk of bias, averaged per item. Yes = low risk of bias, no = high risk of bias, unclear = unclear risk of bias.

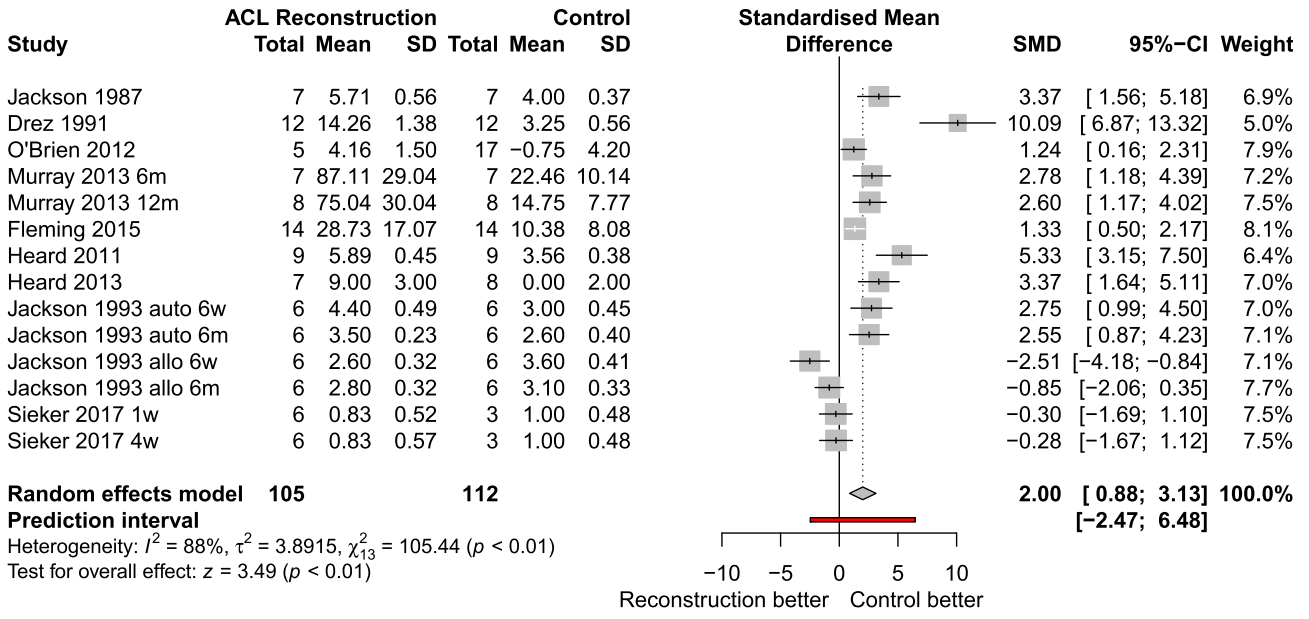

Fig. 3. Effect of anterior cruciate ligament (ACL) reconstruction on the articular cartilage: forest plot of the included studies which used any kind of gross macroscopic assessment to determine the damage of articular cartilage after ACL reconstruction compared with intact control. The forest plot displays relative weight of the individual experiments, standardized mean differences (SMD), and 95% CIs. The diamond indicates the global estimate and its 95% CI. The red bar indicates the prediction interval. Auto = autograft, allo = allograft.

