Single Stage Autologous Cartilage Repair Results in Positive Patient Reported Outcomes For Chondral Lesions of the Knee: A Systematic Review

ABSTRACT

Aim: To perform a systematic review of the clinical literature regarding the efficacy of single stage autologous cartilage repair.

Methods: A systematic review of the literature was performed using PubMed, Scopus, Web of Science, and the Cochrane Library. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.

Results: Twelve studies were identified; however, due to overlapping patient cohorts, nine studies were included for data extraction and analysis. Six studies applied minced cartilage, while three studies utilized enzymatically processed cartilage. Two authorship groups described single stage techniques that exclusively utilized cartilage from the debrided lesion rim, while the remaining groups either utilized healthy cartilage or combined healthy cartilage with cartilage debrided from lesion rim. Among the included techniques, scaffold augments were used in four studies, and three studies implemented bone autograft augmentation. When summarizing patient reported outcome measures for the included studies, single stage autologous cartilage repair demonstrated an average improvement ranging from 18.7 ± 5.3 to 30.0 ± 8.0 amongst the KOOS subsections, 24.3 ± 10.5 for the IKDC subjective score, and 41.0 ± 10.0 for VAS-pain.

Conclusion: Single stage autologous cartilage repair is a promising technique with positive clinical data to date. The current study highlights the overall improvement in patient reported outcomes after repair for chondral defects to the knee with average follow-up ranging from 12 to 201 months and also the heterogeneity and variability of the single stage surgical technique. Further discussion on the standardization of practices for a cost-effective single stage augmented autologous cartilage technique is needed. In the future, a well-designed randomized controlled trial is needed to explore the efficacy of this therapeutic modality relative to established intervention.

Level of Evidence: Systematic review; Level IV

Key words: Single stage autologous cartilage repair, chondral lesions, knee, minced cartilage

What is already known

- Third generation, two stage autologous chondrocyte implantation has shown good clinical outcomes in the treatment of chondral lesions of the knee. However, drawbacks do exist including the cost and potential risks of two procedures.

What are the new findings

- Among the studies reviewed there is significant heterogeneity between the techniques used for single stage autologous cartilage repair for chondral lesions of the knee.
- Single stage augmented autologous cartilage repair is a viable and promising therapeutic intervention for the management of medium sized chondral defects of the knee.

INTRODUCTION

Large chondral defects of the knee can cause debilitating symptoms and eventual joint degradation if left untreated (1). Various cartilage restoration procedures have been proposed with the goal of providing pain relief and improved function. Among these, third generation matrix-induced autologous chondrocyte implantation (ACI) is a popular cell-based treatment modality that has shown positive mid-to-long-term clinical outcomes in the management of chondral defects of the knee (2). It is a two stage procedure that is based on harvesting a patient's cartilage during the first stage and then seeding a three-dimensional matrix scaffold with cultured autologous chondrocytes for subsequent reimplantation (2). Despite promising clinical outcomes, two stage ACI has several major drawbacks. High costs, technical/logistical complexity of the two stage procedure, federal regulatory restrictions, and two postoperative recoveries represent significant limitations to the widespread effectiveness, feasibility, and implementation of this technique (3, 4, 5).

Due to these limitations, recent investigations have focused on the application of single stage cartilage restoration techniques, including enzymatic preparation and mincing. Broadly, enzymatic preparation involves the rapid isolation of chondrocytes, with or without their pericellular matrix (chondrons), from cartilage samples whereas mincing refers to the mechanical degradation of cartilage (6, 7). To date, clinical research has demonstrated sustainable improvement in patient-reported outcome scores with minimal adverse events in patients undergoing single stage procedures at 24 and 60-month follow-up (6, 7). Furthermore, the single stage approach foregoes the expensive chondrocyte culturing phase and need for a second reimplantation surgery, resulting in greater cost-effectiveness (8). Overall, recent clinical evidence

suggests that single stage cartilage restoration procedures may be safe, clinically effective, and economical alternatives to conventional two stage procedures. Therefore, the purpose of the present study was to review the literature reporting clinical outcomes of single stage augmented autologous cartilage repair.

METHODS

Article Identification and Selection

This study was conducted in accordance with the 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (9). In May of 2021, a literature search for studies related to single stage augmented autologous cartilage repair was performed using PubMed, Scopus, Web of Science, and the Cochrane Library. The following search terms were used: "single stage autologous chondrocyte" OR "single treatment autologous chondrocyte" OR "one stage autologous chondrocyte" OR "one treatment autologous chondrocyte" OR "autologous minced cartilage" OR "paste grafting cartilage." The inclusion criteria were as follows: autologous cartilage that is mechanically or enzymatically processed, one stage procedure, treated chondral lesions of the knee, English language, primary clinical study with patient reported outcomes, published in 2011 or later to examine current techniques, and a level of evidence IV or better. Exclusion criteria were as follows: any two-stage procedure, allogenic cartilage, any cadaveric/animal/in vitro study, any editorial article, any survey, any letter to the editor, any special topics, and any expert reviews.

