Clinical and Magnetic Resonance Imaging Outcomes After Microfracture Treatment With and Without Augmentation for Focal Chondral Lesions in the Knee

A Systematic Review and Meta-analysis

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Background: Focal cartilage lesions represent a common source of knee pain and disability, with the potential for the development and progression of osteoarthritis. Currently, microfracture (MFx) represents the most utilized first-line surgical treatment for small, focal chondral lesions. Recent investigations have examined methods of overcoming the limitations of MFx utilizing various augmentation techniques.

Purpose: To perform a systematic review and meta-analysis evaluating clinical and radiographic outcomes in patients undergoing isolated MFx versus MFx augmented with orthobiologics or scaffolds for focal chondral defects of the knee.

Study Design: Systematic review and meta-analysis; Level of evidence, 4.

Methods: A systematic review was performed to identify studies evaluating outcomes and adverse events in patients undergoing isolated MFx versus augmented MFx for focal chondral defects in the knee from 1945 to June 1, 2021. Data were extracted from each article that met the inclusion/exclusion criteria. Meta-analyses were performed for all outcomes reported in a minimum of 3 studies.

Results: A total of 14 studies were identified, utilizing 7 different types of injectable augmentation regimens and 5 different scaffolding regimens. Across the 14 studies, a total of 744 patients were included. The mean patient age was 46.8 years (range, 34-58 years), and 58.3% (n = 434/744) of patients were women. The mean final follow-up time was 26.7 months (range, 12-60 months). The mean chondral defect size ranged from 1.3 to 4.8 cm^2. A post hoc analysis comparing mean improvement in postoperative outcomes scores compared with preoperative values found no significant differences in the improvement in the visual analog scale (VAS), International Knee Documentation Committee (IKDC), or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores between patients undergoing isolated MFx and those undergoing MFx + augmentation. Patients undergoing MFx + augmentation reported significantly greater improvements in the Lysholm score and postoperative MOCART (magnetic resonance observation of cartilage repair tissue) scores compared with the isolated MFx group.

Conclusion: Patients undergoing combined MFx + augmentation reported significant improvements in mean Lysholm and MOCART scores, without significant improvements in VAS, IKDC, or WOMAC scores when compared with patients undergoing isolated MFx.

Keywords: biologic; cartilage; knee; microfracture; scaffold

Focal cartilage lesions represent a common source of knee pain and disability, with the potential for the development and progression of osteoarthritis secondary to the limited inherent capacity for cartilage healing and repair.[2,46] To improve pain and restore function, various cartilage restoration procedures have been popularized, including microfracture (MFx), autologous chondrocyte implantation, and osteochondral autograft and allograft transplantation.[14,41] Chondral restoration procedures seek to promote a structural repair that is comparable with native, hyaline cartilage, effectively improving long-term joint durability.[47]

The American Journal of Sports Medicine
1–14
DOI: 10.1177/03635465221087365

Currently, MFx represents the most commonly utilized first-line treatment for small (<2 mm^2) focal cartilage lesions.[25,36] However, because of the unpredictable quality of repair tissue, consisting predominately of fibrocartilaginous tissue without hyaline articular structure,[11,38] indications have become increasingly restricted as clinical outcomes after MFx have been reported to deteriorate 2 to 3 years after surgery.[17,29,36]

Inconsistent and suboptimal repair tissue quality after MFx has been theorized to arise from the instability of the fibrin clot formed during MFx, which has been reported to detach from the site of injury[10,12,36] as a result of platelet-derived clot retraction.[19,22] Recent investigations have examined methods of overcoming the limitations of MFx utilizing various augmentation techniques, specifically combining MFx with orthobiologics injections,[3,10,21,28,39] or improving clot stabilization using synthetic matrices, scaffolds, or plugs.[9] By improving the quality of repair cartilage and enabling restoration of normal surface morphology and joint articulation, while effectively allowing for appropriate biomechanical loading, the development or progression of secondary osteoarthritis may be prevented or delayed.[7,15] Although multiple individual studies have reported superior cartilage healing as a result of the synergistic effect augmenting MFx with orthobiologics or mechanical support,[3,21,26] no investigation has examined the current state of the literature on augmented MFx outcomes.