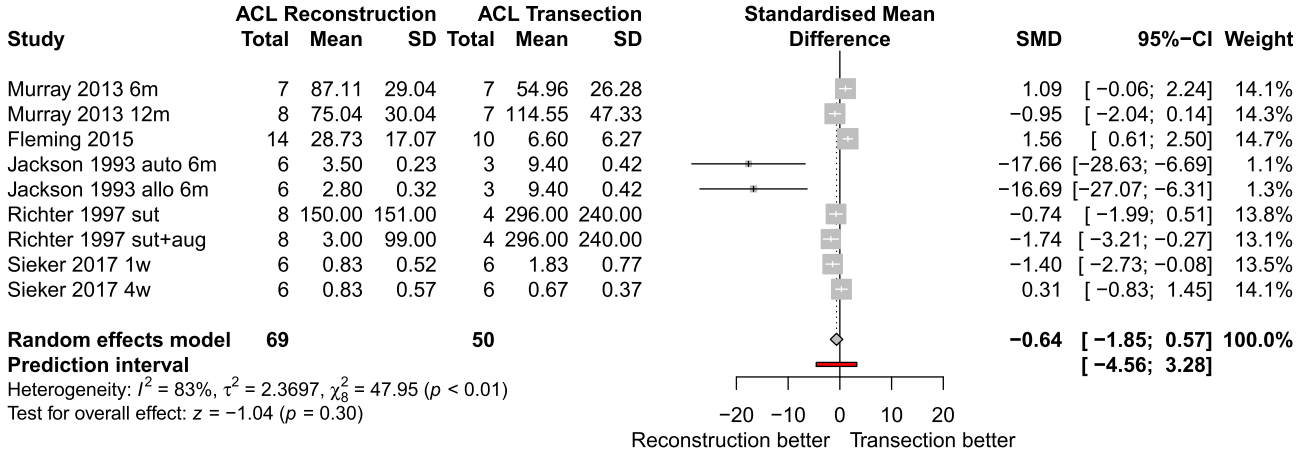

Fig. 4. Effect of ACL reconstruction on the articular cartilage: forest plot of the included studies which used any kind of gross macroscopic assessment to determine the damage of articular cartilage after ACL reconstruction compared with ACL transection. The forest plot displays relative weight of the individual experiments, SMD, and 95% CI. The diamond indicates the global estimate and its 95% CI. The red bar indicates the prediction interval. Auto = autograft, allo = allograft, sut = suture.

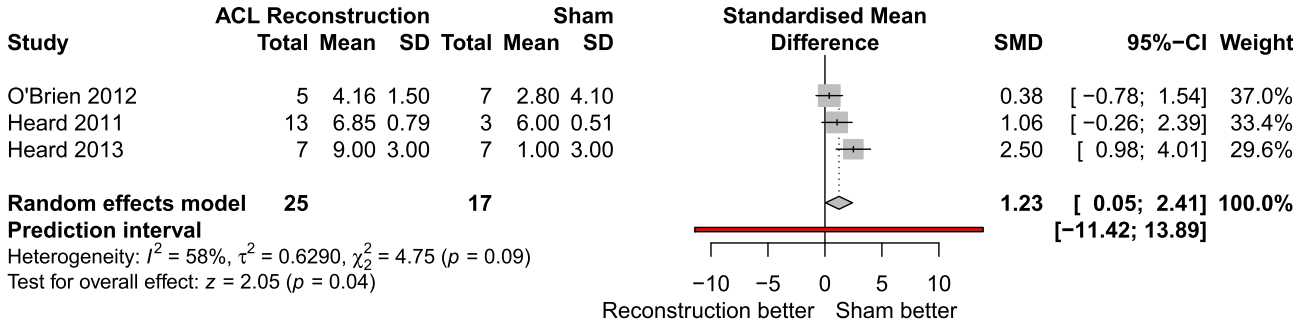

Fig. 5. Effect of ACL reconstruction on the articular cartilage: forest plot of the included studies which used any kind of gross macroscopic assessment to determine the damage of articular cartilage after ACL reconstruction compared with sham. The forest plot displays relative weight of the individual experiments, SMD, and 95% CI. The diamond indicates the global estimate and its 95% CI. The red bar indicates the prediction interval.