Two independent authors (S.P.D. and L.M.F.) reviewed abstracts and performed a subsequent full-text review for all identified articles. Due to the high likelihood of overlapping

patient cohorts in multiple publications, any study by the same authorship group that had the potential to represent the same patients in two or more separate studies was flagged. For these flagged studies, only the most recent study with the longest mean final follow-up was included for data extraction.

Data Extraction and Analysis

Data was extracted in a standardized fashion into a customized spreadsheet. Data that was extracted included first author, year, study design, total number of patients, number of male patients, number of female patients, average age in years at time of surgery, average lesion size (cm^2), average final follow-up in months, patient reported outcome measures (PROMs), presence of radiological outcomes/observations, presence of second look arthroscopy observations/biopsies, membrane used, Knee Injury and Osteoarthritis Outcome Scores (KOOS) outcome scores, International Knee Documentation Committee (IKDC) subjective outcome scores, and Visual Analogue Scale-Pain scores (VAS-pain). Additional data regarding the surgical technique was also extracted. This included the processing system used, cartilage source, concomitant procedures, augmentation, and surgical technique description. Additionally, for manuscripts where data was not reported explicitly in the tables/text, outcomes were extracted from the figures provided by the original authors.

Studies were designated a level of evidence using the classification system described by Wright et al. (10). Bias analysis was performed by two authors (E.M.P., and B.K.) on studies

included for data extraction. The MINORS score was utilized for non-randomized studies (11). The Cochrane-risk-of-bias tool was utilized for randomized studies (12).

RESULTS

Study Selection

A total of 1311 records were identified (**Figure 1**). After the removal of duplicates, 884 records were screened by abstract and title, and 848 records were excluded. Full text eligibility was assessed for 36 studies, and 12 studies were included **(Table 1)**. Of the 12 studies, three studies had an overlapping patient cohort in a subsequent publication by the same authorship group. Thus, only nine studies were included for final data extraction.

Bias analysis was performed using the MINORS criteria for eight studies utilizing single stage augmented autologous cartilage repair techniques (range: 8-18). The Cochrane-risk-of-bias tool was utilized for one randomized controlled trial utilizing a single stage augmented autologous cartilage repair technique. This latter study had an overall low risk of bias (13). The results of the bias analysis are presented in **Tables 2 and 3.**

Study Characteristics and Demographics

Table 1 outlines detailed study characteristics for the included single stage augmented autologous cartilage repair studies. Among the nine studies that were selected for data extraction, a total of 240 patients were involved. The patients had a median age of 32 years (range: 24.2-45.3 years), a median final follow-up of 28.2 months (range: 12-201 months), and a median lesion size of 2.7 cm^2 (range: 2.1-3.2 cm^2).

[Insert Figure 1]

[Insert Table 1]

[Insert Table 2]

[Insert Table 3]

Single Stage Augmented Autologous Cartilage Repair Surgical Techniques

The single stage augmented autologous cartilage repair surgical techniques included in this study are outlined in **Table 4**. These techniques were broadly categorized by the mechanism of cartilage processing. Three authorship groups reported on the use of enzymatic degradation, while six authorship groups reported on the use mechanical processing techniques.

Saris et al. utilized an enzymatic single stage chondron implantation technique termed IMPACT (Instant MSC Product Accompanying Autologous Chondron Transplantation) (14, 15, 16). This system involves recycling debrided articular cartilage from the lesion rim through a rapid enzymatic isolation protocol to isolate chondrons, which are then combined in a 10:90 or 20:80 ratio with allogenic bone marrow derived mesenchymal stem cells (MSCs) using fibrin glue prior to application within the defect. Slynarski et al. utilized a similar technique termed CartiONE (17). This technique involves combining healthy biopsied cartilage with cartilage from the debrided lesion rim. These two sources are then mixed with bone marrow aspirate concentrate that is

harvested from the iliac crest. This mixture is enzymatically processed intraoperatively to isolate chondrocytes and bone marrow mononucleated cells (MNCs) prior to seeding onto a load-bearing PolyActive; PolyVation BV cylindrical scaffold. The final orthobiologics construct is then secured to the articular defect using fibrin glue. The third enzymatic technique was performed by Tseng et al. (18, 19), in which both healthy and debrided cartilage are harvested and minced using a tissue pulverizer. The sample is then processed for 20 minutes with collagenase (Librase, Roche, Germany) and added to a specialized biphasic cylindrical scaffold, which is composed of a deeper polylactic-co-glycolic acid tricalcium phosphate component that was designed to sit in the subchondral bone and a superficial polylactic-co-glycolic acid component that was designed to integrate with the surrounding articular cartilage. This biphasic orthobiologics construct is then press fit into the chondral defect.

