Marrow Stimulation Has Relatively Inferior Patient-Reported Outcomes in Cartilage Restoration Surgery of the Knee

CME

A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Background: Multiple cartilage repair techniques are available for chondral defects in the knee. Optimal treatment is controversial.

Purpose: To evaluate change from baseline in the 5 Knee injury and Osteoarthritis Outcome Score (KOOS) subscales among different cartilage repair techniques of the knee.

Study Design: Systematic review and meta-analysis; Level of evidence, 1A.

Methods: Medline and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched for randomized controlled trials with minimum 1 year follow-up reporting change from baseline KOOS (delta KOOS) subscale values. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed. A meta-analysis was performed on the following surgery types: microfracture (Mfx); augmented microfracture techniques (Mfx + Augment); and culture-based therapies, including autologous chondrocyte implantation (ACI) and matrix-assisted autologous chondrocyte implantation (MACI). A random-effects metaregression model was used.

Results: A total of 14 randomized trials with a total of 775 patients were included. The KOOS Sport and Recreation (Sport) and KOOS Quality of Life (QOL) were the 2 most responsive subscales after operative intervention. Outcomes from Mfx and Mfx + Augment were not different in any of the 5 KOOS subscales (minimum $P > .3$). The mean delta KOOS Sport after ACI/MACI was 9.9 points greater than after Mfx ($P = .021$) and 11.7 points greater than after Mfx + Augment ($P = .027$). Longer follow-up time correlated with greater delta KOOS Sport ($P = .028$). Larger body mass index led to greater delta KOOS QOL ($P = .045$). Larger cartilage defect size correlated with greater delta KOOS Pain and KOOS Activities of Daily Living scores ($P = .023$ and $P = .002$, respectively).

Conclusion: The KOOS Sport and QOL were the most responsive subscales after cartilage restoration surgery of the knee. Culture-based therapies (ACI/MACI) led to clinically relevant improvements in the KOOS Sport score compared with marrow stimulation and may be a more appropriate treatment in younger and more active individuals. There were no benefits to Mfx + Augment over Mfx alone in any of the KOOS subscales.

Keywords: articular cartilage resurfacing; knee articular cartilage; cartilage injury; systematic review and meta-analysis; microfracture; autologous chondrocyte implantation

Injuries of knee cartilage are relatively common. An analysis of 31,516 arthroscopy procedures found chondral lesions in 63% of knees.[7] On the modified Outerbridge scale, 60.2% of these lesions were grade 3 or 4 chondromalacia.[7] Flanigan et al[11] reported that the overall prevalence of full-thickness focal chondral defects in the knee among athletes was 36%; and 14% of these athletes were asymptomatic at the time of diagnosis. Cartilage is an aneural and poorly vascularized tissue with limited repair capacity. It is unclear why cartilage injury can cause pain, effusion, and disability in some patients while remaining asymptomatic in others. Symptomatic lesions frequently require surgical management. Goals of surgery include pain relief and return to activity.

A variety of cartilage restoration procedures are available and include marrow stimulation techniques, consisting of microfracture (Mfx) with or without additional augmentation;

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culture-based therapies, including autologous chondrocyte implantation (ACI) and matrix-assisted autologous chondrocyte implantation (MACI); autograft transplantation techniques, including mosaicplasty and osteochondral autograft transplantation (OAT); and allograft transplantation. Optimal treatment is controversial.

After surgical intervention, patients may modify their activity levels to a tolerable level of pain. Improvements in functional capacity, as measured by patient-reported outcome questionnaires (PROs), may be a more sensitive indicator of disease process recovery than changes in pain scores. There are multiple available PROs that are widely used for assessing pain and functional capacity. The Knee injury and Osteoarthritis Outcome Score (KOOS) is a validated PRO with 5 subscales evaluating the following knee-related domains: Pain, Sport and Recreation (Sport), Quality of Life (QOL), Activities of Daily Living (ADL), and Symptoms. The KOOS has several advantages: the Sport function and QOL subscales are more applicable to the often younger and more physically active patients sustaining focal chondral injuries of the knee.[19] Thus, the KOOS has greater responsiveness in this setting compared with other more generic PROs such as the Western Ontario and McMaster Universities Osteoarthritis Index and 36-Item Short Form Health Survey scores.[19]

We evaluated change from baseline KOOS (delta KOOS) in the 5 subscales across a spectrum of cartilage repair techniques via a systematic review and meta-analysis of available randomized controlled trials (RCTs). We hypothesized that some KOOS domains may be more sensitive to disease recovery after surgical intervention.

METHODS

A systematic review and meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[17] This study was registered through the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42019119874). Institutional review board approval was not obtained for this study, as all analyzed data had been previously reviewed by ethics boards.

Search Strategy

Two independent reviewers conducted the study search. The Cochrane Central Register of Controlled Trials (CENTRAL) and Medline databases were queried. Search terms were KOOS and cartilage. A multistep screening process was performed—first by title review and then by abstract review. Eligible studies were evaluated with full-text review and duplicates were removed. Discrepancies were resolved through consensus agreement with input from the senior author (D.C.C). The search was reperformed before the final statistical analysis.