Table II
Subgroup analysis of the included studies for gross macroscopic assesment

Subgroup (n)	Comparison	SMD (95% CI)
Animal species		
Goats (6)	Reconstruction vs control	2.35 [−.031; 5.01]
Sheep (3)	Reconstruction vs control	3.17 [0.81; 5.53]
Pigs (5)	Reconstruction vs control	1.20 [0.04; 2.37]
Type of reconstruction		
Autograft (5)	Reconstruction vs control	2.88 [1.57; 4.18]
Allograft (9)	Reconstruction vs control	1.51 [0.00; 3.02]
Follow-up		
<3 months (5)	Reconstruction vs control	0.92 [−1.40; 3.24]
≥3 months (9)	Reconstruction vs control	2.57 [1.31; 3.82]
<3 months (2)	Reconstruction vs transection	n.e.
≥3 months (7)	Reconstruction vs transection	−0.84 [−2.47; 0.78]

The standardized mean difference (SMD) and 95% confidence intervals (95% CI) for different subgroups are presented. The n reflects the number of independent comparisons. Duration of follow-up < or ≥3 months = timing of data collection from ACL reconstruction earlier or equal/later than 3 months. n.e. = not estimated

Narrative synthesis

Gross macroscopic assessment

Zimmerman *et al.*[53] and Radford *et al.*[49] were excluded from meta-analysis because attempts to obtain missing data by contacting the authors failed. Zimmerman *et al.*[53] found no noticeable degradation of the cartilaginous surfaces of the intact contra lateral knees. The reconstructed knees showed degradation on both the femoral and tibial surfaces however only the trochlear groove was significantly different from normal. Radford *et al.*[49] noted only slight cartilage degeneration in the non-operated joints. In the operated joints more slight and moderate cartilage degeneration was noted.

Asahina *et al.*[35] was not included in the meta-analysis because only the patellar cartilage was graded. Of the sham animals the patellar articular surface looked intact, while in the ACL reconstruction animals a dull appearance of the patellar articular surface was commonly seen. Obvious cartilage deterioration, such as erosion or ulcer, was seen only in three ACL reconstruction animals.

Medical imaging

Two of the 19 included studies assessed cartilage damage based on medical imaging.

Lopez *et al.*[45] and Mahalingham *et al.*[46] both assessed osteoarthritic change on plain radiographs. Lopez *et al.*[45] found bony proliferation at the exit point of the tibial tunnel in all four reconstructed knees after 8 weeks. No other radiographic changes occurred.

Mahalingam *et al.*[46] found osteophyte formations and loose bone fragments present in the reconstructed knees while the contra lateral knees did not have these characteristics. No other radiographic changes were described.

Histological/histochemical grading

Seven studies were included assessing cartilage damage based on histological or histochemical grading. In total, 14 comparisons could be identified comparing ACL reconstruction with either ACL transection, sham or intact ACL control. However, the outcome measures were not sufficiently comparable for meta-analyses.

Asahina *et al.*[35] found an increase in histological grades (Mankin score) of the patellar articular cartilage with increase of time, whereas the score remained unchanged in the control group. Johnson *et al.*[42,43] measured concentrations of chondroitin sulfate epitopes 3B3 and 7D4 in synovial fluid as a reflection of altered metabolism of articular cartilage. They found that ACL reconstruction did not substantially influence 3B3 and 7D4 concentrations when compared with ACL transection. There was no significant difference between sham reconstruction and ACL reconstruction.

Wang *et al.*[52] measured significantly elevated mRNA expressions of lysyl oxidases (LOXs) (LOX-1,2 and 3) and matrix metalloproteinases (MMPs) (MMP-1,2 and 3) in the autograft and allograft groups at all time points, while there were no significant differences in the mRNA expressions of LOXs and MMPs between the control group and the sham group. In a similar study, Sieker *et al.*[51] measured increased gene expression in both ACL reconstruction and ACL transection groups compared with intact control.

Heard *et al.*[38] measured significantly elevated mRNA expression levels (IL-1B, IL-6, MMP-1,2,3 and 13) in experimental joints when compared with normal joints. In their follow-up study, they found that these mRNA expressions levels had reverted to normal 20 weeks after ACL reconstruction[39].

Histomorphometrics

Only one study included in our systematic review assessed cartilage damage based on histomorphometrics. Sieker *et al.*[51] performed microscopic scoring of the articular cartilage of the medial femoral condyle according to the OARSI guidelines[54]. The microscopic sum score increased significantly from the intact control to both the 1 week and 4 weeks samples of the ACL reconstruction group.