Of the remaining studies, there were five different mechanical processing techniques utilized for single stage augmented autologous tissue-based cartilage repair. A 2011 study by Cole et al. utilized the Cartilage Autograft Implantation System (CAIS, DePuy Mitek, Raynham, MA) (13). This technique consists of harvesting healthy hyaline cartilage from a low weight-bearing surface and morselizing the sample. The processed cartilage is then distributed onto a biodegradable scaffold consisting of 35% polycaprolactone and 65% polyglycolic acid with polydiaxone mesh reinforcement. The construct is then placed into the chondral defect and secured using biodegradable staple anchors. Two groups described a “paste grafting” technique where healthy cartilage from the intercondylar notch is harvested and combined with cancellous bone autograft from the proximal tibia (20, 21, 22, 23, 24, 25). Together, the bone and cartilage is morselized into a paste using a graft impactor (DePuy, Warsaw, IN) and applied to the defect (24).

In 2015, Christensen et al. described a similar mincing technique augmented with bone autograft (26). Cancellous autologous bone is harvested from the proximal tibia, broken down into fragments, and press-fit into the subchondral bony defect. Healthy cartilage is then harvested from the femoral trochlea, manually chipped into fragments, and distributed over the autologous bone graft to fill the cartilage defect. In 2019, Massen et al. described a separate technique where minced cartilage is combined with a Chondro-Gide scaffold (Geistlich Pharma, Princeton, NJ) and secured into the defect with fibrin glue (27). The final technique was described by Cugat et al. in 2020 (28). The authors utilized the CN-Biomatrix technique, where healthy hyaline cartilage is harvested from the edges of the chondral defect, while whole blood is spun in a centrifuge to extract plasma rich in growth factors (PRGF). After mechanical degradation, the particulated articular cartilage is combined with PRGF to form a semisolid matrix that is then evenly distributed over the chondral defect.

When summarizing these single stage techniques based on the harvesting site, two authorship groups described single stage techniques that exclusively utilized cartilage from the debrided lesion rim (14, 15, 16, 28). Massen et al. utilized healthy cartilage from the intercondylar notch or cartilage from the debrided lesion rim (27). Stone et al. and Di Martino et al. described techniques that harvested healthy autologous cartilage from the intercondylar notch, while Cole et al. utilized healthy cartilage from the intercondylar notch or trochlear ridge (21, 22). Christensen et al. harvested healthy cartilage from non-weight bearing portions of the femoral trochlea (26). Slynarski et al., Tseng et al., and Chiang et al. described two separate techniques that combined healthy cartilage from low-load bearing regions of the femoral condyle with cartilage debrided from the lesion rim (17, 18, 19).

In terms of augmentation, scaffolds were used in four studies. Cole et al. reported the use of a 35% polycaprolactone and 65% polyglycolic acid with polydioxanone mesh reinforcement (13). Massen et al. utilized a Chondro-Gide scaffold (Geistlich Pharma, Princeton, NJ), while Tseng et al. utilized a unique biphasic cylindrical scaffold composed of a superficial polylactic-co-glycolic acid (PCGA) and a deeper PCGA-tricalcium phosphate component.(18, 19, 27) Slynarski et al. utilized a PolyActive; PolyVation BV scaffold composed of polyethylene glycol terephthalate and polybutylene terephthalate (17). Slynarski et al. also supplemented their orthobiologics construct with bone marrow mononucleated cells (MNCs) derived from bone marrow aspirate concentrate (BMAC). Cugat et al. was the only group to utilize a blood derived augment and combined mechanically degraded cartilage with plasma rich in growth factor to form the semisolid CN-Biomatrix scaffold (28). Saris et al. utilized allogenic donor bone marrow derived mesenchymal stem cells (MSCs) (14). Bone autograft augmentation was utilized in 3 studies (21, 22, 26).

[Insert Table 4]

Patient Reported Clinical Outcomes

Three major patient reported outcomes were collected in this study. These were the KOOS, the IKDC and the VAS-pain scores. Among the studies included for data extraction, five studies reported on KOOS scores for single stage augmented cartilage repair. This included 112 patients with a median final follow-up of 24 months (range: 12-61 months). There was an improvement from baseline of 18.7 ± 5.3 for the KOOS-Symptoms subsection, 20.0 ± 6.6 for the KOOS-Pain subsection, 19.9 ± 6.1 for the KOOS-Activities of Daily Living (ADL) subsection, 29.4 ± 9.5 for

the KOOS-Sports subsection, and 30.0 ± 8.0 for the KOOS-Quality of Life (QOL) subsection (**Table 5**). Six studies exploring the single stage augmented cartilage repair technique utilized the IKDC subjective survey (**Table 6**). This included 169 patients with a median final follow-up of 24 months (range: 12-201 months). The weighted mean for improvement in IKDC scores from baseline was 24.3 ± 10.5. Four single stage augmented cartilage repair studies reported VAS-pain outcomes (**Table 7**). There was a total of 117 patients with a median final follow-up of 26.1 months (range: 15.9-61 months). The weighted mean improvement in the VAS-pain outcome measure was 41.0 ± 10.0.

