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Do reconstructive techniques for osteochondritis dissecans of the skeletally mature knee work? A systematic review and meta-analysis

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Abstract

Purpose: Osteochondritis dissecans (OCD) is a common cause of knee pain. Management for adult-onset OCD (AOCD) usually involves surgery. Surgical treatments include palliative, reparative and reconstructive techniques. The aim of this systematic review and meta-analysis is to evaluate the efficacy of reconstructive techniques for the treatment of OCD in skeletally mature knees.

Methods: A systematic search was carried out on four databases up to November 2023 (Medline, Embase, Cochrane Library, Web of Science). The study was registered on international prospective register of systematic reviews and performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. Clinical studies on skeletally mature patients were included, which utilised reconstructive techniques such as autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation, osteochondral allograft transplantation surgery or bone marrow-derived cellular transplantation. Demographical data, patient-reported outcome measures and post-operative complications were recorded. Quantitative outcome measures that were comparable across studies were pooled for meta-analysis. A random effects model was used. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test. Statistical significance was set at $p < 0.05$. Risk of bias was assessed using the risk of bias in non-randomised studies - of interventions tool for nonrandomised studies.

Results: Sixteen studies were included with 458 OCD lesions in 432 patients. The average age was 24.9, and 62.6% were male. The mean follow-up time was 61.5 months. At 36 months follow-up, International Knee Documentation Committee (IKDC) subjective, Tegner and EuroQol-visual analogue scale (EQ-VAS) scores improved from 42.4 to 78.6 (standard

Abbreviations: ACI, autologous chondrocyte implantation; ACI-C, ACI with collagen cover; ACI-P, ACI with periosteal cover; ADL, activities of daily living; AOCD, adult-onset osteochondritis dissecans; BMDC, bone marrow-derived cells; BMI, body mass index; CI, confidence interval; CKRS, Cincinnati Knee Rating System; COS, core outcome set; EQ-VAS, EuroQol-visual analogue scale; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; JOCD, Juvenile-onset OCD; KOOS, knee injury and osteoarthritis outcome; LFC, lateral femoral condyle; MACI, matrix-induced autologous chondrocyte implantation; MFC, medial femoral condyle; MOCART, magnetic resonance observation of cartilage repair tissue; MRI, magnetic resonance imaging; OA, osteoarthritis; OATS, osteochondral allograft transplantation surgery; OCD, osteochondritis dissecans; ORIF, open reduction internal fixation; PICOS, Population, Intervention, Comparison, Outcome, Study type; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PROM, patient-reported outcome measure; QALY, quality-adjusted life year; SD, standard deviation; SF-36, 36-Item Short Form Survey; SMD, standard mean difference; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

mean difference [SMD]: 2.47; $p < 0.001$), 2.27–4.99 (SMD: 2.363; $p = 0.002$) and 30.4–57.5 (SMD: 2.390; $p < 0.001$), respectively. Overall complication rate was 8.9%. Smaller OCD lesion sizes resulted in a greater improvement in IKDC subjective (SMD: 2.64 vs. 2.01; $p = 0.038$), EQ-VAS (SMD: 3.16 vs. 0.95; $p = 0.046$) and Tegner scores (SMD: 3.13 vs. 1.05; $p = 0.007$) and had a lower complication rate ($p = 0.008$). Males showed a larger improvement in IKDC subjective scores than females (SMD: 2.56 vs. 1.56; $p = 0.029$), while younger patients had a larger improvement in IKDC subjective scores (SMD: 2.71 vs. 2.12; $p = 0.045$) and fewer complications than older patients ($p = 0.003$). There were no significant differences between cohorts treated with ACI and those treated with non-ACI reconstructive techniques. Publication bias was not detected (n.s.).

Conclusion: Reconstructive techniques used to treat OCD in the skeletally mature knee resulted in significant improvements in clinical and functional outcomes, with a low overall complication rate. Since a younger age leads to a greater improvement in IKDC subjective score and a lower complication rate, surgical intervention should not be delayed, especially in AOCD lesions which are more likely to follow a progressive and unremitting clinical course.

Level of Evidence: Level III.

KEYWORDS

knee, osteochondritis dissecans, PROMs, skeletally mature, systematic review

INTRODUCTION

Osteochondritis dissecans (OCD) is defined as an acquired, idiopathic, potentially reversible lesion of the subchondral bone [27]. Injury results in delamination and sequestration of the affected bone with or without articular damage or instability [27].

The most commonly affected joints are the knee and elbow joints [14]. However, case reports have been published regarding OCD lesions in other articular surfaces, such as the shoulder and ankle. Among OCD knee lesions, the posterolateral aspect of the medial femoral condyle (MFC) is the most commonly affected, and femoral trochlear lesions are the least common [27]. There is no consensus regarding the aetiology of OCD. Suggested causes include ischaemia, acute and repetitive trauma, familial predisposition and inflammation, although the cause is likely to be multifactorial. Repetitive trauma associated with vascular insufficiency is currently the most widely accepted aetiology. This correlates well with the high incidence rate of OCD in athletes [1, 14, 47], with 55% of patients in a multicentre study performed by the European Paediatric Orthopaedic Society performing 'strenuous athletic activity' [23].

OCD is classified as juvenile-onset OCD (JOCD) or adult-onset OCD (AOCD) based on the maturity of the distal femoral physis [27]. Compared to AOCDs, JOCDs are more likely to be lower-grade, with increased propensity for healing using conservative treatment, and a lower risk for subsequent development of knee osteoarthritis (OA) [5]. AOCDs typically are more likely to be unstable and follow an unremitting clinical course [5]. Long-term follow-up studies report that over 50% of AOCDs lead to premature degenerative joint disease [31, 55]. Hence, early surgical intervention is recommended for AOCD [6].

Surgical techniques used to treat OCD can be divided into three categories: (1) palliative techniques such as debridement and lavage; (2) reparative techniques such as bone marrow stimulation (microfracture), internal fixation (open reduction internal fixation or arthroscopic) or drilling and (3) reconstructive techniques such as autologous chondrocyte implantation (ACI) (first and second generation), matrix-induced autologous chondrocyte implantation (MACI), osteochondral allograft transplantation surgery (OATS) or bone marrow-derived cellular (BMDC) transplantation. Palliative or reconstructive treatment does not address underlying articular cartilage damage, and poor results have been reported in AOCD with subsequent degenerative changes [2]. For patients who have failed prior treatment, good outcomes have been reported with subsequent reconstructive techniques that are able to restore both osseous and chondral components of the OCD lesion. Nevertheless, there is currently no consensus regarding the efficacy of reconstructive techniques for AOCD,

and difficulties in restoring articular cartilage in deep OCD lesions still remain [8, 50]. The clinical and functional efficacy of reconstructive techniques for the treatment of AOCD in the knee were evaluated in this systematic review. We hypothesise that patients with smaller lesion size and depth will have a greater improvement in patient-reported outcome measures (PROMs).

MATERIALS AND METHODS

Study selection

This review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The study protocol was registered with international prospective register of systematic reviews (CRD42023452211). Four databases were searched for studies published from inception to 8 December 2023: Medline via PubMed, Embase via OVID, Web of Science and Cochrane Library. A snowball search was also performed, whereby studies that cited any of the included studies and references of the included studies were hand searched. The full search criteria can be found in File S1.

All studies were imported into Mendeley and deduplicated. Title and abstract screening were performed by two authors independently. This was followed by full-text review. The inclusion and exclusion criteria were created following the Population, Intervention, Comparison, Outcome, Study type model. Clinical studies performed on patients who were skeletally mature at the time of surgery were included. Skeletally maturity was defined as when epiphyseal fusion has occurred [4, 20]. The full criteria can be found in File S2.

Data extraction

A standardised Excel spreadsheet was used to tabulate data collected from the included studies. In each study, data were split into the following categories:

1. Study characteristics and demographics
2. Operative findings
3. PROMs
4. Radiographic findings
5. Complications

Data analysis

Quantitative outcome measures that were comparable across studies were included in the meta-analysis. This included PROMs, magnetic resonance observation of cartilage repair tissue (MOCART) scores and complication rates. In general, PROMs are reported such that a higher absolute value means a better functional or clinical outcome. Exceptions include negatively worded concepts such as the Western Ontario and McMaster Universities Arthritis Index score, whereby a lower value indicates less pain/functional limitations.