The purpose of this study was to perform a systematic review and meta-analysis of studies evaluating clinical and radiographic outcomes in patients undergoing isolated MFx versus MFx combined with orthobiologic or scaffold augmentation for a focal chondral defect of the knee. The authors hypothesized that patients undergoing MFx treatment with either orthobiologic or scaffold augmentation would report improved clinical outcomes scores when compared with patients undergoing isolated MFx.

METHODS

A systematic review was performed using the PubMed and Embase databases in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[33] The search was conducted by 2 authors (L.M.F. and S.P.D.) to identify all studies evaluating outcomes comparing MFx alone versus MFx augmented with orthobiologics or mechanical support (matrices, scaffolds, and plugs) for the treatment of focal chondral defects in the knee. The search was conducted for studies published between 1945 to June 1, 2021, using various combinations of the following search terms: "knee" AND "microfracture" AND "focal" AND "chondral defect" AND "orthobiologics" AND "scaffold" AND "matrix" AND "plug" AND "synthetic" AND "outcomes." The same 2 authors independently reviewed each article to determine eligibility based on predetermined inclusion/exclusion criteria. The inclusion criteria were as follows: (1) studies involving human patients with chondral defects of the knee treated with isolated MFx versus MFx augmented with orthobiologics or mechanical support; (2) studies with a minimum of 5 patients; (3) reported clinical outcome scores; (4) minimum 1-year follow-up; (5) studies with level 1, level 2, and level 3 evidence; and (6) English-language articles or articles with English-language translation. The exclusion criteria for articles were as follows: (1) case reports; (2) case series with <5 human participants; (3) review articles; (4) systematic reviews; (5) meta-analyses; (6) animal studies; (7) biomechanical studies; (8) cadaveric studies; or (9) studies not reporting clinical outcomes. Full articles were reviewed by both reviewers independently and if there was ambiguity regarding eligibility, the senior author (J.C.) was consulted for a final decision.

Data were extracted from each article that met the inclusion/exclusion criteria. The following data were recorded: (1) study characteristics (study design, level of evidence, and sample size); (2) patient demographics (age, sex, and body mass index); (3) chondral lesion size; (4) type of intervention (isolated MFx versus MFx + augmentation); (5) presence of a control group; (6) incidence of postoperative complications or adverse events (AEs); and (7) length of follow-up. Preoperative and postoperative patient-reported outcomes (PROs) were collected as well as radiographic outcomes based on MOCART (magnetic resonance observation of cartilage repair tissue) scores. The same 2 authors independently assessed the quality of each study using the Newcastle-Ottawa Scale (Table 1) and the Modified Coleman Methodology Score[20,54] (Table 2).

Statistical Analysis

A series of meta-analyses were performed for all outcomes reported in a minimum of 3 studies. Statistical analysis required both injectable and scaffolding augmentation techniques to be combined into 1 umbrella group defined as "MFx + augmentation." The mean preoperative and

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Submitted October 24, 2021; accepted February 9, 2022.
One or more of the authors has declared the following potential conflict of interest or source of funding: D.M.K. has received support for education from Smith & Nephew and Medwest Associates and a grant from Arthrex. J.C. has received consulting fees from Arthrex, CONMED Linvatec, Ossur, Smith & Nephew, and DePuy Synthes Products; support for education from Arthrex and Smith & Nephew; speaking fees from Linvatec; and hospitality payments from Medical Device Business Services and Stryker. AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.

TABLE 1
Newcastle-Ottawa Scale[54] Assessing the Quality of Studies Included in the Systematic Review[a]

	Selection				Comparability		Outcome			
Study (y)	Representativeness of Treated Cohort	Selection of Comparative Cohort	Ascertainment of Treated Cohort Records	The outcome of Interest Was Not Present at Start	Controls for Age	Controls for Any Additional Factor	Assessment of Outcome	Long Enough Follow-up	Adequacy of Follow-up	Total Quality Score
Wong et al[56] (2013)	★	★	★	★	★	★	★	★	★	9
Hashimoto et al[18] (2019)	★	★	★	★			★	★	★	7
Jin et al[21] (2021)	★	★	★	★			★	★	★	7
Kim et al[26] (2020)	★	★	★	★		★	★	★		7
Kim et al[27] (2017)	★	★	★	★			★	★	★	7
Koh et al[28] (2016)	★	★	★	★	★	★	★	★	★	9
Bisicchia et al[3] (2020)	★	★	★	★			★	★	★	7
Chung et al[4] (2014)	★	★	★	★			★	★		6
Shive et al[47] (2015)	★	★	★	★	★	★	★	★		8
Sofu et al[49] (2017)	★	★	★	★		★	★	★	★	8
Lee et al[31] (2013)	★	★	★	★			★	★	★	7
Papalia et al[40] (2016)	★	★	★	★			★	★	★	7
Stanish et al[53] (2013)	★	★	★	★		★	★	★	★	8
Nguyen et al[39] (2017)	★	★	★	★			★	★	★	7