[Insert Table 5]

[Insert Table 6]

[Insert Table 7]

DISCUSSION

The main findings of this systematic review were the following: 1) significant heterogeneity exists across the single stage augmented autologous cartilage repair studies in terms of harvesting site, processing methods, augmentation, and surgical techniques; and 2) single stage augmented autologous cartilage repair procedures demonstrate an average improvement ranging from 18.7 ± 5.3 to 30.0 ± 8.0 amongst the KOOS subsections, 24.3 ± 10.5 for the IKDC subjective score, and 41.0 ± 10.0 for VAS-pain.

Third generation two stage ACI is a proven and effective treatment modality for the management of large symptomatic chondral defects of the knee. While effective, there are several significant drawbacks to the widespread implementation of two stage ACI, including the cost, logistics and post-operative rehabilitation related to two surgical procedures (3-5). Consequently, a variety of single stage augmented autologous cartilage repair techniques have gained popularity over the past 10 years. In this systematic review, the authors identified a total of twelve studies that investigated outcomes from single stage treatment options using autologous cartilage for the treatment of chondral lesions in the knee; nine of these studies utilized unique patient cohorts and were included for data extraction.

The benefits of restorative treatment options such as MACI and single stage augmented autologous cartilage repair lay in their use of cell-based therapy and the chondrocyte's capacity to produce tissue that is similar to native hyaline cartilage (29). These cartilage repair techniques utilize the ability of chondrocytes to synthesize type II collagen, proteoglycan, and chondroitin

sulfate in order to approximate physiologic cartilage (30). Moreover, there is substantial evidence that suggests positive clinical and histological outcomes for patients treated with two stage ACI or single stage augmented autologous cell-based cartilage repair with studies reporting positive clinical outcomes with up to five-year follow-up (14, 17, 18, 24, 31). Additionally, unlike autografts, cell-based therapy has minimal donor site morbidity, particularly for the management of medium to large chondral defects (32).

Among the single stage techniques included, there were two broadly different cartilage repair techniques: 1) enzymatically processed cartilage and 2) mechanically minced cartilage **(Table 4)**. Of the 12 single stage studies included, three reported the use of enzymatic preparation protocols (14, 17, 18). All three of these studies reported positive clinical post-operative outcomes, and despite the contrast in specifics of each technique, all three studies measured KOOS scores and reported improvements in each subsection. Six of the nine authorship groups using single stage procedures utilized mechanical degradation of autologous cartilage prior to implantation (13, 21, 22, 26, 27, 28). Mechanically processed cartilage has several inherent benefits over enzymatic preparation techniques. While many of these benefits are technical, cost-based, or practical, there is also sufficient pre-clinical data to support the efficacy of mechanical preparation techniques. In-vivo and in-vitro studies have suggested that mincing of cartilage allows for potent chondrocyte activation via fragmentation (33). Thus, mechanical processing of a cartilage autograft leads to outgrowth, proliferation, and differentiation of biologically activated primary chondrocytes (33). This potent outgrowth allows for minced cartilage to fill a defect 10 times larger than the biopsy itself (34). Additionally, optimized tissue engineering constructs can be designed by seeding these chondrocytes embedded in their intact native surrounding matrixes inside scaffolds with or without

other orthobiologic augments (34). Moreover, in-vitro studies have even suggested that minced cartilage has a more favorable potential for cell proliferation and matrix production relative to chondrocytes that were isolated by enzymatic treatment (35). While limited, the initial clinical reports of single stage mechanically processed autologous cartilage repair techniques have shown good translational efficacy.

To date, the highest quality single stage study was performed by Cole et al. in 2011 (13). The authors randomized 29 patients into receiving either microfracture or CAIS. At two-year follow-up, the authors reported an improvement in IKDC scores for the CAIS group that was statistically superior relative to the improvement reported by the microfracture group. Additionally, there was no difference in the number of adverse events reported in each group, suggesting that the CAIS technique is a safe and effective method for treating chondral defects of the knee.

Although current literature lacks other high quality comparative studies between single stage autologous cartilage repair and alternative techniques, it is possible to qualitatively take the clinical outcomes in the present review in the context of prior cartilage studies. The improvement from baseline observed in all KOOS subscales and IKDC following single stage autologous repair exceed previously reported minimal clinically important differences (MCID) thresholds for ACI, as published in a study by Ogura et al. (37). Future studies aimed at establishing clinically significant outcomes specific to single stage autologous techniques are warranted.