We included any randomized trial evaluating cartilage repair surgery of the knee published in the English language in humans since 2003 (to evaluate relatively modern surgical techniques and outcomes), with a minimum of 1-year follow-up. The following data were extracted: number of participants, repair technique, mean delta KOOS values for each subscale, mean age, body mass index (BMI), defect size, length of follow-up, and sex distribution.

Unit of Analysis

The unit of analysis was a "study arm." Control and intervention groups within a study were treated as independent study arms for the purpose of this review. Thus, each published study contributed 2 study arms to the analysis, where the 2 study arms used different surgical techniques to be compared (eg, Mfx as "control" and ACI/MACI as "intervention").

Grouped Surgery Type Definitions

The surgery types were stratified into 6 groups: (1) Mfx; (2) Mfx + Augment (augmented microfracture procedures, including microfracture + adipose-derived mesenchymal stem cell implantation, Mfx + AMIC, and Mfx + CartiFill [Sewon Cellontech Co Ltd]); (3) ACI/MACI; (4) cartilage autograft implantation system (CAIS; DePuy/Mitek); (5) matrix-assisted autologous mesenchymal cell implantation (MAMI); and (6) OAT. Three surgery types were included in the meta-analysis: Mfx, Mfx + Augment, and ACI/MACI. The 3 additional surgery types (CAIS, MAMI, and OAT) were not amenable to meta-analysis, as each of these techniques had only 1 eligible study. Instead, delta KOOS values for these surgery types were compared qualitatively. However, the control groups (Mfx) in these studies were included in the meta-analysis.

Synthesis of Effect Measures

The treatment effect of interest was the mean change in the KOOS between baseline (presurgery) and end of follow-up (of varying duration, but at least 12 months

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postsurgery) for each of the subscales. Note that this is a mean of within-patient differences across patients assigned to a given surgery type in a given study. Studies included in the meta-analysis reported these changes either directly as mean delta KOOS or indirectly as means at baseline and end of follow-up values.

Variance of Effect Measures

Studies also differed in how they reported estimates of dispersion associated with the means, SDs, standard errors, or 95% CIs. We converted all types of dispersion measures to standard errors in accordance with the *Cochrane Handbook*[13] guidelines using within-participant longitudinal correlation values for each subscale based on a previously described cohort.[2]

Meta-analysis

Meta-analyses/regressions were run using the metafamily of commands in Stata 16.0 (StataCorp). The mean delta KOOS was regressed against surgery type using a random-effects metaregression model, employing the empirical Bayes estimator for between-study variance.[3] An exhaustive recent comparative review[24] concluded that the empirical Bayes estimator has lower bias on average than alternative estimators. I^2 values, mean change scores, and 95% CIs for each surgery type from the regression models were reported.

Covariate Analysis

The proportion of male patients and mean age, defect size, BMI, and log-transformed follow-up time were included as covariates of interest for possible associations with delta KOOS. Each covariate analysis was adjusted for surgery type.

Time Course Comparisons

For each KOOS subscale, we examined if there was a differential effect of follow-up time on delta KOOS. Due to the lack of sufficient variance in follow-up time for the small number of Mfx + Augment studies (ie, the slope for Mfx + Augment studies would be unduly influenced by a single study widely separated in follow-up time from the remaining 3 studies that all had very similar mean follow-up times), we restricted follow-up time comparisons to only Mfx and ACI/MACI.

Individual Study Bias Assessments

Risk of bias in individual studies was assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials[20] and is shown in Figure 1. All studies had at minimum some concern for bias because of the lack of patient blinding to the intervention and then having those patients be the assessors of the reported outcome.

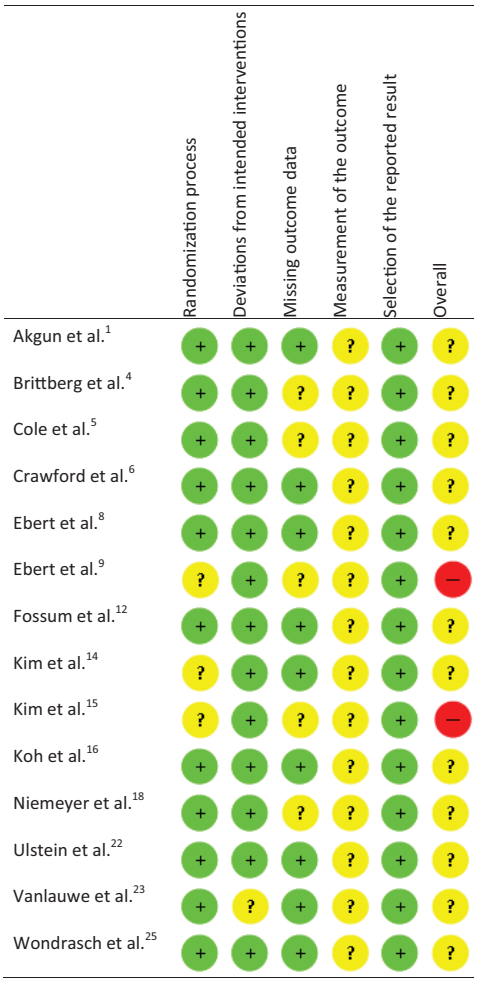

Figure 1. Risk of bias assessment for individual studies.

