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Is osteoarthritis an inevitable consequence of anterior cruciate ligament reconstruction? A meta-analysis

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Abstract

Purpose Although the occurrence of early osteoarthritis (OA) is commonly associated with a history of anterior cruciate ligament (ACL) reconstruction, its exact prevalence in these patients remains unknown. The goal of this study was to review the current literature on long-term radiographic outcome after autologous ACL reconstruction and subsequently perform a meta-analysis to obtain evidence-based prevalences of OA at a mean of 10 years after surgery. In addition, this report aimed at identifying the relationship between meniscal status and the occurrence of radiographic OA in the ACL reconstructed knee.

Methods A systematic review of the literature was performed in PubMed MEDLINE, EMBASE and Cochrane Library databases to identify all studies concerning radiographic outcome after autologous ACL reconstruction with a follow-up of minimum 10 years. Meta-analyses were performed to obtain the average prevalence of OA and the difference between patients with and without meniscectomy. Considered study estimates were the log-transformed odds and odds ratios, the latter expressing the effect of meniscectomy on OA.

Results A total of 16 studies could be included for meta-analysis, accounting for 1554 ACL reconstructions performed between 1978 and 1997. Of these knees, 453 (28 %) showed radiological signs of osteoarthritis (IKDC grade C or D). Furthermore, 50 % of the patients with meniscectomy had osteoarthritis, compared with 16 % of the patients without meniscectomy. The combined odds ratio for meniscectomy equals 3.54 (95 % CI 2.56–4.91).

Conclusions The main finding of this meta-analysis is that the prevalence of radiographic knee OA after ACL reconstruction is lower than commonly perceived. However, associated meniscal resection dramatically increases the risk for developing OA.

Level of evidence Level III.

Introduction

The occurrence of osteoarthritis (OA) is often thought as a near-inevitable consequence after anterior cruciate ligament (ACL) injury, with prevalences of 50–80 % reported a decade after the initial trauma [24, 49]. ACL injuries often present with associated knee lesions: a concomitant meniscal tear is seen in 25–65 % of the cases, while chondral lesions have been noted in approximately 25 % of the ACL-injured knees at the time of initial presentation [26]. Whereas most authors agree on the deleterious effect of a (partial) meniscectomy with regard to the premature development of osteoarthritis (OA) after ACL reconstruction [5, 27], the role of chondral injuries sustained during the index trauma is less clear. Shelbourne et al. [48] found no difference in OA prevalences in a group of subjects presenting with chondral injuries at the time of ACL reconstruction compared to a control group without cartilage lesions.

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Since long, however, ACL tears are often quoted as being responsible for a large percentage of the "young patients with old knees" [24, 50]. Although surgical ACL reconstruction using tendon grafts has become the current standard of care to treat the functionally unstable ACL-deficient knee [49], controversy remains to exist regarding the effect of ACL reconstruction on the development of knee OA in this generally young population. Current literature contains a number of reports suggesting that the prevalence of OA remains unchanged whether or not the ACL is surgically reconstructed [20, 25], but Daniel et al. [7] even detected an increased incidence of OA in the ACL reconstructed group. On the other end of the spectrum, some authors seem to maintain excellent results a decade after ACL reconstruction, with reported OA prevalences of 2–3 % [20, 40].

As current controversy on the occurrence of OA after ACL reconstruction has been fuelled by rather small, heterogeneous and retrospective case series and expert opinions [5, 25, 31, 32, 41, 43], the goal of this study was to compile and systematically review the current literature on long-term outcome after autologous ACL reconstruction and subsequently perform a meta-analysis to obtain evidence-based prevalences of (radiographic) OA. In addition, this manuscript aims at unravelling the relationship between meniscal status and the occurrence of OA in the ACL reconstructed knee.

Materials and methods

This meta-analysis was set up and reported according to the recommendations proposed by the PRISMA statement [33].