LIMITATIONS

Despite the overall promising results from our systematic review, there exist several important limitations. First, there exists significant heterogeneity between the various single-stage cartilage repair techniques beyond just enzymatic preparation and mincing. These include the presence or absence of additional biologic adjuvants and scaffolds, the manufacturer of the system used, the use of fibrin glue, the source and amount of cartilage used, duration of follow-up, functional outcome scores reported, study design, as well as numerous other factors. As such, the currently available literature precludes accurately pooling functional outcomes data with subsequent statistical-based comparisons. Secondly, the majority of the nine studies analyzing single stage techniques reported observational data in the form of case series (Level IV evidence). Only one single stage study was a randomized control trial that directly compared outcomes to a microfracture control (13). Finally, due to the relative lack of randomized and comparative data relative to more established cartilage repair techniques, it was not possible to pursue a meta-analysis that directly compare single-stage procedures to two stage ACI. While these limitations exist, the results from this study are overall promising and suggest that single stage augmented autologous cartilage repair techniques are viable therapeutic interventions with potential logistical and cost benefits for the management of chondral lesions of the knee.

CONCLUSION

Single stage autologous cartilage repair is a promising technique with positive clinical data to date. The current study highlights the overall improvement in patient reported outcomes after repair for chondral defects to the knee with average follow-up ranging from 12 to 201 months and also highlights the heterogeneity and variability in single stage surgical technique. Further discussion on the standardization of practices for a cost-effective single stage augmented autologous cartilage technique is needed. In the future, a well-designed randomized controlled trial is needed to explore the efficacy of this therapeutic modality relative to established interventions.

337 **FIGURE LEGENDS**

338 **FIGURE 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses**

339 **(PRISMA) Flow Diagram for Single Stage Studies**

340 **Figure 1**: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for

341 Single Stage Augmented Autologous Cartilage Repair

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343 **TABLES**
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TABLE 1: Study Characteristics For Single Stage Augmented Autologous Cartilage Repair for Chondral Lesions of the Knee

Author Year	Study Type	Level of Evidence	Number of Patients	Average Age (years)	Lesion Size (cm^2)	Average Final Follow-Up (months)	PROMs	Included in Data Extraction*
Saris(14) 2021	Prospective Case Series	4	35 (24M, 11F)	36	3.2	61	EuroQol-5D, KOOS, VAS	Yes
Di Martino(36) 2021	Retrospective Cohort with Prospectively Collected Clinical Outcomes	3	12 (9M, 3F)	24.2	2.6	84	IKDC, Tegner	Yes
Cugat(28) 2020	Prospective Case Series	4	15 (14M, 1F)	26.8	2.4	15.9	IKDC, Lequenese index, Lysholm, SF-12, Tegner, VAS, WOMAC,	Yes
Slynarski(17) 2020	Prospective Case Series	4	40 (28M, 12F)	35.2	2.09	24	IKDC, KOOS, VAS	Yes
Tseng(18) 2020	Prospective Case Series	4	9 (6M, 4F) [10 patients included in study, 9 completed follow-up]	27.6	Not Provided	60	KOOS, VAS	Yes
Massen(27) 2019	Retrospectively Registered Case Series with Prospective Follow-up	4	27 (15M, 12F)	28.7	3.1	28.2	NAS	Yes
De Windt*(15) 2017	Prospective Case Series	4	35 (24M, 11F)	36	3.2	18	EuroQol-5D, KOOS, VAS	No
Stone(22) 2017	Retrospective Case Series	4	74 (46M, 28F)	45.3	2.16	201	IKDC, NAS,	Yes

							Tegner, WOMAC	
De Windt*(16) 2016	Prospective Case Series	4	10 (8M, 2F)	26	3.6	12	EuroQol-5D, KOOS, VAS	No
Christensen(26) 2015	Prospective Case Series	4	8 (5M, 3F)	32	3.1	12	IKDC, KOOS, Tegner	Yes
Chiang*(19) 2013	Prospective Case Series	4	10 (6M, 4F)	27.6	Not Provided	24	KOOS, VAS	No
Cole(13) 2011	Randomized Controlled Trial	2	20 (14M, 6F) [29 total patients, 20 underwent CAIS, 9 underwent MFX]	32.7	2.75	24	IKDC, KOOS	Yes

M = Male, F = Female, AE = Adverse Event, KOOS = Knee Injury and Osteoarthritis Outcome Score, VAS = Visual Analogue Scale, NAS = Numerical Analogue Scale, IKDC = International Knee Documentation Committee Questionnaire, ICRS = International Cartilage Restoration and Joint Preservation Society, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Score, SF-12 = Short Form-12, MRI = Magnetic Resonance Imaging, MOCART = Magnetic Resonance Observation of Cartilage Repair Tissue, OCD = Osteochondral defects

*For situation where there were multiple studies from the same authorship group that included the same population and outcome measures at different final follow-up dates, only the most recent study at final follow-up was included in data extraction and data analysis. These studies with overlapping populations were still presented in Table 1. The study by Chiang et al. was repeated by Tseng et al. with the same patients at later follow-up. The patients in the studies by De Windt et al. in 2016 and 2017 were included in the study by Saris et al. in 2021. As a result, for these cases data was only extracted from Tseng et al. and Saris et al., respectively.