Nonreporting Bias Assessment

To assess the potential for nonreporting bias in the selection of included studies, we generated funnel plots (Figure 2), both overall and split out separately by surgery type. For each study, we summed delta KOOS across all 5 subscales to create a single score and plotted this against the approximated standard error. If the points on the plot became more asymmetrical as the standard error increased, that was an indication that the smaller studies may be biased toward larger or smaller effect sizes due to nonreporting of "uninteresting" results. As our primary hypothesis was that there might be differences between surgery types, it was also crucial[21] to examine the funnel plots separately by surgery type to assess whether the included studies represented an unbiased picture.

RESULTS

The initial literature search was performed on March 14, 2019, on Medline and CENTRAL databases, yielding 424

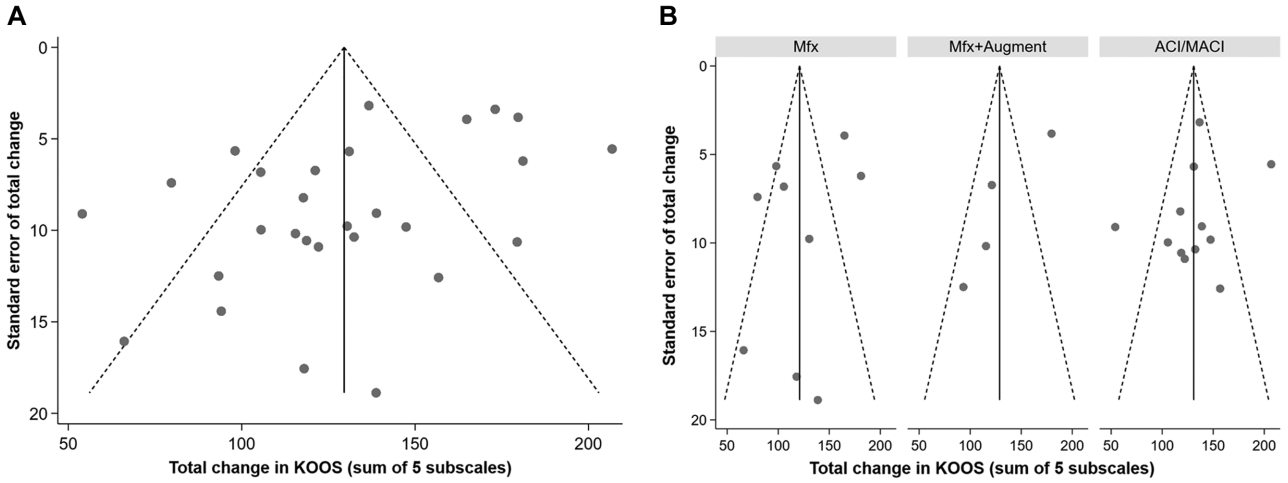

Figure 2. Funnel plots assessing nonreporting bias. (A) Comparison of total delta KOOS with SE across studies included in the meta-analysis. (B) Comparison of total delta KOOS with SE in Mfx, Mfx + Augment, and ACI/MACI groups separately. Asymmetry of points on the plot would suggest increasing nonreporting bias. KOOS, Knee injury and Osteoarthritis Outcome Score; ACI, autologous chondrocyte implantation; MACI, matrix-assisted autologous chondrocyte implantation; mfx, microfracture; Mfx + Aug, augmented microfracture techniques.

studies (Figure 3). After title and abstract review, 18 articles were retrieved for full-text review. Of these, 2 were excluded because they were duplicate patient cohorts; 2 had no KOOS subscale data; 2 had no baseline data, making calculation of delta KOOS impossible; and 1 had inadequate follow-up. Thus, 11 studies remained eligible. On December 6, 2019, the search was performed again before final analysis, which yielded 3 additional studies. In studies where numerical KOOS subscale data were not provided, attempts were made to retrieve data from corresponding authors. In total, the systematic review yielded 14 RCTs evaluating cartilage repair techniques in the knee.

There were 9 study arms evaluating Mfx, 12 study arms evaluating ACI/MACI, 1 study evaluating OAT, 1 study evaluating CAIS, and 1 study evaluating MAMI. Four studies evaluated Mfx + Augment procedures. This included 1 Mfx + adipose-derived mesenchymal stem cell implantation, 1 Mfx + AMIC, and 2 studies evaluating Mfx + CartiFill. In total, 775 patients were included. Baseline patient characteristics by surgery type are shown in Table 1. There were no statistically significant differences between ACI/MACI and Mfx + Augment compared with Mfx in patient sex distribution, age, BMI, defect size, and follow-up time (minimum $P > .05$).

Patient distribution and mean delta KOOS values are presented in Table 2. The 2 most responsive subscales with the greatest change from baseline were the KOOS Sport and KOOS QOL in the Mfx, ACI/MACI, CAIS, MAMI, and OAT study groups. In Mfx + Augment, the 2 most responsive subscales were the KOOS QOL and KOOS Pain. In ACI/MACI, CAIS, MAMI, and OAT, both delta KOOS Sport and delta KOOS QOL values were at minimum 10 points greater than the delta KOOS ADL, KOOS Pain, and KOOS Symptoms.