Meta-analysis was performed using RStudio version 4.0.5 through the 'meta', 'metafor' and 'tidyverse' packages. Due to foreseen heterogeneity in outcome measures, a random-effects model was used [13]. A minimum of two studies reporting the same outcome measure was needed to produce forest plots. When pooling effect sizes, the inverse-variance weighting method was used. For continuous outcomes, the standard mean difference (SMD) was used to pool data. For discrete variables, for example, complication rate, the relative risk (RR) and 95% confidence interval (CI) were reported.

When data were missing, the corresponding author of the study was contacted to attempt to retrieve them. When the standard deviation (SD) was not reported, the estimation method described by Wan et al. was utilised [56]. When the standard error was provided, the SD was calculated using the formula: $SD = SE \times \sqrt{n}$. Data were pooled into three postoperative time periods: 12, 24 and 36 months or more follow-up. If two outcome measures were reported in the same time period, the latter one was used (e.g., if outcomes were reported at 9 and 12 months, those at 12 months were used). Statistical significance was set at $p < 0.05$.

To assess heterogeneity, Higgins and Thompson's I^2 statistic [24] and Cochran's Q test [10] were used. Low heterogeneity was defined as $I^2 \leq 25\%$, moderate heterogeneity was defined as $25\% < I^2 \leq 50\%$ and significant heterogeneity was defined as $I^2 > 50\%$. To reflect the variation in different studies and settings, prediction intervals were shown, providing a range into which effect sizes could be expected to fall into in future studies. Subgroup analyses were performed according to five categories. Analyses were performed if there were a minimum of two studies in each subgroup.

1. Gender: majority of participants are male versus majority of participants are female.
2. Intervention: ACI and MACI versus other reconstructive techniques.
3. Lesion size: ≤4 versus >4 cm^2.
4. Location of defect: majority of OCDs located on MFC versus majority of OCDs located on lateral femoral condyle.
5. Age: average age ≤25 versus >25 years old.

Bias

Risk of bias was assessed using Cochrane's risk of bias 2.0 tool for randomised trials, which contains five domains [52]. Risk of bias in non-randomised studies - of interventions was used for nonrandomised studies, containing seven domains [51]. Summary tables from risk of bias assessments are presented using the 'robvis' package in RStudio [33]. Funnel plots and Egger's regression test were used to assess publication bias.

RESULTS

A total of 3092 studies were identified from four databases. Sixteen studies were included for qualitative and quantitative analysis. The PRISMA flowchart is shown in Figure 1. Two studies did not separate skeletally immature from mature patients when reporting outcome measures and hence were excluded [44, 48]. Four studies [9, 16, 32, 54] previously included in a systematic review [47] on the treatment of adult OCD with ACI were excluded as they contained patients whose cause of osteochondral defect was something other than OCD (e.g., degenerative, traumatic lesion, OA). Details of included trials and their population characteristics are shown in Table 1. Perioperative findings are documented in Table 2.

PROMs

36 months or more follow-up

PROMs were reported by all included studies (Table 3). Carey et al. reported only postoperative PROMs; hence, no comparison with pre-operative values could be made. International Knee Documentation Committee (IKDC) subjective scores showed a significant improvement after reconstructive treatment at 36 months (10 studies [$n = 500$]; SMD: 2.47; 95% CI: 1.96–2.97; $p < 0.001$; $I^2 = 52\%$) (File S3). Statistically significant improvements were seen in Tegner score (nine studies [$n = 258$]; SMD: 2.363; 95% CI: 1.218–3.508; $p = 0.001$; $I^2 = 52\%$) (File S4), EuroQol-visual analogue scale (EQ-VAS) scores (six studies [$n = 396$]; SMD: 2.390; 95% CI: 0.338–4.442; $p = 0.030$; $I^2 = 51\%$) (File S5), IKDC objective scores (four studies [$n = 278$]; RR: 8.92; 95% CI: 1.002–79.4; $p = 0.050$; $I^2 = 42\%$) (File S6), knee injury and osteoarthritis outcome (KOOS) Pain (two studies [$n = 186$]; SMD: 0.795; 95% CI: 0.624–0.966; $p = 0.011$; $I^2 = 0\%$) (File S7) and KOOS other symptoms (two studies [$n = 186$]; SMD: 1.580; 95% CI: 1.129–2.031; $p = 0.014$; $I^2 = 18\%$) (File S8). Improvements in other PROMs were also noted, but they were not statistically significant: Cincinnati Knee Rating System (three studies [$n = 178$]; SMD: 11.710; 95% CI: −13.880–37.301; n.s.; $I^2 = 49\%$) (File S9), Lysholm scores (four studies [n = 196]; SMD: 4.106; 95% CI: −1.983–10.194; n.s.; $I^2 = 47\%$) (File S10), KOOS Sport

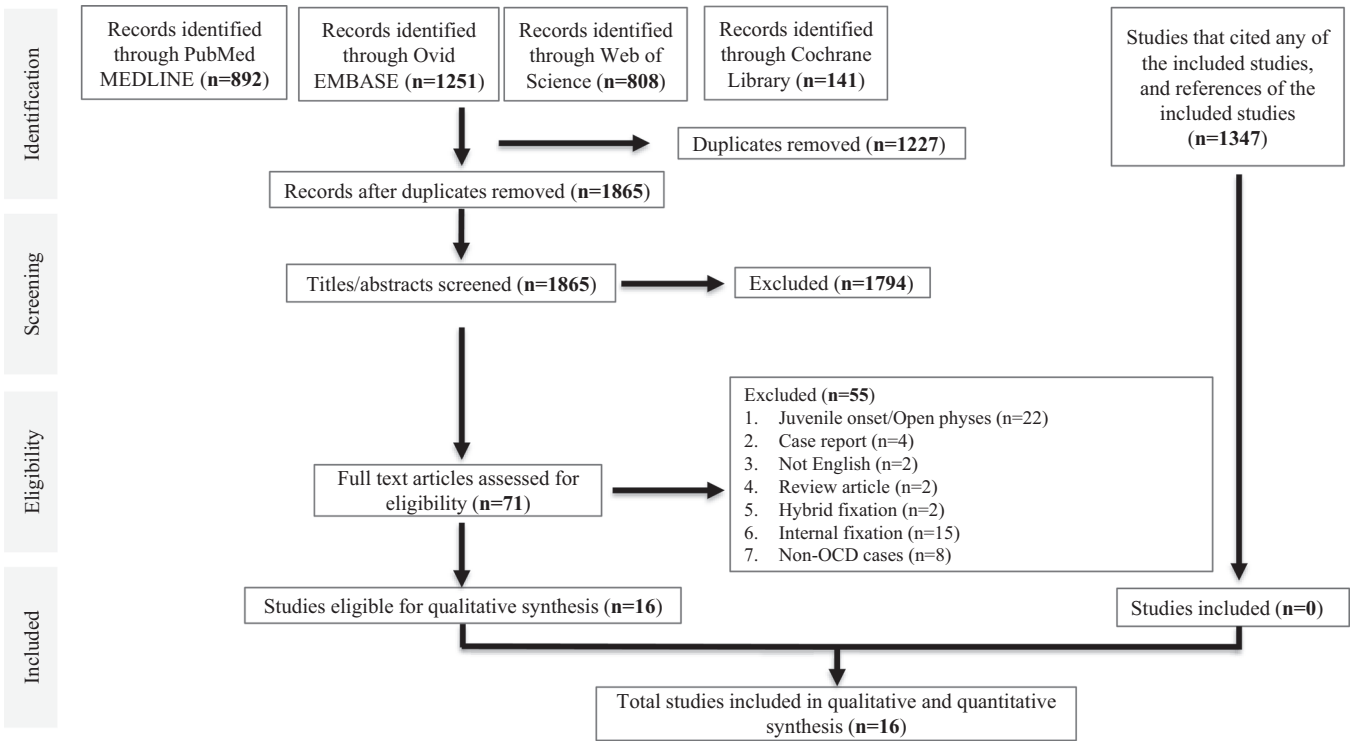

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis diagram.