TABLE 2: MINORS Bias Score for Single Stage Augmented Autologous Cartilage Repair

Author	Year	Title	Study Design	Total Score
Saris	2021	Five-Year Outcome of 1-Stage Cell-Based Cartilage Repair Using Recycled Autologous Chondrons and Allogenic Mesenchymal Stromal Cells: A First-in-Human Clinical Trial	Prospective	11
Di Martino	2021	Osteochondral autograft transplantation versus autologous bone-cartilage paste grafting for the treatment of knee osteochondritis dissecans	Retrospective	18
Cugat	2020	A novel autologous-made matrix using hyaline cartilage chips and platelet-rich growth factors for the treatment of full-thickness cartilage or osteochondral defects: Preliminary results	Prospective	11
Slynarski	2020	Single-Stage Autologous Chondrocyte-Based Treatment for the Repair of Knee Cartilage Lesions: Two-Year Follow-up of a Prospective Single-Arm Multicenter Study	Prospective	12
Tseng	2020	The five year outcome of a clinical feasibility study using a biphasic construct with minced autologous cartilage to repair osteochondral defects in the knee	Prospective	10
Massen	2019	One-Step Autologous Minced Cartilage Procedure for the Treatment of Knee Joint Chondral and Osteochondral Lesions: A Series of 27 Patients With 2-Year Follow-up	Retrospective	12
Stone	2017	Articular cartilage paste graft for severe osteochondral lesions of the knee: a 10- to 23-year follow-up study	Retrospective	8
Christensen	2015	Autologous Dual-Tissue Transplantation for Osteochondral Repair	Prospective	10

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TABLE 3: Cochrane Risk of Bias Tool For Randomized Controlled Trials

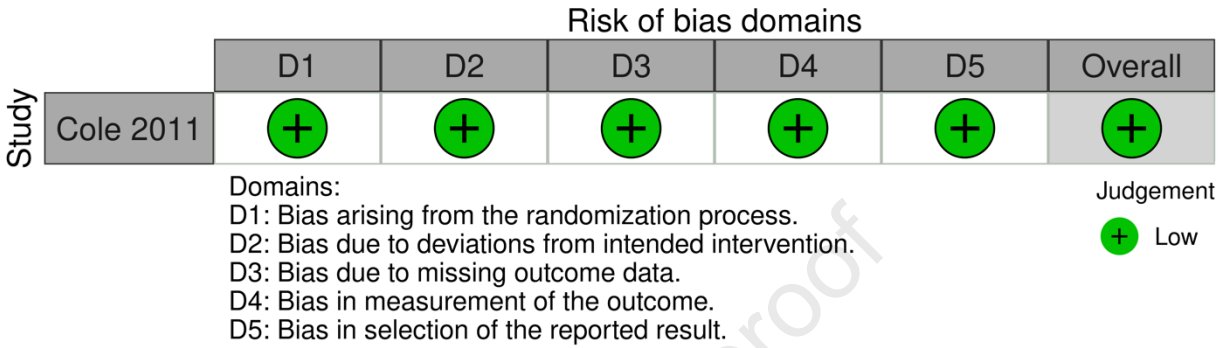

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TABLE 4: Procedure Description for Single Stage Augmented Autologous Cartilage Repair

Author Year	System	Cartilage Source	Processing Technique	Concomitant Procedures	Augmentation (BMAC, scaffold, MSCs)	Surgical Technique Description
Saris(14) 2021 De Windt(15) 2017 De Windt(16) 2016	IMPACT	Debrided lesion rim	Enzymatically	None	Allogenic donor bone marrow derived MSCs	Debrided cartilage from defect was enzymatically processed to isolated chondrons, which were combined in a ratio of 10:90-20:80 with MSCs, suspended in fibrin glue, and delivered into the defect
Di Martino(21) 2021	Paste Graft	Healthy margin of intercondylar notch	Mechanically	None	Autologous bone graft	Healthy cartilage harvested from the ipsilateral margin of the intercondylar notch + cancellous bone autograft from proximal tibia were morselized into a paste delivered into the defect
Cugat(28) 2020	CN-Biomatrix	Cartilage taken from rim of lesion	Mechanically	None	Plasma rich in growth factors (PRGF)	Healthy cartilage from the rim of the lesion was combined with PRGF prepared using the Endoret© PRGF© system protocol and was placed into defect was Biomatrix scaffold could form
Slynarski(17) 2020	CartiONE	Healthy femoral condyle and debrided lesion	Enzymatically	None	Autologous bone marrow mononucleated cells (MNCs) and Scaffold	Healthy cartilage from a low-load bearing area of the femoral condyle was combined with 14mL of BMAC taken from the ipsilateral iliac crest and chondrocytes and bone marrow mononucleated cells were seeded into a 15 or 18 mm cylindrical scaffold which was press fit into the defect and sealed with fibrin glue
Tseng(18) 2020 Chiang(19) 2013	Collagenase (Librase)	Healthy femoral condyle and debrided lesion	Enzymatically	None	Scaffold	Healthy cartilage was taken from the non-articulating margin of the affected femoral condyle and morselized via a power-driven tissue pulverizer and then further enzymatically dissociated with collagenase before being implanted into a scaffold which was press fit into the defect.
Massen(27) 2019	Minced Cartilage	Intercondylar notch or rim of debrided lesion	Mechanically	Patellar realignments (6), reconstructions of MPFL (4), tibial osteotomies (3), extractions of osteosynthetic material (2), osteosyntheses (2), cancellous bone grafts (2), femoral osteotomy (1), microfracture	Scaffold	Debrided cartilage or cartilage from the healthy low-weight bearing intercondylar notch was minced into paste and used to cover the defect with the addition of either fibrin glue (femoral condyle) or a scaffold (trochlear or patellar)