The meta-analysis comparing means (with standard deviations) for each subscale are listed in Figure 4 and Table 3. The 2 subscales that showed the largest delta KOOS differences between marrow stimulation and non–marrow stimulation procedures were the KOOS Sport and KOOS QOL. In the KOOS Sport, ACI/MACI procedures resulted in statistically significant benefits compared with Mfx ($P = .02$). The mean delta KOOS Sport after ACI/MACI procedures was 9.9 points greater than after Mfx and 11.7 points greater than after Mfx + Augment. The mean delta KOOS QOL after ACI/MACI was 6.6 points greater than after each of Mfx and Mfx + Augment, although this narrowly missed reaching the usual statistical significance ($P = .06$). There were no differences in delta KOOS between Mfx and Mfx + Augment in any of the 5 subscales (minimum $P > .3$).

The results of covariate analysis, adjusting for surgery type, found 4 significant relationships. There was a linear relationship between delta KOOS Sport and follow-up time ($P = .028$). The mean follow-up time ranged between 12 and 118 months. Larger mean BMI correlated with greater delta KOOS QOL ($P = .045$). The mean BMI ranged between 24.1 and 29; and larger defect size was associated with greater delta KOOS Pain and KOOS ADL ($P = .023$ and $P = .002$, respectively). Mean defect sizes ranged between 240 and 510 mm^2. These relationships are represented in Appendix Figure A1 (available in the online version of this article).

A subanalysis was performed to evaluate trends in delta KOOS with follow-up time between ACI/MACI and Mfx. The mean follow-up time was 41.4 months after Mfx (range, 1-9.8 years) and 42 months after ACI/MACI (range, 2-5 years). There were no statistically significant differences (minimum $P > .25$) when comparing mean delta KOOS trends and follow-up time in any of the KOOS subscales

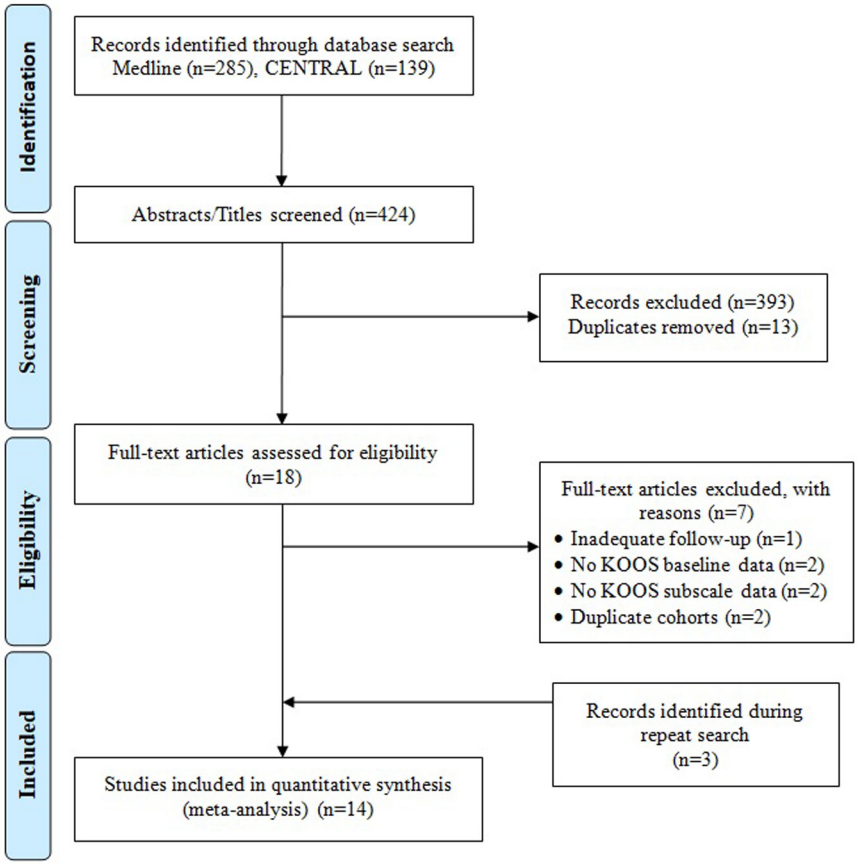

Figure 3. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. KOOS, Knee injury and Osteoarthritis Outcome Score.