[a]Each study was judged on 3 broad perspectives: the selection of study groups, the comparability of the groups, and the ascertainment of the outcomes measured. A star indicates that the study met the requirements for that characteristic. A maximum of 9 stars could be awarded to each study.

TABLE 2
Modified Coleman Methodology Score Assessing the Quality of Studies Included in the Systematic Review[a]

	Criteria Part A							Criteria Part B			Total		
Study (Y)	Study Size	Mean Duration of Follow-up	No. of Treatment Procedures	Type of Study	Diagnostic Certainty	Description of Surgical Procedure	Description of Rehab Procedures	Outcome Criteria	Procedure for Assessing Outcomes	Subject Selection Process	Total (Part A)	Total (Part B)	Total Score
Wong et al[56] (2013)	7	5	10	15	5	5	10	7	11	5	57	23	80
Hashimoto et al[18] (2019)	0	0	10	10	5	5	10	7	11	14	40	32	72
Jin et al[21] (2021)	10	2	10	5	5	10	10	9	6	11	52	26	78
Kim et al[26] (2020)	10	2	10	10	5	10	10	7	11	15	57	33	90
Kim et al[27] (2017)	4	2	10	10	5	10	10	7	11	13	51	31	82
Koh et al[28] (2016)	10	5	10	5	5	10	10	7	11	15	55	33	88
Bisicchia et al[3] (2020)	4	2	0	10	5	10	0	7	11	15	31	33	64
Chung et al[4] (2014)	10	2	10	5	5	10	10	7	11	15	52	33	85
Shive et al[47] (2015)	10	5	10	10	5	0	0	7	6	5	40	18	58
Sofu et al[49] (2017)	7	5	10	5	5	10	10	7	10	13	52	30	82
Lee et al[31] (2013)	7	2	10	10	5	10	10	7	11	5	54	23	77
Papalia et al[40] (2016)	7	5	0	5	5	10	10	7	6	5	42	18	60
Stanish et al[53] (2013)	10	2	10	10	5	10	10	7	11	13	57	31	88
Nguyen et al[39] (2017)	4	2	10	10	5	10	10	7	11	10	51	28	79

[a]Each study was judged on 2 broad perspectives: (A) details about the study characteristics and (B) details about the outcomes collected. The maximum score for each section varied and a higher score indicated higher quality. A maximum of 90 points could be awarded to each study.[20]

postoperative outcome scores were calculated, while standard deviations or ranges were extracted from each study when available. Random-effects models with inverse variance for weighting were used to calculate the pooled improvement in PROs when comparing postoperative to preoperative scores among eligible studies. Studies reporting the visual analog pain score (VAS) on either a 10- or 100-point scale were converted to a 10-point scale and included in the meta-analysis. Studies solely providing the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscale scores without explicitly reporting postoperative data were excluded from the meta-analysis. Heterogeneity was determined with I^2 tests and values. Subgroup analyses were performed to evaluate differences in outcomes between patients undergoing isolated MFx versus MFx + augmentation. Forest plots were generated to visualize outcomes from individual studies as well as pooled summary estimates. Statistical significance was defined a priori as $P < .05$. Statistical analysis was conducted using RStudio