				(1), and meniscal debridement (1)		
Stone(22) 2017	Paste Graft	Intercondylar notch	Mechanically	Partial meniscectomy (20), meniscus allograft transplantation (19), chondroplasty (17), microfracture (17), autograft ACL reconstruction (8), osteotomy (7), meniscus repair (6), allograft ACL reconstruction (3)	Autologous bone graft	Cartilage autograft with underlying subchondral bone was taken from the ipsilateral intercondylar notch, was morselized into a paste and impacted into the defect
Christensen(26) 2015	Autologous Dual-Tissue Trans-plantation	Femoral Trochlea	Mechanically	None	Autologous bone graft	Proximal tibia autograft was harvested and press-fit into the bony portion of defect and hyaline cartilage taken from non-weight bearing portion of femoral trochlea was chipped into fragments and applied over the defect with fibrin glue
Cole(13) 2011	CAIS	Intercondylar notch or trochlear ridge	Mechanically	None	Absorbable copolymer foam of 35% polycaprolactone and 65% polyglycolic acid with polydiaxone mesh reinforcement	Hyaline cartilage was harvested from the intercondylar notch or trochlear ridge before being minced and dispersed over a scaffold with fibrin sealant. The scaffold was sized to the lesion and secured to the defect with two or more biodegradable staple anchors. The scaffold was secured such that the minced cartilage fragments were facing the subchondral bone.

Table 5: Knee Injury and Osteoarthritis Outcome Scores (KOOS) for Single Stage Augmented Autologous Cartilage Repair

Study Author Year	**Improvement in KOOS Scores**				
	Symptoms	Pain	ADL	Sports	QOL
Saris(14) 2021	17.1	17.2	20.5	24.5	28.1
Slynarski(17) 2020	18.9	18.6	19.9	25.3	22.4
Tseng(18) 2020	4.4	8.2	5.7	19.9	35.1
Christensen(26) 2015	26.2	20.1	10.6	33.0	35.0
Cole(13) 2011	24.5	32.8	28.9	48.9	44.4
Weighted Mean (Standard Deviation)	18.7 (± 5.4)	20.0 (± 6.6)	19.9 (± 6.1)	29.4 (± 9.5)	30.0 (± 8.0)

Table 5: Improvement in KOOS subsections for 5 studies with 112 patients treated by single stage autologous cartilage repair with a median final follow-up of 24 (12-61) months.
ADL = Activities of Daily Living; QOL = Quality of Life

*Values in black were exact integers provided by study authors. Values in red were not specific numerical integers provided by the respective author; they were extrapolated from the figures provided in the respective study. The distance from the x-axis to the point that represented the mean value for each outcome measure was recorded. This was divided by the distance from the x-axis to the value on the figure that represented a score of 100. This fraction was multiplied by 100 to get a KOOS subsection score. The distance was measured by calculating the number of pixels in a column that was orthogonal to the x axis.

384 TABLE 6: International Knee Documentation Committee Subjective Scores (IKDC) for Single Stage Augmented Autologous Cartilage Repair
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Study Author Year	Improvement in IKDC Scores
Di Martino(21) 2021	34.2
Cugat(28) 2020	36.1
Slynarski(17) 2020	23.9
Stone(22) 2017	14.4
Christensen(26) 2015	32.2
Cole(13) 2011	43.9
Weighted Mean (Standard Deviation)	24.3 (± 10.5)

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387 Table 6: Improvement in IKDC scores for 6 studies with 169 patients treated by single stage autologous cartilage repair with a median final follow-up of 24 (12-201) months.
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TABLE 7: Visual Analogue Scores for Pain (VAS) for Single Stage Augmented Autologous Cartilage Repair

Study Author	Decrease in VAS-Pain Scores
Saris(14) 2021	30.6
Cugat(28) 2020	54.0
Slynarski(17) 2020	36.6
Massen[+](27) 2019	54.0
Weighted Mean (Standard Deviation)	41.0 (± 10.0)

Table 7: Improvement in 100-point VAS/NAS pain scores over 4 studies with 117 patients treated with single stage autologous cartilage repair at a median final follow-up of 26.1 (15.9-61) months.
[+]Used NAS instead of VAS
*Values in black were exact integers provided by study authors. Values in red were not specific numerical integers provided by the respective author; they were extrapolated from the figures provided in the respective study. The distance from the x-axis to the point that represented the mean value for each outcome measure was recorded. This was divided by the distance from the x-axis to the value on the figure that represented a score of 100. This fraction was multiplied by 100 to get a VAS subsection score. The distance was measured by calculating the number of pixels in a column that was orthogonal to the x axis.