TABLE 1
Baseline Patient Characteristics by Surgery Type[a]

	% Male	Age, y	BMI	Defect Size, mm^2	Follow-up Time, mo
Mfx	0.52 ± 0.22	39.47 ± 8.55	25.95 ± 1.23	338.56 ± 105.90	41.44 ± 33.11
Mfx + Aug	0.36 ± 0.23	45.25 ± 8.40	26.03 ± 1.61	439.50 ± 73.40	21.85 ± 6.76
P vs Mfx	.254	.268	.932	.083	.187
ACI/MACI	0.67 ± 0.10	35.94 ± 3.30	25.83 ± 1.28	362 ± 99.20	42 ± 18.80
P vs Mfx	.058	.226	.820	.605	.963
CAIS	0.70	32.70	27	275	24
MAMI	0.57	32.30	24.10	290	24
OAT	0.57	32.70	27.9	300	117.60

[a]Data are provided as means or mean ± SD. *P* values are listed for surgery types and included in the meta-analysis (Mfx serving as the control). ACI, autologous chondrocyte implantation; BMI, body mass index; CAIS, cartilage autograft implantation system; MACI, matrix-assisted autologous chondrocyte implantation; MAMI, matrix-assisted autologous mesenchymal cell implantation; Mfx, microfracture; Mfx + Aug, augmented microfracture techniques; OAT, osteochondral autograft transplantation.

between Mfx and ACI/MACI. In the KOOS Sport and KOOS QOL, there were fairly linear positive relationships with (log) follow-up time and delta KOOS after Mfx. There were slight trends after Mfx toward decreasing delta KOOS values with longer follow-up in KOOS ADL, KOOS Symptoms, and KOOS Pain. Again, this was not statistically significant when compared with ACI/MACI. These are graphically represented in Appendix Figure A2 (available online).

TABLE 2
Mean Delta KOOS by Surgery Type[a]

	Studies (n)	Patients (n)	ADL	QOL	Pain	Sport	Symptoms
Mfx	9	287	22.79	**27.80**	24.64	**27.97**	20.42
Mfx + Augment	4	116	25.18	**27.01**	**30.04**	26.40	23.83
ACI/MACI	12	332	20	**34.26**	22.20	**37.32**	17.47
CAIS	1	19	28.85	**44.39**	32.79	**48.91**	24.49
MAMI	1	7	25	**50**	24.61	**50**	23.47
OAT	1	14	7.50	**25**	11.80	**41.30**	8.50

[a]Bolded values denote the 2 subscales within each surgery type with the greatest magnitude of change. ACI, autologous chondrocyte implantation; ADL, Activities of Daily Living; CAIS, cartilage autograft implantation system; KOOS, Knee injury and Osteoarthritis Outcome Score; MACI, matrix-assisted autologous chondrocyte implantation; MAMI, matrix-assisted autologous mesenchymal cell implantation; Mfx, microfracture; Mfx + Augment, augmented microfracture techniques; OAT, osteochondral autograft transplantation; QOL, Quality of Life; Sport, Sport and Recreation.

TABLE 3
Mean Delta for KOOS Subscales[a]

	n	I^2	Mean ± SD	95% CI	Difference vs Mfx (*P* Value)
KOOS Sport					
Mfx	9	0.55	27.97 ± 5.34	23.27-32.67	
Mfx + Augment	4	0.64	26.40 ± 5.49	19.67-33.13	–1.84 (.74)
ACI/MACI	12	0.82	37.32 ± 10.49	30.77-43.87	9.90 (.02)
Overall	25	0.84	31.70 ± 9.83	27.50-35.9	
KOOS QOL					
Mfx	9	0.69	27.80 ± 6.17	22.96-32.64	
Mfx + Augment	4	0.84	27.01 ± 9.08	17.29-36.73	–0.04 (.99)
ACI/MACI	12	0.69	34.26 ± 6.53	29.79-38.72	6.63 (.06)
Overall	25	0.77	30.75 ± 7.40	27.44-34.06	
KOOS Symptoms					
Mfx	9	0.85	20.42 ± 7.11	15.39-25.46	
Mfx + Augment	4	0.87	23.83 ± 7.76	15.69-31.97	3.65 (.41)
ACI/MACI	12	0.81	17.47 ± 6.08	13.64-21.31	–3.03 (.36)
Overall	25	0.87	19.59 ± 6.96	16.66-22.51	
KOOS Pain					
Mfx	9	0.88	24.64 ± 8.94	18.44-30.85	
Mfx + Augment	4	0.80	30.04 ± 5.96	23.53-36.56	4.97 (.36)
ACI/MACI	12	0.91	22.20 ± 8.26	17.31-27.09	–2.46 (.53)
Overall	25	0.90	24.25 ± 8.34	20.81-27.69	
KOOS ADL					
Mfx	9	0.93	22.79 ± 10.78	15.49-30.08	
Mfx + Augment	4	0.90	25.18 ± 9.26	15.63-34.72	2.33 (.70)
ACI/MACI	12	0.93	20 ± 8.63	14.93-25.06	–2.84 (.52)
Overall	25	0.93	21.81 ± 9.34	18.02-25.61	

[a]ACI, autologous chondrocyte implantation; ADL, Activities of Daily Living; KOOS, Knee injury and Osteoarthritis Outcome Score; MACI, matrix-assisted autologous chondrocyte implantation; Mfx, microfracture; Mfx + Augment, augmented microfracture techniques; QOL, Quality of Life; Sport, Sport and Recreation.