Search strategy

A systematic review of the literature was performed in order to identify all studies concerning the long-term outcome after autologous ACL reconstruction in the human knee. "Long-term" outcome was defined as a mean follow-up of minimum 10 years. The PubMed MEDLINE, EMBASE and Cochrane Library databases were searched from their earliest entry points to October 2010, including articles published online as "Epub ahead of print". The computerized search was performed using combinations of the following search terms: "anterior cruciate ligament or ACL", "reconstruction", "autologous", "treatment", "long-term", "outcome", "follow-up", "results" and "(osteo)arthritis or osteoarthrosis".

Selection

Searches were limited to studies published in English and French. Studies reporting on long-term outcome after ACL reconstruction without radiographic evaluation were excluded. Reports with a mean follow-up less than 10 years were excluded as well. In addition, each reference list from the identified articles was manually checked to verify that relevant articles were not missed for the current review.

Data extraction

Each study was evaluated for the following variables: study type; mean follow-up after ACL reconstruction; operative technique; time period of surgery; number of patients with radiographs at final follow-up; number of patients with meniscectomy prior to, at the time of or after ACL reconstruction within this group; number of patients with radiographic OA of operated knee. Relevant data from each included study were extracted and recorded on multiple worksheets.

Osteoarthritis

The definition of OA in this meta-analysis was exclusively based on radiological criteria, due to the obvious lack of reported data combining both clinical and radiological aspects of OA. Furthermore, the presence of different radiological classification systems for OA used in the studied reports (e.g., Kellgren and Lawrence, Ahlbäck, Fairbanks, IKDC…) necessitated the development of a conversion method for the various OA scores in order to allow subsequent statistical analysis. Due to its widespread use and reliability [30], the "IKDC radiographic grading system" [14] was chosen as the reference classification to which other scores were translated to best effort (see Table 1). With regard to OA, IKDC grade A and B were considered as being normal or nearly normal, while IKDC grades C and D were considered to represent OA of the knee.

Some studies reported on the presence of OA in either the medial or lateral tibiofemoral compartment or in the patellofemoral joint, but most authors did not specify the localization of the degenerative changes. Therefore, it was decided to pool all available data in one general group of "knee OA".

Meniscectomy

Many included reports mention a subpopulation of meniscectomized patients at final follow-up. The radiographic outcome of this subset of patients was studied separately in order to evaluate the impact of meniscectomy on the prevalence of OA. Although some authors specify the location of the meniscal resection, that is, in the medial or lateral compartment and most of them do not elaborate on

Table 1 Schematic depiction of the conversion of the published OA scores into the IKDC score

Kellgren&Lawrence [19]	Ahlbäck [1]	Modified Fairbank [10]	International Knee Documentation Committee (IKDC) [14]		OA
Grade 0		Grade 0	**IKDC A**	No or doubtful changes in the knee joint	Normal
Grade 1	Grade 0	Grade 1	**IKDC B**	Small osteofytes, slight sclerosis, flattening of femoral condyles	Minmial OA
Grade 2			**IKDC C**	Joint space narrowing less than 50%	Osteoarthritis
Grade 3	Grade 1	Grade 2			
Grade 4	Grade 2	Grade 3	**IKDC D**	Joint space narrowing between 50% and 100%	
	Grade 3				
	Grade 4				
	Grade 5				

the amount of meniscal resection, for the purpose of this meta-analysis all patients who underwent partial or total meniscectomy prior, at the time of or after surgery, were pooled together. Subjects treated with meniscal repair were appointed to the non-meniscectomy group, unless failure of the suture was reported during follow-up.