TABLE 1 Demographics.

References	Country	Age at surgery (years)	Sex (% male)	BMI	No. of patients	No. of OCD lesions	Lesion classification	Laterality (%)	Symptom duration (years)	Follow-up (months)	Prior treatment (%)	Exclusion criteria
Aydın et al. 2020	Turkey	24.2 ± 7.7	N/A	23.4 (20–26)	17	19	ICRS stage IV	N/A	1.3	72 (60–108)	None	Inflammatory arthritis Instability of the knee joint Prior meniscectomy BMI > 26 kg/m^2 Deformities of the varus >3° and valgus >5° Early osteoarthritis Patellar malalignment Chondrocalcinosis
Baldassarri et al. [3]	Italy	19.1 ± 5.0	11 (61)	N/A	18	18	ICRS stages II and III	Right: 10 (56) Left: 8 (44)	N/A	60	3–6 months of conservative therapy	Advanced OA Concomitant ACL or PCL deficiency Infective, metabolic or inflammatory pathologies
Carey et al. [7]	Sweden	26.1 (14–52)	33 (60)	N/A	55	61	N/A	Right: 33 (54.1) Left: 28 (45.9)	8 (1–42)	228 (120–312)	None: 24 (39) Fragment excision ± chondroplasty: 18 (29) Drilling ± fixation: 18 (29) Bone grafting: 1 (2)	N/A
Cole et al. [11]	United States	30.5 ± 9.5	30 (75)	27.5 ± 4.8	40	54	Outerbridge grades III and IV	N/A	N/A	43 (18–53)	Debridement: 20 (50) Microfracture: 9 (23) Subchondral drilling: 6 (15) Abrasion arthroscopy: 3 (8) Marrow stimulation: 1 (3) Bone graft: 1 (3)	Previous ACI treatment on the ipsilateral knee Total meniscectomy Widespread OA or inflammatory arthritis in the affected knee
Cotter et al. [12]	United States	26.01 ± 9.96	26 (67)	26.54 ± 4.77	37	39	N/A	Right: 20 (51.3) Left: 19 (48.7)	4.54 ± 4.38	88 ± 40	ORIF: 17 (44) Loose body removal: 13 (33) Microfracture: 21 (53) ACI: 1 (3) OATS: 1 (3)	Received bone graft or DeNovo NT tissue graft Allograft transplant in another joint

(Continues)

TABLE 1 (Continued)

References	Country	Age at surgery (years)	Sex (% male)	BMI	No. of patients	No. of OCD lesions	Lesion classification	Laterality (%)	Symptom duration (years)	Follow-up (months)	Prior treatment (%)	Exclusion criteria
Filardo et al. [17]	Italy	21 ± 6	23 (72)	N/A	32	34	ICRS stages III and IV	N/A	N/A	72 ± 12	Meniscectomy: 2 (6) ACL reconstruction: 1 (3) Patellar realignment: 1 (3) Drilling: 1 (3) Shaving: 4 (12) Loose body removal: 1 (3)	N/A
Filardo et al. [18]	Italy	25.5 ± 7.7	19 (70)	N/A	27	27	ICRS stages III and IV	N/A	N/A	24	Loose body removal: 5 (19) Shaving: 3 (11) Fragment fixation: 2 (7) Debridement: 1 (4) Microfracture: 1 (4)	Noncorrected axial deviations (>5% from normal axis). Infectious, neoplastic, metabolic and inflammatory disorders.
Fonseca and Balacó [19]	Portugal	27.5 ± 7.9	9 (75)	N/A	12	12	ICRS stages III and IV	N/A	N/A	52 ± 25	N/A	N/A
Keyhani et al. [25]	Iran	23.7 ± 6.2	12 (75)	21.3 (20–24)	16	16	Clanton and Delee classification stages II–IV	Right: 9 (56.3) Left: 7 (43.8)	1.17 (0.58–1.75)	36	N/A	Concomitant knee injuries Gross malalignment, instability, systemic diseases and past history of knee surgery
Kon et al. [28] (OATS)	Italy	21.7 ± 6.1	4 (44.4)	N/A	9	9	ICRS stages III and IV	N/A	N/A	147 ± 114	Bone-cartilage paste graft: 1 (11)	N/A
Kon et al. [28] (BC graft)	Italy	24.4 ± 9.0	7 (70)	N/A	10	10	ICRS stages III and IV	N/A	N/A	46 ± 5	Loose body removal: 2 (20) Meniscectomy: 1 (10) ACL reconstruction: 1 (10) Microfracture: 1 (10)	N/A
Kon et al. [28] (ACI)	Italy	19.8 ± 4.6	20 (71.4)	N/A	28	28	ICRS stages III and IV	N/A	N/A	62 ± 16	Loose body removal: 8 (29) Meniscectomy: 1 (4) Patellar realignment: 2 (7)	N/A
Kon et al. [28] (scaffold)	Italy	27.5 ± 6.4	4 (50)	N/A	8	8	ICRS stages III and IV	N/A	N/A	31 ± 6	Loose body removal: 2 (25) Meniscectomy: 2 (25) Shaving: 2 (25) Fragment fixation: 1 (13)	N/A

TABLE 1 (Continued)

References	Country	Age at surgery (years)	Sex (% male)	BMI	No. of patients	No. of OCD lesions	Lesion classification	Laterality (%)	Symptom duration (years)	Follow-up (months)	Prior treatment (%)	Exclusion criteria
Kon et al. [28] (BMDC)	Italy	25.4 ± 12.6	4 (57.1)	N/A	7	7	ICRS stages III and IV	N/A	N/A	28 ± 17	None	N/A
Krishnan et al. [30]	England	23.8	N/A	N/A	9	9	N/A	N/A	7.2 (2.5–12)	4 ± 1	N/A	N/A
Ochs et al. [38]	Germany	29.2 ± 9.4	18 (69)	26.1 ± 5.5	26	26	ICRS stages III and IV	N/A	N/A	39.8 ± 12.0	13 patients (50%) underwent previous surgery	Open epiphysial plates Osteoarthritis Rheumatoid knee arthritis
Paatela et al. [39]	Finland	24 ± 8	17 (49)	24.9 ± 4.3	35	35	N/A	N/A	5 ± 4.8	18	Meniscectomy: 2 (6) Microfracture: 3 (9) High tibial osteotomy: 1 (3) Removal of loose bodies: 21 (60) Arthroscopy: 8 (23)	N/A
Perdisa et al. [43]	Italy	25.5 ± 7.7	19 (70)	23.0 ± 2.7	27	27	ICRS stages III and IV	N/A	N/A	60	Loose body removal: 5 (19) Shaving: 3 (11) Cartilage repair procedure: 2 (7) Fragment fixation: 2 (7) Meniscectomy: 2 (7) Debridement: 1 (4)	Knee misalignment >5 degrees, infectious, neoplastic, metabolic and inflammatory diseases.
Steinhagen et al. [50]	Germany	29.3 ± 7.5	14 (67)	N/A	21	21	ICRS stages III and IV	Right: 12 (57) Left: 9 (43)	2.4 ± 2.1	36	Arthroscopic drilling Microfracture Fragment excision	N/A
Stone et al. [53]	United States	24	6 (85.7)	N/A	7	7	N/A	N/A	2.1 (0.3–7.3)	84 ± 43	OATS: 2 (8) Refixation: 3 (13) Drilling: 2 (8)	Multicompartmental or bilateral cartilage degradation

Abbreviations: ACI, autologous chondrocyte implant; ACL, anterior cruciate ligament; ICRS, International Cartilage Repair Society; OA, osteoarthritis; OATS, Osteochondral Autograft Transfer System; OCD, osteochondritis dissecans; PCL, posterior cruciate ligament.