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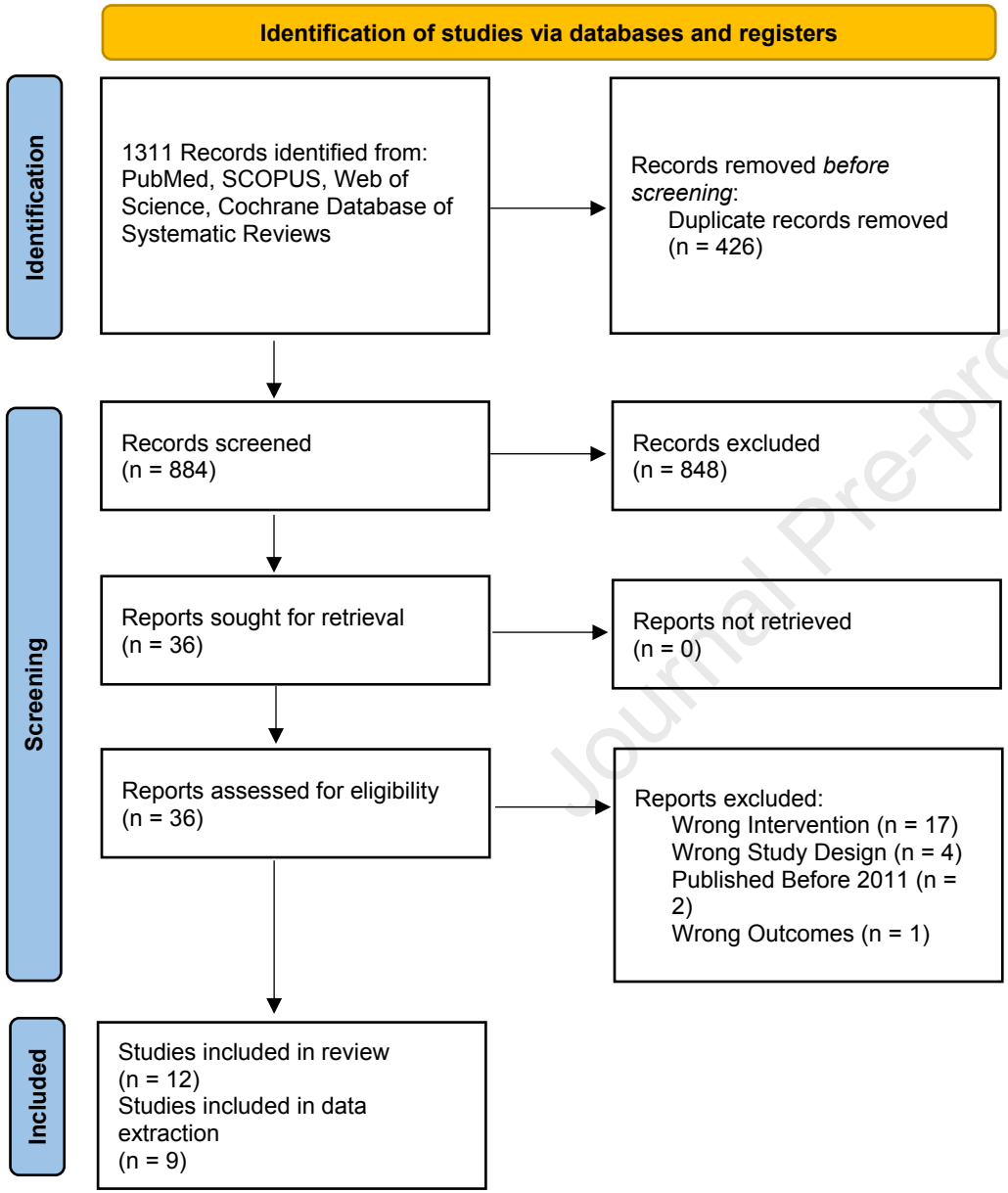

Abbreviations

VAS, visual analogue scale
KOOS, knee injury and osteoarthritis outcome score
IKDC, internal knee documentation committee
ACI, autologous chondrocyte implantation
MINORS, Methodological Index for Non-Randomized Studies
PROM, patient reported outcome measure
IMPACT, Instant MSC Product Accompanying Autologous Chondron Transplantation
RCT, randomized controlled trial
MSC, mesenchymal stem cells
MNC, mononucleated cells
CAIS, Cartilage Autograft Implantation System
PRGF, plasma rich in growth factors
ADL, activities of daily living
QOL, quality of life
CT, computed tomography
WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index
SF-12, 12-item short form