Statistical analysis

Meta-analyses were performed to obtain the average prevalence of OA and the difference between patients with and without meniscectomy. Considered study estimates are the log-transformed OA odds and odds ratios (and risk ratios), the latter expressing the effect of meniscectomy on OA. Differences between studies reflect true variability ("heterogeneity") and sampling variability. Heterogeneity was quantified by the I^2 statistic [16], which is the percentage of total variation in study estimates that is due to heterogeneity and tested by Cochran's χ^2-test. The random-effects approach of DerSimonian and Laird [8] was used to take into account the heterogeneity in the combination of the results of the studies. A random-effects meta-regression [51] with the average length of follow-up per study is used to evaluate the relation with OA and to verify whether the effect of meniscectomy on OA depends on the average length of follow-up reported in the specific study. To illustrate the between-study heterogeneity, the observed proportion OA per study was plotted versus the number of patients in funnel plots with 99 % prediction limits around the overall proportion OA. These limits indicate the range wherein 99 % of the observed proportions are expected, if there were no heterogeneity. Prediction limits were constructed based on the binomial distribution with a continuity correction. P values smaller than 0.05 are considered significant. All analyses have been performed using SAS software, version 9.2 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA).

Results

The computerized search using the aforementioned search terms delivered 211 studies describing outcome after ACL reconstruction. Abstracts and, if necessary, full text articles were studied to detect the mean duration of follow-up. In this manner, 39 studies considering ACL injury (i.e., treated and non-treated) with a mean follow-up of more than 10 years were identified. After the exclusion of articles on conservative treatment, primary ACL repair (i.e., suture), isolated extra-articular, allograft and synthetic reconstructions, 24 studies could be withheld for in-depth analysis. Subsequently, 3 studies were excluded due to the presence of biasing concomitant surgical procedures in the ACL reconstructed knees (i.e., meniscal allograft transplantation and high tibial osteotomy). Two studies by the same research group [2, 4] were excluded because a later

published report described the identical patient population with longer follow-up and was conversely included [39]. Unfortunately, another 3 manuscripts were excluded due to inaccurate or incomplete reporting on patient numbers or OA criteria at final follow-up [28, 52, 53]. Finally, 16 reports could be included for systematic review and meta-analysis [5, 9, 11, 15, 20–22, 25, 31, 32, 38–40, 43, 46, 47]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [33, 34] depicts the number of studies identified, included and excluded as well as the reasons for exclusion (see Fig. 1).

Study characteristics

A total number of 1554 subjects could be included in this review. This number represents all patients available for radiographic examination at the time of follow-up, not at