TABLE 2 Operation findings.

References	Defect location	Defect depth (mm)	Defect size (cm^2)	Intervention	Surgical technique	Concomitant procedures	Postop rehabilitation
Aydın et al. 2020	N/A	12.0 ± 1.2	7.66 ± 1.88	MACI + bone graft	Autologous chondrocytes seeded onto scaffold and fixed with fibrin gel. Bone grafts from iliac crest were used.	None	Full ROM and quadriceps-strengthening exercises in the fourth week. PWB at 6th week and FWB at 12th week.
Baldassarri et al. [3]	MFC: 15 (83.3%) LFC: 3 (16.7%)	7.7 ± 3.9	2.03 ± 0.6	BMDC transplantation	PRF gel is produced from the patient's venous blood. Bone marrow is harvested and concentrated in a centrifuge. The OCD lesion is coated with a collagen scaffold and loaded with bone marrow concentrate. PRF gel is applied to cover the lesions.	None	CPM (0°–35°; 1 cycle/min) was initiated on the first postop day for 6–8 h per day. PWB at 6 weeks and FWB at 10 weeks postop.
Carey et al. [7]	MFC: 43 (70.5) LFC: 15 (24.6) Trochlea: 1 (1.6) Patella: 2 (3.3)	6.2 (1–15)	6.0 (0.9–12.3)	ACI-P + bone graft (16% of cases)	Cultured chondrocytes are injected into the defected, which is covered with a periosteum flap. If bone loss was >8 mm in depth, autogenous bone graft was used.	None: 43 (70.5) ACI of another region: 5 (8.2) Proximal tibia osteotomy: 5 (8.2) ACL reconstruction: 4 (6.6) Hardware removal: 2 (3.3) Tibial tubercle osteotomy: 1 (1.6) Loose body removal: 1 (1.6)	CPM for 48 h after surgery. Protected weight bearing for 10–12 weeks.
Cole et al. [11]	MFC: 26 (65) LFC: 11 (28) Trochlea: 3 (8)	N/A	5.4 ± 4.6	ACI-P	Cultured chondrocytes are injected into the defect, which is covered with a periosteum flap.	Tibial tubercle osteotomy: 2 (5) Lateral release of patella retinaculum: 1 (2.5) Tibial osteotomy: 1 (2.5) Bone graft: 1 (2.5) Loose body removal: 1 (2.5)	N/A
Cotter et al. [12]	MFC: 24 (53.3) LFC: 21 (46.7)	N/A	4.6 ± 1.7	OATS	A sizing guide is driven into the defect and the donor condyle. The allograft is transplanted and impacted into the defect.	Meniscal allograft transplantation: 6 (15.4) High tibial osteotomy: 3 (7.7) Distal femoral osteotomy: 4 (10.3)	Hinged knee brace for 4-6 weeks. PWB at 6 weeks and FWB as tolerated.

TABLE 2 (Continued)

References	Defect location	Defect depth (mm)	Defect size (cm^2)	Intervention	Surgical technique	Concomitant procedures	Postop rehabilitation
Filardo et al. [17]	MFC: 24 (70.6) LFC: 10 (29.4)	N/A	3 ± 1	MACI + bone graft	Laboratory-expanded autologous chondrocytes grown on a three-dimensional hyaluronan-based scaffold (hyalograft C) is implanted into the defect. Bone graft harvested from medial tibial head.	Patellar realignment: 1 (2.9%) Meniscectomy: 1 (2.9%)	CPM 6 hrs daily with 1 cycle per minute until 90° of flexion is achieved. FWB 6–10 weeks after surgery.
Filardo et al. [18]	MFC: 17 (63.0) LFC: 10 (37.0)	N/A	3.4 ± 2.2	OATS	The defect was templated to produce the graft. The graft was implanted into the defect with a press-fit technique.	Tibial osteotomy: 2 (7.4) Femoral osteotomy: 2 (7.4) Patellar realignment: 1 (3.7) Meniscectomy: 1 (3.7) Meniscal allograft: 1 (3.7) implant: 1 (3.7)	Weight touchdown with crutches on third to fourth weeks. FWB 6–8 weeks after surgery.
Fonseca and Balacó [19]	MFC: 11 (91.7) LFC: 1 (8.3)	N/A	2.3 ± 0.5	OATS	The defect was templated to produce the graft. The graft was implanted into the defect with a press-fit technique.	None	Touch-down weight bearing for the first 6 weeks.
Keyhani et al. [25]	MFC: 12 (75) LFC: 4 (25)	N/A	1−4	OATS	The defect was templated to produce the graft. The graft was implanted into the defect from central to the periphery and posterior to anterior.	None	PWB after 6 weeks and FWB after 3 months.
Kon et al. [28] (OATS)	MFC: 8 (88.9) LFC: 1 (11.1)	N/A	2.4 ± 1.0	OATS	The defect was templated to produce the graft from a nonweight-bearing region of the femoral condyle. The graft was implanted into the defect with a press-fit technique.	Meniscectomy: 1 (11.1) Patellar realignment: 1 (11.1) Tibial plateau drilling: 1 (11.1)	N/A
Kon et al. [28] (BC graft)	MFC: 7 (70) LFC: 3 (30)	N/A	2.9 ± 1.0	Bone-cartilage paste graft	Subchondral bone in the defect site was penetrated until bleeding. Cartilage and bone were harvested, morselized into a paste, then used to cover the defect.	Loose body removal: 4 (40)	N/A
Kon et al. [28] (ACI)	MFC: 19 (67.9) LFC: 9 (32.1)	N/A	2.6 ± 0.9	ACI-C + bone graft	Cultured chondrocytes are seeded onto a hyaluronic acid scaffold, which is implanted into the defect, which is covered with a collagen flap.	ACL: 1 (3.6) Meniscectomy: 2 (7.1)	N/A

(Continues)

TABLE 2 (Continued)

References	Defect location	Defect depth (mm)	Defect size (cm^2)	Intervention	Surgical technique	Concomitant procedures	Postop rehabilitation
Kon et al. [28] (scaffold)	MFC: 4 (50) LFC: 4 (50)	N/A	3.0 ± 1.0	Biomimetic osteochondral scaffold	A porous three-dimensional composite three-layer structure was cut to the size of the defect and implanted using press-fitting.	Meniscal allograft: 1 (12.5) Tibial osteotomy: 1 (12.5) Femoral osteotomy: 1 (12.5)	N/A
Kon et al. [28] (BMDC)	MFC: 7 (100) LFC: 0 (0)	N/A	2.7 ± 0.9	BMDC	PRF gel is produced from the patient's venous blood. Bone marrow is harvested and loaded onto a hyaluronic acid membrane. The OCD lesion is coated with the membrane and PRF gel is applied to cover the lesions.	ACL: 1 (14.3) Meniscectomy: 2 (28.6) Tibial osteotomy: 1 (14.3)	N/A
Krishnan et al. [30]	MFC: 27 (73) LFC: 6 (16) Patella: 4 (11)	<8	5.8 (1–15)	ACI-C	Cultured chondrocytes are seeded onto a hyaluronic acid scaffold, which is implanted into the defect. This is covered with a collagen flap.	None	Limb was elevated for 12 h. FWB at 24 h. Daily physiotherapy for 2 weeks.
Ochs et al. [38]	MFC: 22 (84.6) LFC: 4 (15.4)	8.7 ± 2.4	5.3 ± 2.3	MACI + Bone graft	Autologous chondrocytes seeded onto scaffold and fixed with fibrin gel, together with monocortical cancellous cylinders from iliac crest.	ACL: 1 (3.6) Tibial osteotomy: (7.1)	PWB for 6 weeks; FWB after 12 weeks.
Paatela et al. [39]	N/A	N/A	7.8 ± 4.3	ACI-P	Cultured chondrocytes are injected into the defect, which is covered with a periosteum flap.	None	N/A
Perdisa et al. [43]	N/A	N/A	3.4 ± 2.2	Biomimetic Osteochondral Scaffold	A three-layer scaffold (made from type I collagen and hydroxyapatite) designed to reproduce the structure of the osteochondral unit was cut to the size of the defect and implanted using press-fitting.	High tibial osteotomy: 2 (7.4) Distal femoral osteotomy: 2 (7.4) Patellar realignment: 1 (3.7) Meniscectomy: 1 (3.7)	Early isometric and isotonic exercises, quadriceps strengthening. FWB at 4 weeks.