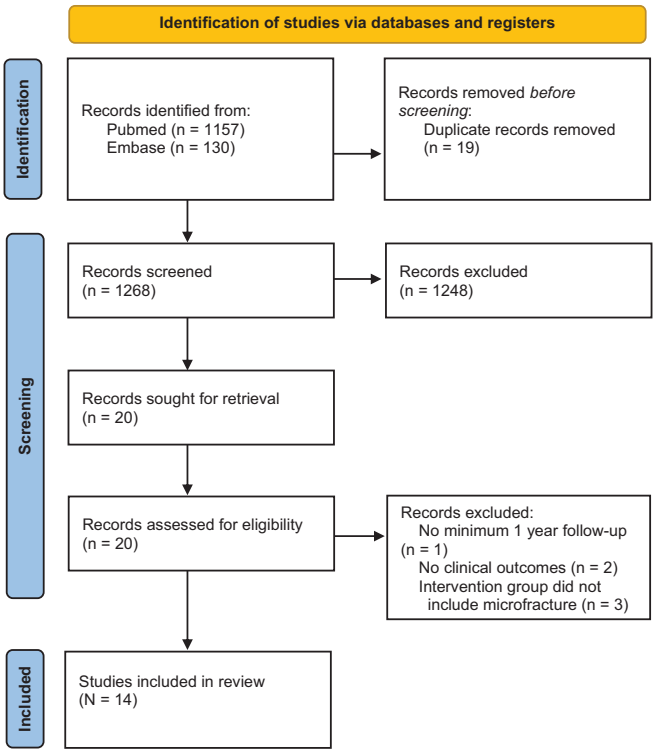

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram outlining the selection process of the included studies for the systematic review.

software Version 4.0.4 (R Foundation for Statistical Computing).

RESULTS

A total of 1268 articles were screened for eligibility. After full-text review and application of inclusion/exclusion criteria, a total of 14 studies were identified for further analysis[¶] (Figure 1).

No disagreements regarding study inclusion were encountered between the 2 independent authors. Of the 14 studies included, 43% (n = 6/14) were level 1 evidence,[3,26,31,39,47,53] 50% (n = 7/14) level 2 evidence,[4,18,21,27,28,40,56] and 7% (n = 1/14) level 3 evidence[49] (Table 3). A total of 71.4% (n = 10/14) of articles consisted of control group patients undergoing isolated MFx, while 14.3% (n = 2/14) of studies had control groups undergoing MFx + high tibial osteotomy (HTO),[21,27] with the remaining control groups consisting of patients undergoing MFx + HTO + postoperative hyaluronic acid (HA) injection[56] (7.1%; n = 1/14), or MFx + intraoperative HA injection[18] (7.1%; n = 1/14) (Table 3).

Across the 14 studies, a total of 744 patients were included. The mean patient age was 46.8 years (range, 34-58 years), and 58.3% (n = 434/744) of patients were women. The mean final follow-up time was 26.7 months (range, 12-60 months). The mean size of chondral lesions at the time of surgery ranged from 1.3 to 4.8 cm^2 (Table 3).

Injectable orthobiologics were utilized in 57% (n = 8/14)[3,18,21,28,31,39,40,56] of studies, while 43% (n = 6/14)[4,26,27,47,49,53] of studies reported the use of scaffolding orthobiologics) (Table 4). Seven different types of injectable augmentation regimens were reported in 8 studies: bone marrow aspirate concentrate,[21] bone marrow–derived mesenchymal stem cells (MSCs),[18] bone marrow–derived MSCs + HA,[56] MSCs (adipose-derived) + fibrin glue,[28] platelet-rich fibrin,[40] platelet-rich plasma (PRP),[31,40] and stromal vascular fraction.[39] Five different scaffolding regimens were reported in 6 studies: atelocollagen + thrombin + fibrin,[26,27] biomembrane cover,[4] BST-CarGel polymer,[47] BST-CarGel polymer + whole blood,[53] and an HA-based scaffold[49] (Table 4).

The VAS pain score was reported in 71.4% (n = 10/14) of studies, while the International Knee Documentation Committee score (IKDC) was reported in 57% (n = 8/14) of articles (see Figures 2 and 3). Lysholm scores were reported in 35.7% (n = 5/14)[28,31,39,49,56] of studies and Knee injury and Osteoarthritis Outcome scores (KOOS) were reported in 28.6% (n = 4/14).[18,21,26,27] After adjusting for age, baseline PROs, and time of evaluation, any significant reported differences in the improvement of scores between the 2 comparison groups were inconsistent across all the studies.

The results of the post hoc analysis showed no significant difference in mean improvement in VAS[3,4,27,31,49] (Figure 2), IKDC[4,21,26,27,31] (Figure 3), or WOMAC[3,21,39,47] (Figure 4) scores in patients undergoing isolated MFx versus MFx + augmentation. Significant improvements were appreciated in Lysholm scores[31,39,49] (Figure 5) and postoperative MOCART scores[18,26,27] in patients undergoing MFx + augmentation compared with isolated MFx (Figure 6).