inclusion. Subjects per study ranged from 25 to 502 and mean follow-up ranged from 10 to 24.5 years, and 11 out of the 16 included papers had a mean follow-up between 10 and 12 years. One study exclusively studied female subjects [25], while another had a male/female ratio of 55/3 [46]. The effect of gender on long-term outcome after ACL reconstruction could not be assessed because the vast majority of papers did not publish separate results for male and female subjects. The presence or absence of associated meniscal lesions necessitating resection before, during, or after ACL reconstruction was mentioned in 11 out of 16 included articles, accounting for a total of 614 meniscectomized subjects on a total of 1264 (48.6 %). Only 5 of the included reports were set up as a prospective study, with the remaining 11 studies being retrospective in nature. The main study characteristics are summarized in Table 2.
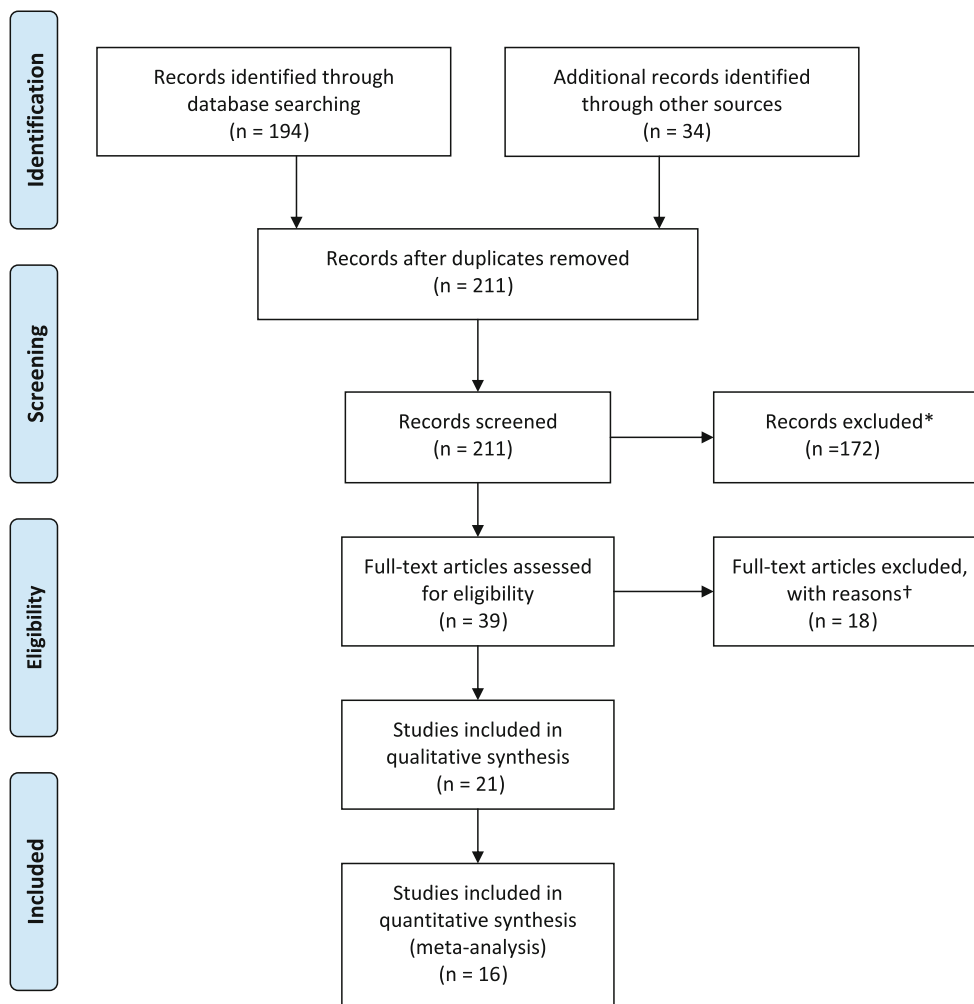

Fig. 1 The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram[17], depicting the number of studies identified, included and excluded as well as the reasons for exclusion. *Records excluded because mean follow-up equalled less than 10 years, or no radiographic analysis performed. †Reasons for exclusion of articles: conservative treatment, primary repair, isolated extra-articular reconstruction, synthetic or allograft reconstruction, presence of biasing concomitant procedures (i.e., osteotomy or meniscal allograft transplantation