TABLE 2 (Continued)

References	Defect location	Defect depth (mm)	Defect size (cm^2)	Intervention	Surgical technique	Concomitant procedures	Postop rehabilitation
Steinhagen et al. [50]	MFC: 17 (81) LFC: 4 (19)	N/A	6.6 ± 2.1	MACI + Bone graft	Autologous chondrocytes seeded onto scaffold and fixed with fibrin gel, together with bone graft.	None	Immobilisation with brace for 48 h. Touch down weight bearing for 6 weeks.
Stone et al. [53]	MFC: 5 (71.4) LFC: 2 (28.6)	3 ± 2	3.3 ± 1.5	Bone-cartilage paste graft	Subchondral bone in the defect site was penetrated until bleeding. Cartilage and bone were harvested, morselized into a paste, then used to cover the defect.	None	NWB for 4 weeks, CPM for 6 h daily.

Abbreviations: ACI-C, autologous chondrocyte implantation with collagen cover; ACI-P, autologous chondrocyte implantation with periosteum cover; ACL, anterior cruciate ligament; BMDC, bone marrow-derived cells; CPM, continuous passive motion; FWB, full weight bearing; LFC, lateral femoral condyle; MACI, matrix-induced autologous chondrocyte implantation; MFC, medial femoral condyle; OATS, osteochondral autograft transfer system; OCD, osteochondritis dissecans; PRF, platelet-rich fibrin; PWB, partial weight bearing; ROM, range of motion.

(two studies [$n = 186$], SMD: 2.163; 95% CI: −6.547–10.873; n.s.; $I^2 = 85\%$) (File S11); KOOS QoL (two studies [$n = 186$]; SMD: 2.689; 95% CI: −6.294–11.671; n.s.; $I^2 = 91\%$) (File S12) and KOOS ADLs (three studies [$n = 222$]; SMD: 2.78; 95% CI: −3.11–8.70; n.s.; $I^2 = 43\%$) (File S13).

24 months follow-up

PROMs at 24 months follow-up were pooled for IKDC subjective scores (File S14), IKDC objective scores (File S15), KOOS ADLs (File S16), Tegner score (File S17) and EQ-VAS scores (File S18). Compared to preoperative values, improvement was statistically significant for Tegner scores (three studies [$n = 176$], SMD: 1.280; 95% CI: 1.115–1.444; $p < 0.001$; $I^2 = 0\%$) and EQ-VAS scores (two studies [$n = 104$], SMD: 3.511; 95% CI: −12.162–19.184; n.s.; $I^2 = 61\%$).

12 months follow-up

PROMs at 12 months follow-up were pooled for IKDC subjective scores (File S19), KOOS ADLs (File S20), Tegner scores (File S21) and EQ-VAS scores (File S22). Compared to preoperative values, improvement was statistically significant for EQ-VAS scores (two studies [$n = 104$]; SMD: 2.847; 95% CI: −14.121–19.814; n.s.; $I^2 = 64\%$) and KOOS ADLs (two studies [$n = 144$]; SMD: 1.859; 95% CI: −4.455–8.172; n.s.; $I^2 = 66\%$).

Subgroup analyses

Comparing OCD lesion sizes ≥4 cm^2 with <4 cm, larger lesions have a smaller improvement in IKDC subjective score ($p = 0.038$) (Table 4), Tegner score ($p = 0.007$) (Table 5) and EQ-VAS score ($p = 0.046$) (Table 6). Improvement in IKDC subjective scores was greater in males than in females ($p = 0.029$). There were no significant differences between ACI and non-ACI treatments regarding IKDC subjective scores, Tegner score or EQ-VAS score. Comparing patients with an average age ≤25 years old with those >25, the younger cohort had a greater improvement in IKDC subjective scores ($p = 0.045$) and had a lower complication rate ($p = 0.003$).

Radiographical findings and complications

Six studies evaluated patients with high-resolution magnetic resonance imaging (Table 7) [3, 17, 18, 38, 43, 53]. On average, complete filling of the lesion was

TABLE 3 Patient-reported outcome measures.

References	IKDC subjective	IKDC objective[a]	ICRS	KOOS ADLs	KOOS pain	KOOS other symptoms
Aydın et al. 2020	N/A	N/A	Preop: 29.75 ± 7.15 6 M: 85.66 ± 13.70 24 M: 86.03 ± 12.47 60 M: 87.58 ± 12.83	N/A	N/A	N/A
Baldassarri et al. [3]	Preop: 46.8 ± 9.7 12 M: 68 ± 8.8 24 M: 80 ± 8.5 36 M: 87 ± 8.9 48 M: 89 ± 8.7 60 M: 88 ± 9.0 Final FU: 89.3 ± 8.1	N/A	N/A	Preop: 47.8 ± 6.8 12 M: 68 ± 9.5 24 M: 78 ± 9.3 36 M: 86 ± 8.9 48 M: 92 ± 7.0 60 M: 94 ± 4.9 Final FU: 94.3 ± 9.4	N/A	N/A
Carey et al. [7]	N/A	N/A	N/A	Postop: 85.5 (25–100)	Postop: 79.3 (25–100)	Postop: 60.2 (25–90)
Cole et al. [11]	N/A	N/A	N/A	Preop: 63.5 ± 19.3 12 M: 87.1 ± 12.9 24 M: 87.8 ± 13.4 36 M: 87.5 ± 12.8 48 M: 86.7 ± 15.2	Preop: 51.5 ± 16.8 12 M: 76.4 ± 15.4 24 M: 77.7 ± 17.6 36 M: 76.6 ± 15.4 48 M: 79.5 ± 16.5	Preop: 54.8 ± 19.5 12 M: 78.7 ± 13.1 24 M: 76.8 ± 15.6 36 M: 75.7 ± 15.2 48 M: 77.9 ± 17.4
Cotter et al. [12]	Preop: 33 Final FU: 58	N/A	N/A	Preop: 62 Final FU: 83	Preop: 50 Final FU: 70	Preop: 55 Final FU: 69
Filardo et al. [17]	Preop: 38 ± 12 12 M: 73 ± 20 24 M: 81 ± 20 72 M: 81 ± 20	Preop: 0% 12 M: 53% 24 M: 76% 72 M: 65%	N/A	N/A	N/A	N/A
Filardo et al. [18]	Preop: 48.4 ± 17.8 12 M: 76.0 ± 12.8 24 M: 82.3 ± 12.2	Preop: 40.7% 12 M: 59.3% 24 M: 84.6%	N/A	N/A	N/A	N/A
Fonseca and Balacó [19]	N/A	N/A	N/A	N/A	N/A	N/A
Keyhani et al. [25]	Preop: 53.4 ± 12.2 36 M: 84.3 ± 7.8	Preop: 0% 36 M: 93.8%	N/A	N/A	N/A	N/A
Kon et al. [28] (mean)[b]	Preop: 40.1 ± 14.3 Final FU: 77.2 ± 21.3	Preop: 6.5% Final FU: 69.4%	N/A	N/A	N/A	N/A
Kon et al. [28] (OATS)	Preop: 36 Final FU: 71	N/A	N/A	N/A	N/A	N/A
Kon et al. [28] (BC graft)	Preop: 49 Final FU: 88	N/A	N/A	N/A	N/A	N/A
Kon et al. [28] (ACI)	Preop: 38 Final FU: 88	N/A	N/A	N/A	N/A	N/A
Kon et al. [28] (scaffold)	Preop: 40 Final FU: 84	N/A	N/A	N/A	N/A	N/A
Kon et al. [28] (BMDC)	Preop: 42 Final FU: 78	N/A	N/A	N/A	N/A	N/A
Krishnan et al. [30]	N/A	N/A	N/A	N/A	N/A	N/A
Ochs et al. [38]	Preop: 50.5 ± 16.1 Final FU: 78.4 ± 13.4	Final FU: 30.8%	N/A	N/A	N/A	N/A