DISCUSSION

The results of this systematic review and meta-analysis indicate that Sport and QOL are the 2 most responsive KOOS subscales, showing the greatest magnitude of change from baseline after cartilage repair of the knee. Delta KOOS Sport and KOOS QOL also revealed the largest differences in outcomes between marrow stimulation (Mfx and Mfx + Augment) and culture-based therapies (ACI/MACI).

Pain level may not be the most sensitive indicator of the disease recovery process after cartilage restoration surgery in the knee. Active, motivated patients may modify their activity to a tolerable level of pain. Ebert et al[10] compared commonly used PROs after MACI in the knee and found that KOOS Sport and KOOS QOL were the most responsive PRO measures. This is in line with our findings. Roos and Lohmander[19] had suggested the minimal clinically important difference (MCID) in the KOOS to be 8 to 10 points. In this study, the mean delta KOOS Sport score after ACI/MACI exceeded the MCID over marrow stimulation procedures. KOOS Sport is one of the most relevant domains for determining patient satisfaction in this

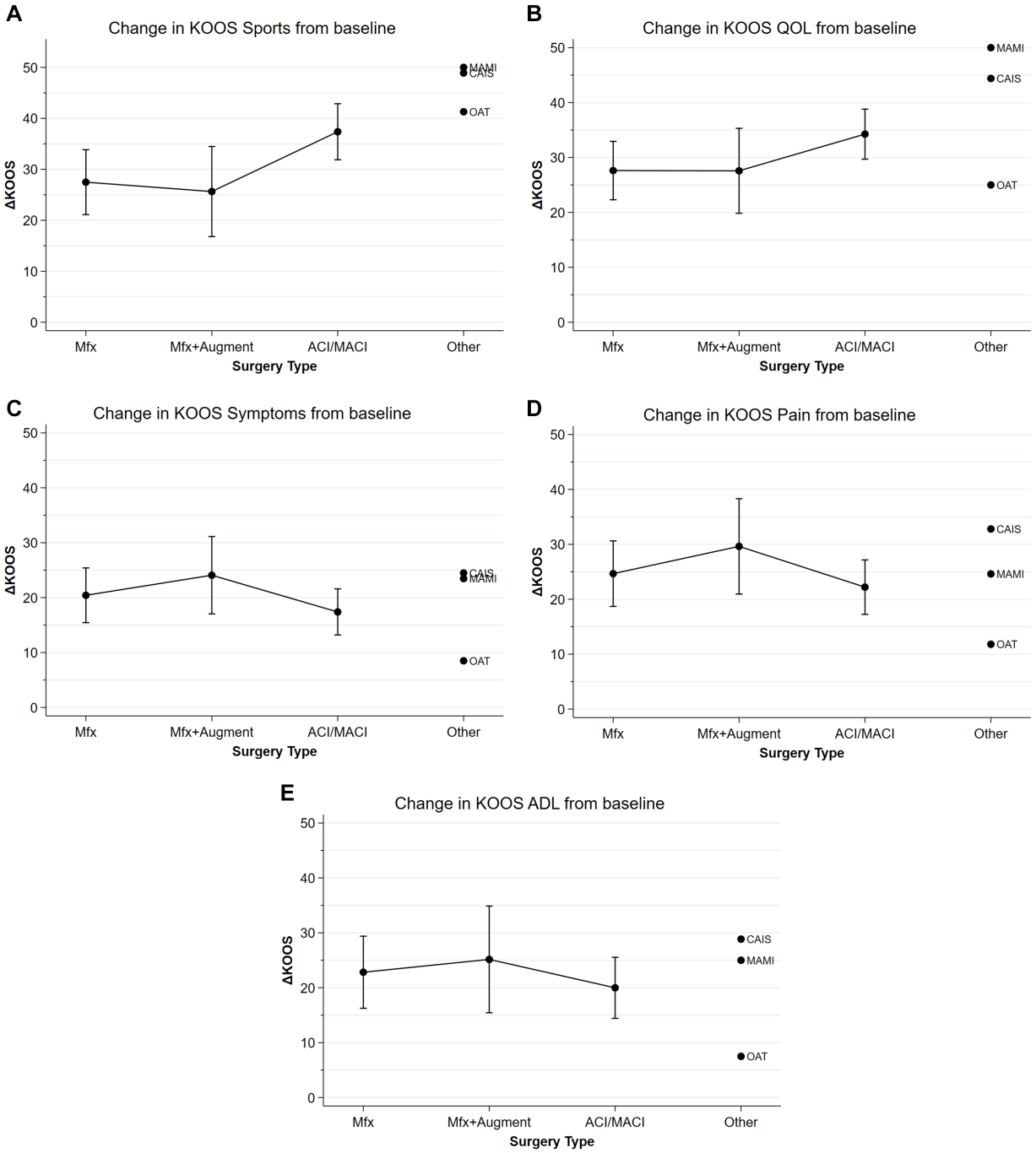

Figure 4. Mean delta KOOS by surgery type for each subscale. (A) Sport and Recreation (Sport). (B) Quality of Life (QOL). (C) Symptoms. (D) Pain. (E) Activities of Daily Living (ADL). CAIS, cartilage autograft implantation system; KOOS, Knee injury and Osteoarthritis Outcome Score; MACI, matrix-assisted autologous chondrocyte implantation; MAMI, matrix-assisted autologous mesenchymal cell implantation; Mfx, microfracture; Mfx+Augment, augmented microfracture techniques; OAT, osteochondral autograft transplantation.

setting.[10] These findings suggest that culture-based therapies lead to clinically superior subjective sport function compared with marrow stimulation. Within marrow stimulation, we did not find any patient-reported differences between Mfx and Mfx + Augment in any of the 5 domains evaluated by KOOS. With consideration of value-based care, the added surgical time or monetary cost of augmentation of Mfx may not be warranted over Mfx alone.