Table 2 Summary of the main characteristics of the included studies

Study	Year of publication	Study type	Surgical procedure	Time period	OA classification	Mean follow-up (years)	Number of subjects (total)	Total OA¥	Meniscectomy§	OA− meniscectomyΠ	OA+ meniscectomyΠ
Cohen et al. [5].	2007	Retrospective	Arthroscopic BPTB	1986–1991	Modified Fairbank	11.2	62	49 (79 %)	41 (66 %)	14 (67 %)	35 (85 %)
Drogset et al. [9]	2006	Prospective	Open BPTB	1986–1988	Ahlbäck	16	32	4 (12 %)	N/A	N/A	N/A
Fink et al. [11]	2001	Retrospective	Open BPTB	1981–1983	Modified Fairbank	11	46	23 (50 %)	N/A	N/A	N/A
Hertel et al. [15]	2005	Retrospective	Open BPTB	1987–1991	IKDC	10.7	67	16 (24 %)	32 (48 %)	4 (11 %)	12 (38 %)
Kessler et al. [20]	2008	Retrospective	Open BPTB	1989–1997	Kellgren and Lawrence	11.1	60	2 (3 %)	0 (0 %)	2 (3 %)	N/A
Lebel et al. [21]	2008	Prospective	Arthroscopic BPTB	1993–1994	IKDC	11.6	101	18 (18 %)	34 (34 %)	6 (9 %)	12 (35 %)
Lerat et al. [22]	1998	Retrospective	Open BPTB + ITB*	1979–1986	Ahlbäck	11.7	89	13 (15 %)	47 (53 %)	2 (5 %)	11 (23 %)
Lohmander et al. [25]	2004	Retrospective	Open BPTB	1986	Kellgren and Lawrence	12	41	23 (56 %)	N/A	N/A	N/A
Meuffels et al. [31]	2009	Retrospective	Open BPTB	1994–1996	Kellgren and Lawrence	10	25	12 (48 %)	17 (68 %)	N/A	N/A
Meystre et al. [32]	1998	Retrospective	Open hamstrings + ITB*	1985–1987	IKDC	10	27	5 (18 %)	12 (44 %)	0 (0 %)	5 (42 %)
Oiestad et al. [38]	2010	Prospective	Open and arthroscopic BPTB	1990–1997	Kellgren and Lawrence	12.4	181	133 (73 %)	106 (59 %)	43 (57 %)	90 (85 %)
Pernin et al. [39]	2010	Retrospective	Open BPTB + ITB*	1978–1983	IKDC	24.5	92	50 (54 %)	48 (52 %)	17 (39 %)	33 (69 %)
Pinczewski et al. [40]	2007	Prospective	Open BPTB or hamstrings	1993–1994	IKDC	10	128	3 (2 %)	N/A	N/A	N/A
Salmon et al. [43]	2006	Retrospective	Arthroscopic BPTB	1989	IKDC	13	43	9 (21 %)	N/A	N/A	N/A
Seon et al. [46]	2006	Retrospective	Arthroscopic BPTB	1991–1996	Kellgren and Lawrence	11.3	58	25 (43 %)	33 (57 %)	5 (20 %)	20 (61 %)
Shelbourne et al. [47]	2009	Prospective	Open BPTB	1982–1994	IKDC	14.1	502	50 (10 %)	244 (49 %)	18 (7 %)	32 (13 %)

* ITB = extra-articular augmentation by ITB tenodesis

¥ Total OA = total number of subjects with radiographic OA (IKDC C or D)

§ Meniscectomy = number of meniscectomized subjects

Π OA ± Meniscectomy = subjects showing radiographic OA without or with meniscectomy, respectively
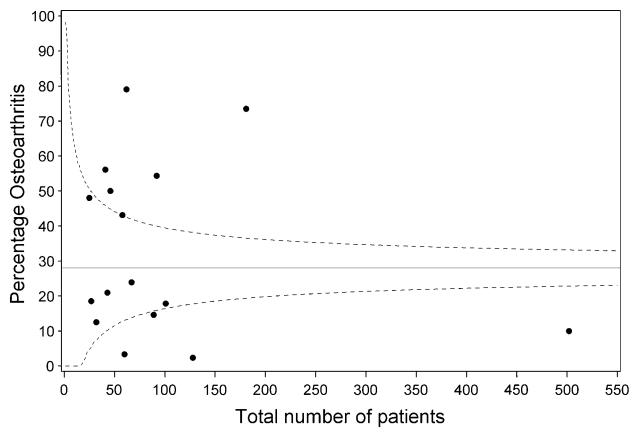
Fig. 2 Funnel plot with each *dot* representing the observed percentage OA of a single study, *dashed lines* represent the 99 % prediction limits, the *horizontal line* the overall % patients with OA
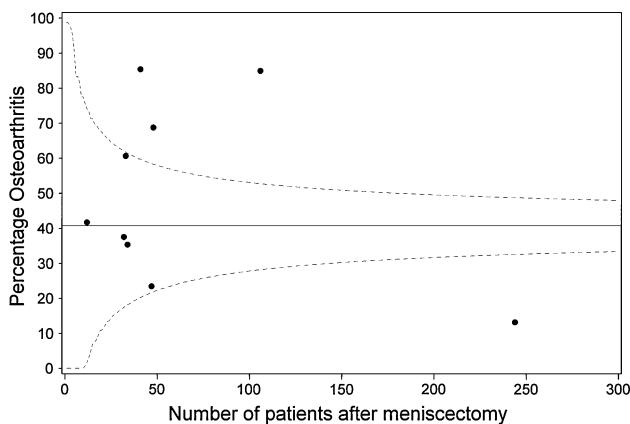