KOOS sport	KOOS QoL	WOMAC	Lysholm score	Tegner score	SF-36 physical health	EQ-VAS	CKRS
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	Preop: 1.7 ± 1.3 36 M: 5.2 ± 2.6 Final FU: 5.3 ± 2.7	N/A	Preop: 43 ± 6.8 12 M: 68.5 ± 5.1 24 M: 71 ± 4.6 36 M: 85 ± 8.5 Final FU: 87.4 ± 7.3	N/A
Postop: 53.9 (0–100)	Postop: 52.7 (13–100)	N/A	Postop: 75.4 (25–100)	Postop: 9.1 (5–14)	N/A	N/A	N/A
Preop: 27.5 ± 22.1 12 M: 55.3 ± 22.8 24 M: 63.2 ± 27.1 36 M: 60.8 ± 25.0 48 M: 63.6 ± 25.9	Preop: 21.9 ± 14.4 12 M: 46.0 ± 22.3 24 M: 53.1 ± 25.0 36 M: 50.2 ± 22.6 48 M: 59.6 ± 22.3	N/A	N/A	N/A	Preop: 35.4 ± 10.5 12 M: 43.7 ± 8.7 24 M: 45.9 ± 7.9 36 M: 45.9 ± 7.7 48 M: 45.5 ± 9.9	N/A	Preop: 3.1 ± 1.1 6 M: 5.6 ± 1.6 12 M: 6.5 ± 2.2 24 M: 6.7 ± 2.0 36 M: 6.4 ± 2.1 48 M: 6.8 ± 2.0
Preop: 27 Final FU: 53	Preop: 21 Final FU: 52	Preop: 38 Final FU: 15	N/A	N/A	Preop: 33 Final FU: 41	N/A	N/A
N/A	N/A	N/A	N/A	Preop: 2 ± 1 24 M: 5 ± 3 72 M: 5 ± 3	N/A	Preop: 52 ± 18 12 M: 78 ± 15 24 M: 86 ± 9.7 72 M: 83 ± 14	N/A
N/A	N/A	N/A	N/A	Preop: 2.4 ± 1.7 12 M: 3.6 ± 1.2 24 M: 4.5 ± 1.6	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	Preop: 20 ± 9 Final FU: 71 ± 22	N/A
N/A	N/A	N/A	Preop: 44.3 ± 9.4 36 M: 86.3 ± 10.7	Preop: 2.8 ± 1 36 M: 5.6 ± 2	N/A	N/A	N/A
N/A	N/A	N/A	N/A	Preop: 1.9 ± 1.7 Final FU: 4.8 ± 2.6	N/A	Preop: 51.7 ± 16.9 Final FU: 83.5 ± 18.3	N/A
N/A	N/A	N/A	N/A	Preop: 2.9 Final FU: 4.3	N/A	N/A	N/A
N/A	N/A	N/A	N/A	Preop: 2.8 Final FU: 5.9	N/A	N/A	N/A
N/A	N/A	N/A	N/A	Preop: 1.5 Final FU: 5.0	N/A	N/A	N/A
N/A	N/A	N/A	N/A	Preop: 1.1 Final FU: 3.3	N/A	N/A	N/A
N/A	N/A	N/A	N/A	Preop: 2.1 Final FU: 5.4	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	Preop: 1.51 Final FU: 2.88	Preop: 27.5 Final FU: 76.2
N/A	N/A	N/A	Preop: 53.2 ± 18.0 Final FU: 88.5 ± 9.5	Preop: 3.5 ± 0.8 Final FU: 4.6 ± 1.2	N/A	N/A	Preop: 51.7 ± 13.0 Final FU: 84.6 ± 11.7

(Continues)

TABLE 3 (Continued)

References	IKDC subjective	IKDC objective[a]	ICRS	KOOS ADLs	KOOS pain	KOOS other symptoms
Paatela et al. [39]	N/A	N/A	N/A	N/A	N/A	N/A
Perdisa et al. [43]	Preop: 48.4 ± 17.8 12 M: 79 ± 8.8 24 M: 82.2 ± 12.2 36 M: 88 ± 8.2 48 M: 88 ± 9.1 60 M: 90.1 ± 12.0	Preop: 40.1% 24 M: 84.6% 60 M: 92.6%	N/A	N/A	N/A	N/A
Steinhagen et al. [50]	Preop: 37.2 ± 13.6 6 M: 53 ± 11.5 12 M: 65 ± 13.5 36 M: 70.3 ± 14.0	N/A	N/A	N/A	N/A	N/A
Stone et al. [53]	Preop: 39 (IQR, 33.0–39.9) Final FU: 60.9 (IQR, 55.2–91.4)	N/A	N/A	N/A	N/A	N/A

Abbreviations: ADL, activities of daily living; CKRS, Cincinnati knee rating system; EQ-VAS, EuroQol Visual Analogue scale; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; IQR, interquartile range; KOOS, Knee Injury and Osteoarthritis Outcome Score; QoL, quality of life; SF-36, 36-Item Short Form Survey; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

achieved in 53.3% of patients, and chondral integration was seen in 64.8% of patients. MOCART scores were reported in four studies [18, 38, 43, 53], with an average pooled value of 70.4 (95% CI: 56.4–84.4) (File S23). The average pooled complication rate was 8.9% (95% CI: 3.43%–21.3%) (File S24). Compared with those with ≤4 cm^2 lesion size, patients with lesion sizes >4 cm^2 are more likely to develop postoperative complications ($p = 0.008$) (Table 8). There were no differences in complication rates between ACI and non-ACI groups.

Bias

There was no evidence of publication bias, with Egger's regression test showing no statistically significant asymmetry in the funnel plot (intercept = 0.893; 95% CI: −1.44 to 3.23; n.s.) (File S25).

No studies had serious or critical risk of bias. Seven studies had moderate risk of bias [3, 11, 12, 17, 19, 25, 50]; the remainder had low risk of bias. Postoperative rehabilitation protocol was not reported in three studies [11, 28, 39], leading to bias in the 'deviation from intended intervention' category. The exclusion criteria were not reported in seven studies [7, 17, 19, 28, 30, 39, 50], leading to bias in the 'selection of participants category'. By nature, PROMs are subjective, leading to bias in the 'measurement of outcomes category' (File S26).

DISCUSSION

Reconstructive techniques used to treat AOCD lesions of the knee result in significantly improved short to mid-term PROMs with a low overall complication rate of 8.9%. Smaller OCD lesion sizes resulted in a greater improvement in IKDC subjective, EQ-VAS and Tegner scores and had a lower complication rate. Males showed a larger improvement in IKDC subjective scores than females, while younger patients had a larger improvement in IKDC subjective scores and fewer complications than older patients.

Reconstructive techniques treat both the cartilage and subchondral bone together, leading to the repair of osteochondral defects, fixation of fragments and maintenance of joint stability [27]. ACI is a technique that aims to create repair tissue mimicking hyaline (type II) articular cartilage. A two-stage autograft technique, ACI, utilises an arthroscopic biopsy of healthy cartilage from a nonweight-bearing region, which is grown for several weeks and then implanted into the OCD lesion [15]. The lesion is then covered with either a periosteal patch (first generation) or a synthetic collagen patch (second generation) [47].