There have been several systematic reviews and meta-analyses on the topic of cartilage restoration in the past

with conflicting results. A recent meta-analysis by Zamborsky and Danisovic[26] reported that ACI, MACI, and OAT had significantly superior results compared with Mfx. We were also able to show superiority of ACI/MACI over Mfx and augmented Mfx procedures. We suggest that in less physically active and older patients, Mfx may be an appropriate and low-cost treatment method that can offer subjective pain relief and ability to perform ADLs comparable with other therapies (Mfx + Augment, ACI/MACI). For more active and younger patients, we can expect clinically relevant improvements in subjective sport function with culture-based therapies that correlate with patient satisfaction.[10]

The results of the covariate analysis revealed some interesting associations. Larger mean BMI correlated with greater improvements in knee-related quality of life after surgical treatment. The mean BMI ranged from 24 to 29, and thus these results cannot be extrapolated to obese patient populations. There was greater improvement in patient-reported Sport function with longer follow-up time. We also found that larger mean chondral defect size was associated with greater improvements in subjective pain levels and ability to perform ADLs. This may suggest that larger defects create more pain and disability, but we were unable to evaluate baseline KOOS data for individual patients due to lack of reporting.

There are some concerns over the durability of clinical results after Mfx. The results of this study do not suggest that Mfx has significantly worse results with longer follow-up time compared with ACI/MACI in the intermediate term (average follow-up time was 3.5 years). We did see a trend toward decreasing the mean delta KOOS Pain and KOOS ADL in Mfx; however, as stated, this did not reach statistical significance. Perhaps with longer follow-up, this relationship may have become significant. With an average follow-up time of 3.5 years, these data are insufficient for evaluation of long-term outcomes. Highlighting the concerns over durability, a recent meta-analysis showed higher failure rates in Mfx compared with ACI at 10 years, which is a considerably longer follow-up time compared with our study.[26]

Study Limitations

There are several limitations to this study. We were unable to analyze concomitant and previous procedures due to variable reporting. MAMI, CAIS, and OAT were each evaluated by 1 RCT and were not suitable for meta-analysis. Due to the nature of the procedures, study participants were not blinded; and by Cochrane standards, all studies had at minimum some concern for bias. Our results analyzed outcomes in the intermediate term, and thus longer follow-up is needed. We also excluded several RCTs that did not report delta KOOS subscale data. This could be a source of selection bias. We encourage future studies to utilize KOOS and provide delta KOOS subscale values for reader interpretation. Another major limitation of this study is that we only analyzed KOOS scores and, due to reporting gaps and study power, were unable to exhaustively evaluate many potentially relevant covariates as possible effect modifiers. The decision to limit attention to KOOS was made at study initiation to simplify the comparison of improvement in different knee-related domains between surgery types.

Study Strengths

There are several strengths to this study. To our knowledge, this is the largest systematic review and meta-analysis of RCTs evaluating KOOS subscales. Despite the large number of studies, baseline characteristics between the 3 main study groups were similar. We were able to demonstrate relative superiority of culture-based therapies (ACI/MACI) over marrow stimulation in PROs.

CONCLUSION

Patient-reported sport and recreational activity and knee-related quality of life as measured by delta KOOS Sport and KOOS QOL showed the greatest improvement after cartilage repair of the knee. Culture-based therapies (ACI and MACI) led to statistically and clinically significant benefits over marrow stimulation (Mfx and Mfx + Augment) in KOOS Sport scores, and thus they may be a more appropriate treatment in younger and more active patient populations. There were no patient-reported differences between Mfx and Mfx + Augment in any of the 5 KOOS subscales.

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REFERENCES

1. Akgun I, Unlu MC, Erdal OA, et al. Matrix-induced autologous mesenchymal stem cell implantation versus matrix-induced autologous