Fig. 3 Funnel plot with each *dot* representing the observed percentage OA of a single study for the patients with meniscectomy, *dashed lines* represent the 99 % prediction limits, the *horizontal line* the overall % patients with OA
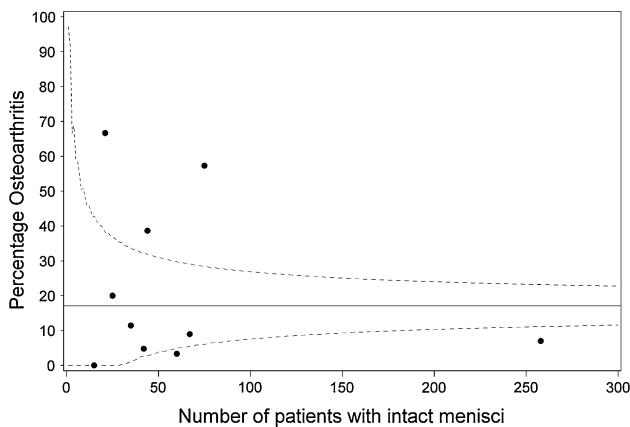

Fig. 4 Funnel plot with each *dot* representing the observed percentage OA of a single study for the patients with meniscectomy, *dashed lines* represent the 99 % prediction limits, the *horizontal line* the overall % patients with OA

## Prevalence of osteoarthritis and relation with meniscectomy

The combined estimate for the prevalence of OA (IKDC C or D) from the random-effects meta-analysis on 1554 included knees equals 27.9 % (95 % CI 16.3–43.5 %). There is, however, a large amount of heterogeneity between the studies in the reported percentage of OA (see funnel plot Fig. 2), with >90 % of the variation being due to between-study heterogeneity, ($I^2 = 95.8$ %). Although there is a strong link between meniscectomy and OA, >90 % of the variation in separate analyses on patients with and without meniscectomy is attributable to between-study heterogeneity ($I^2 = 92.7$ and 95.3 %, respectively) (see Figs. 3, 4). Further, a meta-regression reveals that there is no evidence for a relation between OA and average length of follow-up, with the odds ratio (OR) expressing the effect of 1-year increase on the odds for OA equals 1.07 (95 % CI 0.89–1.30, p = n.s.). It should be noted, however, that the range of values for the average follow-up is restricted: 11 of the 16 included studies have an average length of FU between 10 and 12 years.

The combined estimate for the prevalence of OA from the random-effects meta-analysis equals 16.4 % (95 % CI 7.0–33.9 %) in patients without meniscectomy and 50.4 % (95 % CI 27.4–73.1 %) in patients with meniscectomy. The combined odds ratio equals 3.54 (95 % CI 2.56–4.91), meaning that the odds for having OA is 3.54 times higher after meniscectomy. The forest plot (see Fig. 5) reveals that the effect estimates range in the same order of magnitude.