The overall complication rate of 8.9% is lower than that reported in the literature for both ACI [32] and nonACI procedures. This could be because the studies in this review only included patients with

KOOS sport	KOOS QoL	WOMAC	Lysholm score	Tegner score	SF-36 physical health	EQ-VAS	CKRS
N/A	N/A	N/A	Preop: 57.6 ± 25.6 Final FU: 70.6 ± 15	N/A	N/A	Preop: 13.0 ± 10.2 Final FU: 17.5 ± 6	N/A
N/A	N/A	N/A	N/A	Preop: 2.4 ± 1.7 12 M: 3.7 ± 1.5 24 M: 4.4 ± 1.6 36 M: 4.6 ± 1.6 48 M: 4.8 ± 2.0 60 M: 5.0 ± 1.7	N/A	N/A	N/A
N/A	N/A	N/A	Preop: 64.1 ± 2.9 6 M: 79 ± 2.4 12 M: 83 ± 2.4 36 M: 90.1 ± 2.5	N/A	N/A	N/A	N/A
N/A	N/A	Preop: 32.1 (IQR 17.1–51.8) Final FU: 0 (IQR 0-18)	N/A	Preop: 2.0 (IQR, 2.0–2.8) Final FU: 6.0 (IQR, 4.8–8.5)	N/A	N/A	N/A

[a]IKDC objective criteria: A (normal); B (nearly normal); C (abnormal); D (severely abnormal). % of normal (grade A) knees is presented in the table.
[b]Kon et al. report mean outcome scores across the whole cohort.

osteochondral defects caused by OCD rather than acute trauma. Martinčič et al. noted in their study that the incidence of OA at 10-year follow-up was greater in those with trauma than those with OCD. The superior results in the OCD cohort could be due to biological factors (younger age at operation; 24 vs. 37 years old), but also due to biomechanical factors, since patients with OCD still have intact menisci and ligaments [32].

Despite acceptable short and mid-term outcomes, ACI can be prohibitively expensive and requires two surgeries which is a major drawback [28]. A cost-effectiveness study showed that first-generation ACI (ACI-P) costs USD $66,752 and second-generation ACI (ACI-C) costs USD $66,939.50 [49]. The incremental cost per quality-adjusted life year (QALY) gained is USD $9466 for ACI-P and USD $9243 for ACI-C [49]. The price for OATS in the knee is £16,166.63 (USD $20,606) with an incremental cost per QALY of £2765 (USD $3524) [35]. Given the large difference, this review explored whether or not the outcomes of ACI differed from the outcomes of non-ACI reconstructive techniques.

Although subgroup analyses failed to show a conclusive superiority between ACI and non-ACI techniques, there was a trend towards better improvement in PROMs and lower complication rates in the ACI cohort. However, the average age in studies that utilised ACI was lower than those that utilised non-ACI techniques (22.3 vs. 24.6 years old), and it is known from previous studies that a younger age results in better outcomes no matter what surgical technique is used [5]. Furthermore, the studies that utilised non-ACI reconstructive techniques had smaller sample sizes and shorter follow-up times, which precludes any definitive conclusion. Compared with microfracture, a procedure that is known to generate the less structurally organised and durable type I fibrocartilage instead of hyaline (type II) cartilage [41], systematic reviews have failed to conclude that ACI is more cost-effective. Given the ability of alternative reconstructive techniques such as OATS and BMDC transplantation to overcome the intrinsic limitations of ACI, future studies with longer follow-up times are need to either confirm the findings in this review or ascertain if there is indeed a superior technique.

Subgroup analyses showed that the complication rate was higher in those with larger lesion size and increased patient age. This agrees with the findings from a systematic review investigating long-term outcomes after ACI for cartilage defect repair, although the lesion size used to separate cohorts was 4.5 cm^2 rather than 4 cm^2 used in this review [40]. Filardo et al. conclude that defect size has a strong influence on subjective IKDC scores ($p = 0.004$) and return to sport activity ($p = 0.048$) [17]. The same findings were replicated in several other studies [16, 18, 30, 50]. However, this was not a unanimous

TABLE 4 Subgroup meta-analyses exploring IKDC scores.

	Number of studies	Number of knees	SMD	95% Confidence interval	I^2 (%)	*p* Value
Intervention						**0.761**
Non-ACI	10	141	2.40	1.75–3.06	48.4	
ACI	4	109	2.53	1.58–3.47	52.0	
Gender						**0.029**
Male	12	233	2.56	2.08–3.04	42.2	
Female	2	17	1.56	−3.60–6.71	0.9	
Lesion size (cm^2)						**0.038**
>4	4	93	2.01	1.62–2.40	0	
≤4	10	157	2.64	2.01–3.28	22.5	
Age (years old)						**0.045**
>25	6	103	2.12	1.65–2.60	0%	
≤25	7	147	2.71	1.76–3.67	30.5	

Note: Bold values indicate statistical significance.

Abbreviations: ACI, autologous chondrocyte implantation; IKDC, International Knee Documentation Committee; SMD, standard mean difference.

TABLE 5 Subgroup meta-analyses exploring Tegner scores.

	Number of studies	Number of knees	SMD	95% Confidence interval	I^2 (%)	*p* Value
Intervention						0.610
Non-ACI	9	129	2.36	1.22–3.51	52	
ACI	3	88	3.67	−7.11 to 14.44	33.5	
Gender						0.910
Male	10	200	2.80	1.05–4.55	42.5	
Female	2	17	2.59	−19.38 to 24.56	43.0	
Lesion size (cm^2)						**0.007**
≤4	10	182	3.13	1.40–4.86	12	
>4	2	35	1.05	0.42–1.68	0	
Age (years old)						0.112
≤25	6	122	3.79	0.58–6.99	39.1	
>25	6	95	1.73	0.86–2.60	10	

Note: Bold values indicate statistical significance.

Abbreviations: ACI, autologous chondrocyte implantation; IKDC, International Knee Documentation Committee; SMD, standard mean difference.

finding, with some suggesting no correlation between lesion size and clinical outcome [28, 37, 39]. In the skeletally mature, perhaps lesions with a larger surface area are suggestive of early degenerative joint disease [40].

As noted by Kocher et al., age was the only independent multivariate predictor of Lysholm score improvement in skeletally immature patients [26]. Yet in skeletally mature patients, both age and lesion size are also independent risk factors for clinical outcomes, postoperative activity and return to sports [34, 36, 40]. In this review, improvement in IKDC scores was greater in younger patients, agreeing with findings from Kon et al. [28]. Perhaps,

TABLE 6 Subgroup meta-analyses exploring EQ-VAS scores.

	Number of studies	Number of knees	SMD	95% Confidence interval	I^2 (%)	*p* Value
Intervention						0.090
Non-ACI	3	92	3.62	−2.09 to 9.32	43.2	
ACI	3	106	1.27	−0.47 to 3.00	35.6	
Lesion size (cm^2)						**0.046**
≤4	4	126	3.16	−0.09 to 6.40	46.0	
>4	2	72	0.95	−4.37 to 6.28	43.2	
Age (years old)						0.053
≤25	2	30	4.61	−6.09 to 6.31	46.0	
>25	4	168	1.41	0.41–2.41	43.2	

Note: Bold values indicate statistical significance.

Abbreviations: ACI, autologous chondrocyte implantation; EQ-VAS, EuroQol Visual Analogue scale; IKDC, International Knee Documentation Committee; SMD, standard mean difference.

younger patients, especially those with open physes, have a growth potential that leads to better healing capacity.

Previous studies have reported that knees that have undergone prior surgery are more likely to experience complications after surgery for OCD. This review was unable to assess this since results in the included studies were not separated based on whether or not patients had prior surgery. Minas et al. reported that survivorship of ACI was significantly lowered in patients who had previously received marrow stimulation treatment ($p = 0.004$). Yet several other retrospective studies were unable to find such correlation [21, 22, 48]. Perhaps this is due to different surgical techniques, whereby compared to ACI, OATS is less susceptible to disturbances of the subchondral bone due to previous marrow stimulation [48]. Gender has also been reported to affect clinical outcomes after OCD surgery. Consistent with the literature, the majority of patients in this review were male [46]. Ross et al. performed a systematic review evaluating the impact of gender on outcomes after surgical treatment of knee OCD. No significant differences were noted in terms of clinical and functional outcomes, despite the sex-related difference in the prevalence of OCD lesions. This review found that males had a greater improvement in IKDC subjective scores compared to females ($p = 0.029$). This is in agreement with Kreuz et al. who also found significantly greater IKDC scores in males compared to females ($p < 0.05$) [29]. Perhaps gender-related differences in anatomy, such as patellar tracking and lower isokinetic muscle strength, lead to differences in clinical outcomes [46]. Additional variables such as BMI index >25 [45] and African–American race [42] have been identified as risk factors influencing clinical outcomes. Unfortunately, analyses could not be performed due to the heterogeneity in clinical outcomes reported. Multicentre randomised controlled trials are needed to provide level I evidence regarding the influence of various co-variates such as lesion size, age, BMI, previous knee surgery, lesion location and gender on the outcomes of OCD surgery.