chondrocyte implantation in the treatment of chondral defects of the knee: a 2-year randomized study. *Arch Orthop Trauma Surg*. 2015;135(2):251-263.
2. Anderson DE, Robinson KS, Wiedrick J, Crawford DC. Efficacy of fresh osteochondral allograft transplantation in the knee for adults 40 years and older. *Orthop J Sports Med*. 2018;6(11):2325967118805441.
3. Berkey CS, Hoaglin DC, Mosteller F, Colditz GA. A random-effects regression model for meta-analysis. *Stat Med*. 1995;14(4): 395-411.
4. Brittberg M, Recker D, Ilgenfritz J, Saris DBF; SUMMIT Extension Study Group. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: a 5-year follow-up of a prospective randomized trial. *Am J Sports Med*. 2018;46(6):1343-1351.
5. Cole BJ, Farr J, Winalski CS, et al. Outcomes after a single-stage procedure for cell-based cartilage repair: a prospective clinical safety trial with 2-year follow-up. *Am J Sports Med*. 2011;39(6):1170-1179.
6. Crawford DC, DeBerardino TM, Williams RJ III. NeoCart, an autologous cartilage tissue implant, compared with microfracture for treatment of distal femoral cartilage lesions: a Food and Drug Administration (FDA) phase 2 prospective, randomized clinical trial after 2 years. *J Bone Joint Surg Am*. 2012;94(11):979-989.
7. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. *Arthroscopy*. 1997;13(4):456-460.
8. Ebert JR, Edwards PK, Fallon M, Ackland TR, Janes GC, Wood DJ. Two-year outcomes of a randomized trial investigating a 6-week return to full weightbearing after matrix-induced autologous chondrocyte implantation. *Am J Sports Med*. 2017;45(4):838-848.
9. Ebert JR, Fallon M, Zheng MH, Wood DJ, Ackland TR. A randomized trial comparing accelerated and traditional approaches to postoperative weightbearing rehabilitation after matrix-induced autologous chondrocyte implantation: findings at 5 years. *Am J Sports Med*. 2012;40(7):1527-1537.
10. Ebert JR, Smith A, Wood DJ, Ackland TR. A comparison of the responsiveness of 4 commonly used patient-reported outcome instruments at 5 years after matrix-induced autologous chondrocyte implantation. *Am J Sports Med*. 2013;41(12):2791-2799.
11. Flanigan DC, Harris JD, Trinh TQ, Siston RA, Brophy RH. Prevalence of chondral defects in athletes' knees: a systematic review. *Med Sci Sports Exerc*. 2010;42(10):1795-1801.
12. Fossum V, Hansen AK, Wilsgaard T, Knutsen G. Collagen-covered autologous chondrocyte implantation versus autologous matrix-induced chondrogenesis: a randomized trial comparing 2 methods for repair of cartilage defects of the knee. *Orthop J Sports Med*. 2019;7(9):2325967119868212.
13. Higgins JPT, Thomas J, Chandler J, et al, eds. 2019. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.0. Cochrane; September 2006. Updated July 2019. Accessed February 20, 2020. www.training.cochrane.org/handbook/
14. Kim MS, Chun CH, Wang JH, et al. Microfractures versus a porcine derived collagen-augmented chondrogenesis technique for treating knee cartilage defects: a multicenter randomized controlled trial. *Arthroscopy*. 2020;36(6):1612-1624.
15. Kim MS, Koh IJ, Choi YJ, Pak KH, In Y. Collagen augmentation improves the quality of cartilage repair after microfracture in patients undergoing high tibial osteotomy: a randomized controlled trial. *Am J Sports Med*. 2017;45(8):1845-1855.
16. Koh YG, Kwon OR, Kim YS, Choi YJ, Tak DH. Adipose-derived mesenchymal stem cells with microfracture versus microfracture alone: a 2-year follow-up of a prospective randomized trial. *Arthroscopy*. 2016;32(1):97-109.
17. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.
18. Niemeyer P, Laute V, Zinser W, et al. A prospective, randomized, open-label, multicenter, phase 3 noninferiority trial to compare the clinical efficacy of matrix-associated autologous chondrocyte implantation with spheroid technology versus arthroscopic microfracture for cartilage defects of the knee. *Orthop J Sports Med*. 2019;7(7):2325967119854442.
19. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1:64.
20. Sterne JAC, Savović J, Page MJ, et al. A revised Cochrane Risk of Bias 2 Tool (RoB 2): a revised tool for assessing risk of bias in randomized trials. *BMJ*. 2019;366:l4898.
21. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomized controlled trials. *BMJ*. 2011;343:D4002.
22. Ulstein S, Årøen A, Røtterud JH, Løken S, Engebretsen L, Heir S. Microfracture technique versus osteochondral autologous transplantation mosaicplasty in patients with articular chondral lesions of the knee: a prospective randomized trial with long-term follow-up. *Knee Surg Sports Traumatol Arthrosc*. 2014;22(6):1207-1215.
23. Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP; TIG/ACT/01/2000&EXT Study Group. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. *Am J Sports Med*. 2011;39(12):2566-2574.
24. Veroniki AA, Jackson D, Viechtbauer W, et al. Methods to estimate the between-study variance and its uncertainty in meta-analysis. *Res Synth Methods*. 2016;7(1):55-79.
25. Wondrasch B, Risberg MA, Zak L, Marlovits S, Aldrian S. Effect of accelerated weightbearing after matrix-associated autologous chondrocyte implantation on the femoral condyle: a prospective, randomized controlled study presenting magnetic resonance imaging-based and clinical outcomes after 5 years. *Am J Sports Med*. 2015; 43(1):146-153.
26. Zamborsky R, Danisovic L. Surgical techniques for knee cartilage repair: an updated large-scale systematic review and network meta-analysis of randomized controlled trials. *Arthroscopy*. 2020; 36(3):845-858.