Discussion

The major finding of this study is that the prevalence of OA after ACL reconstruction is probably lower than commonly thought. The purpose of this meta-analysis was to compile all available evidence on long-term radiographic outcome after ACL reconstruction, as to date controversy remains to exist due to a number of dispersed, heterogeneous retrospective case series and expert opinions. From the early days on, ACL rupture has been linked with the occurrence of premature OA in the injured knee [13, 17, 29]. Remarkably, contemporary ACL reconstruction techniques have not been able to change this common belief. Indeed, many still consider early OA as an almost inevitable consequence of ACL reconstruction, with reported OA prevalences between 50 and 100 % [18, 23]. This first-ever meta-analysis on ACL reconstruction and OA shows that the use of these dramatically high prevalences is not justifiable on the basis of the available evidence in current literature. On the contrary, our results indicate that the

Fig. 5 Forest plot depicting odds ratio's considering the relation between OA and meniscectomy
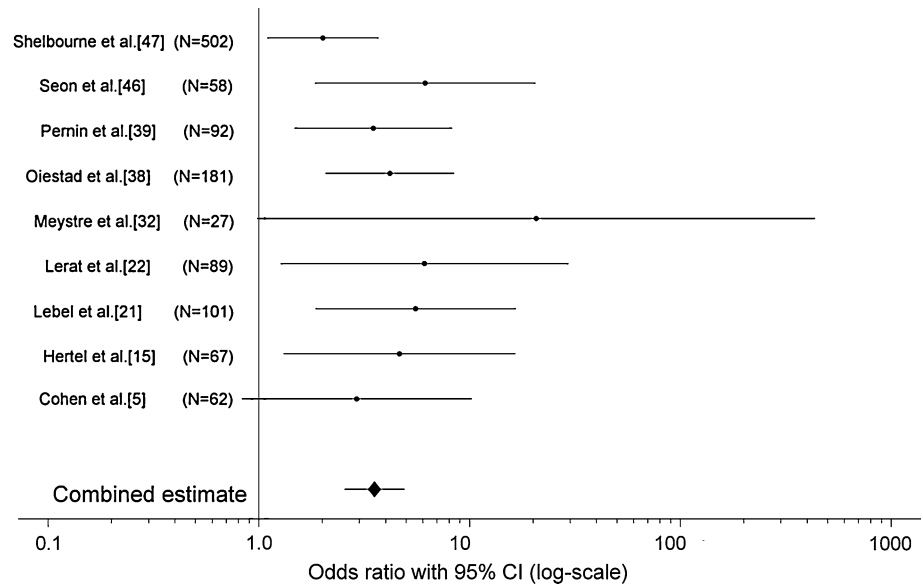
prevalence of knee OA after ACL reconstruction is significantly lower than commonly perceived. Indeed, the combined estimate from the random-effects meta-analysis equals 28 %, and the upper limit of the 95 % CI for this estimate is lower than 50 % (43.5 %). In this view, our results are in line with a recent systematic review on this topic by Oiestad et al. [37], stating that "we should discontinue reporting that subjects with ACL injury have a prevalence of knee OA between 50 and 100 %". However, that paper was a systematic review on long-term outcome after ACL injury, not ACL reconstruction, thus pooling the results of patients who were either conservatively or surgically treated (by a variety of techniques and grafts). By ranking the included papers on the basis of their respective modified Coleman Methodological Score (CMS) [6], the highest rated studies reported low prevalence of knee OA for individuals with isolated ACL injury (0–13 %) and a prevalence of knee OA between 21 and 48 % for subjects with combined injuries [37].

The question remains: can ACL reconstruction prevent the occurrence of early OA? To date, a direct proof to confirm or reject this statement stays difficult to deliver. One of the main issues in this debate is the lack of controlled, prospective studies on the long-term natural history of the ACL-deficient knee. The advent of modern ACL reconstruction in the 1980 s was merely driven by the superior short- and mid-term results with regard to stability and knee function when compared to non-operative treatment. However, some early reports on conservative ACL treatment had already shown unfavourable long-term results with very high rates (i.e., 60–90 %) of early OA in the ACL-deficient knee. [3, 17, 45] To the contrary, other authors have reported much better functional and radiographic results after non-operative treatment. For example,

Neumann et al. [36] treated ACL-injured patients with activity modification and physical therapy and reported a prevalence of only 15 % OA at 15 years of follow-up. The true natural history of these injuries may never be known due to the existence of asymptomatic ACL-deficient subjects or so-called copers, patient selection bias, or conservative treatment heterogeneity in published reports.