Discussion

The ACL is the most commonly injured ligament undergoing surgical intervention in humans, aiming to restore the knee joint stability and secondary preventing osteoarthritis[55].

However, it is unclear if ACL reconstruction could prevent or delay the onset of degenerative changes in the knee[4,5]. In humans it is either not acceptable or very challenging to conduct randomized clinical trials to investigate the effects of ACL reconstruction on cartilage damage. In experimental animal studies several options to assess cartilage damage after ACL reconstruction have been described, for example gross macroscopic assessment, histological/histochemical grading or biomechanical characterization. Therefore, we performed a systematic review of all animal studies on the effect of ACL reconstruction on the articular cartilage, aiming to summarize the effect of ACL reconstruction on articular cartilage in experimental animals and to discuss the translation of this effect to human research.

From this systematic review and meta-analysis, it becomes clear that ACL reconstruction does not prevent cartilage damage in ACL injured joints from being significantly greater than in intact control (naive or sham-operated) joints. Moreover, results on histology, imaging and histomorphometrics support that ACL reconstruction has a destructive effect on the articular cartilage. When we analyzed gross macroscopic damage due to ACL reconstruction compared to sham control, this destructive effect on the articular cartilage of ACL reconstruction remained.

There was no effect of ACL reconstruction on gross macroscopic damage to the articular cartilage compared with ACL transection. Only Sieker *et al.*[51] compared the effect on articular cartilage of ACL reconstruction with ACL transection using other methods of measurement than gross macroscopic. Their results on histology and histomorphometrics show no difference between ACL reconstruction and ACL transection.

Based on our results in this systematic review we conclude that ACL reconstruction does not have a protective effect of on the articular cartilage in animals.

Some methodological issues which might have jeopardized the interpretation of the experimental animal data and the subsequent translation to the clinical setting have to be discussed.

First, preferably, all experiments should be performed in a similar manner when their results are being combined in a meta-analysis. However, the heterogeneity of the various animal studies was substantial. To account for the expected heterogeneity, a random effects model was used. Unfortunately, it was not possible to unravel the sources of heterogeneity completely by performing subgroup analyses due to too low numbers of independent comparisons within most subgroups. However, heterogeneity could partly be explained by species, follow-up duration and type of graft used. In addition, we conducted sensitivity analyses to increase our confidence in the results. Posthoc a sensitivity analyses were performed for studies using the original ACL for reconstruction purposes[38,39,48,50]. Excluding these studies from our analyses showed similar results.

To assess gross macroscopic damage of the cartilage different scales are being reported. A SMD was calculated to be able to perform a meta-analysis. However, we would recommend to use a standardized scale for assessment of gross macroscopic damage of the cartilage in future research, this would improve comparability between studies[54,56–58].

Our subgroup analyses showed that in goats no effect of ACL reconstruction on gross macroscopic damage could be observed compared to intact controls. However, due to the small number of animals per subgroup the results must be interpreted with caution. In addition, 4 out of 6 goat comparisons included in our subgroup analysis are from the same study by Jackson *et al.*[41] which might have influenced our results.

It should be taken in to account that animal species differ not only in gross joint anatomy but also in details, such as chondrocyte density, cartilage thickness and metabolic differences, which will influence the outcome of the specific OA model[59,60]. Spontaneous OA has been reported for multiple large animal models and should be taken into account[54,61,62].

Only including the most commonly used animal model would hamper our aim to conduct an evidence based systematic review, including all experimental animal literature within the field. Additionally, the most commonly used model does not need to be the best model.

There is no single animal model that is able to mirror all variants and aspects of human OA. Therefore, to translate animal research to humans, multiple animal models should be assessed, as different animal models represent different aspects of the disease.

Second, our risk of bias analysis revealed that poor reporting of essential details of animal studies in the included articles is a serious concern. Information on key measures to reduce bias, such as adequate randomization and blinding, was frequently missing. Regrettably, this is common in animal studies, and limits our ability to draw reliable conclusions[30–32]. For future research we recommend to improve reporting of measures to reduce risks of bias, and guidelines have been developed to improve the quality of animal studies[63,64].