Limitations

The inclusion of level IV evidence case series leads to limited external validity and selection bias. The longest follow-up period was 19 years [7], but most studies had a follow-up time of 5 years or less, precluding the analysis of long-term complications such as the development of degenerative joint disease. Sample size was limited, increasing the chance of a type II error and reducing the power to detect predictors of success and failure. Variables such as duration of symptoms, prior treatments, concomitant procedures and postoperative rehabilitation protocols varied between studies, likely influencing outcomes.

There was low to moderate between-study heterogeneity in most of the pooled effect sizes, and Cochran's *Q* test did not reach statistical significance for any of the pooled effect sizes. Subgroup analyses showed that lesion size accounted for some of the heterogeneity, with the remaining heterogeneity likely being down to differing surgical techniques and postoperative rehabilitation protocols, and different lesion classification systems. Some studies did not report preoperative

TABLE 7 Radiographic findings and complications.

References	Radiographic healing (%)	MOCART (final follow-up)	Complications	Complication rate (%)	Treatment	Notes
Aydın et al. 2020	N/A	N/A	Arthrofibrosis: 1 (5.3) Patellofemoral pain: 1 (5.3)	10.5	Arthroscopic release Debridement Aggressive physical therapy and rehabilitation	Progressive limitation in ROM occurred in three patients. Full ROM was achieved in one of these patients after long-term rehabilitation. In another patient, an arthrotomy and release procedure was performed one year later, although a flexion loss of 40° persisted.
Baldassarri et al. [3]	Complete filling of lesion: 13 (72.2) Chondral integration: 14 (77.8) Osteointegration: 8 (44.4)	N/A	None	0	N/A	N/A
Carey et al. [7]	N/A	N/A	Hypertrophic tissue, loose bodies, arthrofibrosis.	N/A	Revision ACI: 8 (13.1) Osteotomy: 2 (3.3) TKA: 2 (3.3)	Subsequent osteotomy for the two knees happened 20 and 24 years after index ACI surgery. Subsequent TKA for the two knees happened 12 and 18 years after index ACI surgery.
Cole et al. [11]	N/A	N/A	Cartilage injury 5 (12.5) Graft overgrowth 5 (12.5) Graft complication 4 (10.0) Graft delamination 3 (7.5) Chondromalacia 3 (7.5) Others 15 (37)	37	Debridement of cartilage lesion 10 (25) Loose body removal 3 (7.5) Microfracture 2 (5.0) Others 7 (18)	19% resulted in treatment failure. Not all patients who had a complication met the definition of treatment failure.
Cotter et al. [12]	N/A	N/A	Infection: 1 (2.5) Skin dehiscence: 1 (2.5) Acute haematoma: 1 (2.5) Graft failure: 2 (5.1%) Peroneal nerve injury: 1 (2.5)	15.1	Evacuation and washout Revision OCA Unicompartmental knee arthroplasty	All who did not RTS identified continued discomfort and/or lack of confidence in their knee. In the two patients with graft failure, this occurred at an average of 6.2 years after the index procedure.
Filardo et al. [17]	>50% filling of lesion: 15 (88)	N/A	Cartilage delamination: 4 (12)	12	OATS Second cartilaginous implant	N/A
Filardo et al. [18]	Complete filling of lesion: 76% Chondral integration: 71%	67.0 ± 25.7	N/A	N/A	N/A	N/A

TABLE 7 (Continued)

References	Radiographic healing (%)	MOCART (final follow-up)	Complications	Complication rate (%)	Treatment	Notes
Fonseca and Balacó [19]	N/A	N/A	Reflex sympathetic dystrophy: 1 (8.3)	8.3	N/A	At final follow-up, according to ICRS classification, seven patients were in class I, four in class II and one in class IV. The only case in class IV had had a stage IV lesion preoperatively.
Keyhani et al. [25]	N/A	N/A	0 (however, one had continued pain)	0	N/A	At the final visit, all patients (except one) were asymptomatic and returned to their previous activity levels. Serial MRI showed bone healing and continuous chondral healing was attained within 6 and 9 months, respectively.
Kon et al. [28]	N/A	N/A	N/A	N/A	N/A	N/A
Krishnan et al. [30]	N/A	N/A	Knee stiffness: 1 (11)	11	Manipulation under anaesthesia	N/A
Ochs et al. [38]	Complete filling of lesion: 8 (34.8) Chondral integration: 15 (65.2)	62.4 ± 18.9	0	0	N/A	In one case (3.8%), a partial delamination that had occurred postoperatively before 6 months
Paatela et al. [39]	N/A	N/A	Insufficient repair tissue fill: 3 (8.6) Repair tissue detached: 7 (20) Subchondral cysts: 1 (2.9)	31.4	Microfracture, repeat ACI	All with insufficient repair tissue were treated with microfracture.
Perdisa et al. [43]	Complete filling of lesion: 9 (50.0) Chondral integration: 15 (83.3)	81.4 ± 11.8	N/A	N/A	N/A	N/A
Steinhagen et al. [50]	N/A	N/A	Loose body: 1 (5)	5	Arthroscopic removal	Two patients required prolonged rehabilitation due to swelling and a limited ROM.
Stone et al. [53]	Complete filling of lesion: 5 (71.4) Chondral integration: 5 (71.4)	67.9 ± 15.2	N/A	N/A	N/A	Five patients needed additional surgery. Two patients experienced traumatic events and were regrafted.

Abbreviations: ACI, autologous chondrocyte implantation; ICRS, International Cartilage Repair Society; MOCART, magnetic resonance observation of cartilage repair tissue; MRI, magnetic resonance imaging; OCA, osteochondral allograft; ROM, range of motion; RTS, return to sport; TKA, total knee arthroplasty.

TABLE 8 Subgroup meta-analyses exploring complication rates.

	Number of studies	Number of knees	Proportion	95% Confidence interval	I^2 (%)	*p* Value
Intervention						0.610
Non-ACI	4	85	0.05	0.003–0.516	0	
ACI	7	198	0.12	0.040–0.318	36.8	
Age (years old)						**0.003**
≤25	7	143	0.05	0.015–0.157	0	
>25	4	140	0.25	0.107–0.476	38.2	
Lesion size (cm^2)						**0.008**
≤4	6	127	0.04	0.006–0.189	0	
>4	5	156	0.23	0.108–0.415	35.5	

Note: Bold values indicate statistical significance.

Abbreviations: ACI, autologous chondrocyte implantation; IKDC, International Knee Documentation Committee.

PROMs [7]. The PROMs that were reported were heterogeneous, and there is a lack of a core outcome set.

CONCLUSION

Reconstructive techniques used to treat OCD of the knee resulted in significant short and medium-term improvements in clinical and functional outcomes, with a low overall complication rate of 8.9%. Smaller lesion size and younger age lead to a greater improvement in IKDC subjective score, Tegner score and EQ-VAS scores and a lower complication rate. Males showed a greater improvement in IKDC subjective scores than females. There were no significant differences between cohorts treated with ACI and those treated with non-ACI reconstructive techniques. Reconstructive surgery is a valuable treatment option for OCD of the knee, and surgical intervention should not be delayed, especially in AOCD lesions which are more likely to follow a progressive and unremitting clinical course.

AUTHOR CONTRIBUTIONS

Victor Lu performed full-text screening, data collection and data analysis and wrote the manuscript. Tak Man Wong conceptualised the study and edited previous versions of the manuscript. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article [and/or] in its Supporting Information.

ETHICS STATEMENT

This is a systematic review. The research ethics committee confirmed that no ethical approval is required. All authors have reviewed the final version and have consented to publication.

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