Additionally, this meta-analysis confirmed that meniscectomy should be considered as an important risk factor for developing OA after ACL reconstruction, with 42 % of patients showing radiographic OA compared to 19 % of patients with a preserved meniscal status (OR = 3.54). Recent cadaveric experiments by Musahl et al. [35] have confirmed the secondary stabilizing effect of both the medial and lateral meniscus in the ACL-deficient knee. These authors showed that the medial meniscus functions as an important secondary restraint to anterior tibial translation in the ACL-deficient knee (i.e., during the Lachman test), while the lateral meniscus has a relatively more important secondary restraining role to the combined axial and rotatory loads (i.e., during the pivot-shift examination). In this view, anterior or rotatory instability in the absence of a functional ACL results in excess shearing forces being applied at the meniscus, thus giving rise to meniscal damage, degenerative tears and pain necessitating resection of the meniscus. Most authors have reported higher rates of subsequent meniscal injuries after conservatively managed ACL ruptures when compared to ACL reconstructed knees, with incidences as high as 98 % in chronic ACL-deficient knees [18, 20]. Even in a recent RCT published in the New England Journal of Medicine questioning the need for prompt ACL reconstructive surgery [12], the conservatively treated cohort experienced 33 % more meniscal tears after the ACL injury. As this

meta-analysis has clearly identified meniscectomy as the risk factor of utmost importance with regard to the development of early OA, the occurrence of OA can be directly related to the inability of the ACL-injured knee to protect its menisci. In other words, this meta-analysis supports the statement that "the key to lowering the risk of knee OA is decreasing the rate of meniscectomy" [42].

The limitations of this meta-analysis are as follows:

1. One could argue that the existence of cartilage lesions at the time of ACL reconstruction is not taken into account in this meta-analysis, thus probably compromising interpretation of the results. Let alone the fact that the prevalence of chondral injuries at the time of ACL reconstruction is rarely reported in the included reports, multiple authors previously have not been able to find a correlation between an osteochondral injury diagnosed at primary arthroscopy after ACL injury and subsequent knee OA [36, 48].

2. As stated before, a major difficulty arises when comparing long-term outcome studies after ACL reconstruction with regard to the varying OA classifications used in these reports. In order to facilitate meta-analysis, the Ahlbäck [1], Kellgren and Lawrence [19] and modified Fairbank[10] classifications were all translated into the IKDC radiographic grading [14], to the best effort. A particular difficulty arose with the interpretation of the K&L classification, especially with the description of K&L grade II, which has been notoriously inexact, due to initial description of the developers [44]. We decided, in accordance with Meuffels et al. [31] and Oiestad et al. [38] to consider K&L grade II as "osteoarthritis" (i.e., IKDC grade C), unless explicitly stated otherwise in the individual report.

3. There is a considerable amount of variability between the studies in the reported prevalences of OA. The formal analysis and the funnel plot indicate that this variability largely exceeds the sampling variability, that is, reflects true differences (heterogeneity) between the studies, both in the combined group (all subjects irrespective of meniscectomy) and the subgroups.

Conclusion

In conclusion, this meta-analysis on the relation between ACL reconstruction and the development of OA has shown that the prevalence of OA is definitely lower than commonly perceived. However, associated meniscal resection dramatically increases the risk for developing OA (OR 3.54). This finding bears the inherent consequence of attempting a repair of meniscus injuries sustained at the time of ACL tear, as well as contemplating reconstruction of the ruptured ACL in order to protect the menisci from excessive shear forces, subsequent tearing and the premature development of OA. Moreover, in an era of questioning the cost-effectiveness of surgical procedures, the results of this study have the potential to justify current clinical practice regarding ACL-injured subjects. Finally, these results should be used as a baseline for upcoming long-term outcome studies on recent ACL techniques and to counsel ACL-injured patients in an evidence-based way.

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