Translation of animal research to the clinical field is of course not straightforward due to several methodological aspects as well as anatomical differences. Regarding translation from pre-clinical animal models to clinical practice, several aspects should be addressed.

It is important to realize that no animal model is a perfect match to represent the full clinical situation. However, when there is no or very limited (quality) evidence from human studies, systematic reviews of animal studies can be used to answer the question. Reasons for synthesizing animal evidence include the intervention still being in development (e.g., never tested on humans or still in the preclinical phase), or that clinical experiments are considered unethical (e.g., gross macroscopic assessment of cartilage damage after ACL reconstruction in humans). Considering evidence from animal studies might change the assessment of the likely magnitude of the effect or might potentially increase our certainty in the evidence[65]. When the results of a review like this will be used to inform the clinical field, the indirectness of the results need to be taken into account.

First, the consistency of the direction of effect between species does provide some reassurance that the direction of effect might be similar in humans. Gross macroscopic cartilage damage is expected to be limited when assessed less than 3 months after the intervention[34]. This is a likely explanation for our observation that ACL reconstruction is not effective in studies with a follow-up of less than 3 months. Regrettably, this systematic review, with an average follow-up of 23 weeks (range 1–104 weeks), does not provide results on the long term effect of ACL reconstruction. Damage to the articular cartilage would be expected to be progressive over time.

Second, in humans arthroscopic procedures are used for ACL reconstruction instead of the invasive open procedures used in animal experiments. This should be taken into account when observing the effect of animal reconstructive surgery. Arthroscopic procedures are presumed to have less detrimental effect on cartilage compared with extensive open procedures used in animal experiments, which could improve the outcome of ACL reconstruction on the articular cartilage[7]. In animal studies reconstructive ACL arthroscopic procedures are lacking.

Third, in these animal studies ACL reconstructions were performed in a healthy knee. Damage to the articular cartilage was only due to the surgery performed. In contrast, in the clinical setting, ACL reconstruction is performed in a knee that has undergone a trauma large enough to cause the ACL injury. Often due to the impact of this trauma concomitant injury is reported to for example the cartilage directly or the menisci[66]. Literature has shown that when ACL injury is combined with meniscal tears the risk of developing OA is higher[66–68].

Therefore, we expect that the observed effect of ACL reconstruction on articular cartilage damage in the clinical situation might be overestimated due to the concomitant injuries.

Considering the results of this systematic review, it is likely that in humans with isolated ACL injury ACL reconstruction has no protective effect on the articular cartilage. This is in accordance with clinical research comparing ACL reconstruction and conservative treatment in isolated ACL injury patients. Tsoukas *et al.* found after 10 years a similar incidence of radiological OA between the two groups[69]. Kessler *et al.* found a significant lower rate of OA after conservative treatment[70]. Both studies used radiographs to assess OA which is obviously not the most sensitive method[15–17]. To assess early cartilage damage in humans an ethical and feasible method is needed[71].

In addition, our systematic review showed that there is a need for animal studies with better comparability and better reporting on detail to reduce bias. Adoption of standardized scoring systems in OA research has been advocated by several authors[54,72,73]. Improving the quality and comparability of preclinical research would as well improve the translation of animal research to the clinical field.

In conclusion, this systematic review with an average follow up of included studies of 23 weeks (range 1–104 weeks) demonstrates that, in animals, ACL reconstruction does not protect articular cartilage from damage. The consistency of the direction of effect, provides some reassurance that the direction of effect in humans

might be the same. However, this needs to be further investigated and confirmed in humans.

Contributions

- Conception and design (CD, GH, CRH)
- Screening of abstracts and full text (CD, PS)
- Analysis and interpretation of the data (CD, GH, KEW, CRH)
- Drafting of the article (CD, PS)
- Critical revision of the article for important intellectual content (GH, KEW, CRH)
- Final approval of the article (CD, PS, GH, KEW, CRH)
- Statistical expertise (GH, KEW, CRH)
- Collection and assembly of data (CD, PS, GH)

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Conflict of interest
All authors declare to have no conflict of interest.

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Supplementary data

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