When performing a subanalysis of studies without a concomitant HTO procedure, the results were unchanged. The results of the subanalysis showed no significant difference in mean improvement in the VAS (Figure 7), IKDC (Figure 8), or WOMAC (Figure 9) scores. A significant difference was still appreciated in postoperative MOCART scores (Figure 10). A subanalysis was not required for Lysholm scores because none of the studies previously reported in the post hoc analysis included HTOs.

When performing a subanalysis of studies by separating augmentation interventions into injectable augmentation and scaffold augmentation, meta-analyses were limited to 3 outcome scores because of the relatively few studies. Subanalyses of scaffold-only augmentation techniques demonstrated no significant difference in mean improvement in the VAS (Figure 11) or IKDC (Figure 12) scores, while subanalyses of injectable-only augmentation techniques also demonstrated no significant difference in the mean improvement of WOMAC scores (Figure 13). These results are unchanged from our analysis that grouped injectable and scaffold techniques together.

The most commonly reported AEs were postoperative knee pain[5] and arthralgias.[30] No significant differences in the reported incidence of postoperative complication or

[¶]3, 4, 18, 21, 26-28, 31, 39, 40, 47, 49, 53, 56.

TABLE 3
Summary of the 14 Studies Included in the Systematic Review[a]

Summary of Included Studies

#	Author (y)	Study Design	Level of Evidence	N	Mean/ median Age, range	BMI	Size of Lesion, cm^2	Follow-up Length, mo	Category	Intervention Group	Control Group
1	Wong et al[56] (2013)	RCT	2	56	Control: 49 Interv: 53	Control: 23.89 Interv: 23.81	5	25	Injectable	HTO + MFx + MSCs (BM) + HA (3 wks postop)	HTO + MFx + HA (3 wks postop)
2	Hashimoto et al[18] (2019)	RCT	2	11	44.1	25.29	Control: 4.4 ± 3.2 Interv: 3 ± 0.9	12	Injectable	MFx + MSCs (BM)	MFx + HA
3	Jin et al[21] (2021)	Retrospective Cohort	2	91	56.38	25.8	Control: 2.4 ± 0.8 Interv: 2.3 ± 0.9	Control: 36.5 ± 8.2 Interv: 33.6 ± 6.6	Injectable	HTO + MFx + BMAC	HTO + MFx
4	Kim et al[26] (2020)	RCT	1	100	50.3	25	Control: 4.67 ± 2.54 Interv: 3.98 ± 1.94	12, 24	Scaffold	MFx + Atelocollagen gel + Thrombin & Fibrin glue	MFx
5	Kim et al[27] (2017)	RCT	2	28	56	24	Control: 2.9 ± 1 Interv: 3.6 ± 1.3	3, 6, 12	Scaffold	HTO + MFx + Atelocollagen gel + Thrombin & Fibrin glue	HTO + MFx
6	Koh et al[28] (2016)	Prospective Cohort	2	80	39	27	Control: 4.8 ± 1.9 Interv: 4.6 ± 1.7	3, 12, 24	Injectable	MFx + MSCs (adipose) + Fibrin glue	MFx
7	Bisicchia et al[3] (2020)	RCT	1	40	48	25	Control: 3.1 ± 1.5 Interv: 3.2 ± 1.7	1, 3, 12	Injectable	MFx + SVF	MFx
8	Chung et al[4] (2014)	Prospective Cohort	2	36	Control: 44.3 Interv: 47.4	NR	Control: 1.5 ± 1 Interv: 1.3 ± 0.8	6, 24	Scaffold	MFx + Biomembrane cover	MFx
9	Shive et al[47] (2015)	RCT	1	60	Control: 40.1 Interv: 34.3	Control: 25.7 Interv: 27.6	Control: 2.08 ± 1.22 Interv: 2.41 ± 1.5	60	Scaffold	MFx + BST-CarGel polymer	MFx
10	Sofu et al[49] (2017)	Retrospective Cohort	3	43	Control: 43 Interv: 40	Control: 23.6 Interv: 23	3.6 ± 1.3	3, 12, 24	Scaffold	MFx + HA-based scaffold	MFx
11	Lee et al[31] (2013)	RCT	1	49	46	Control: 28 Interv: 27	>4	1, 6, 12, 24	Injectable	MFx + PRP	MFx
12	Papalia et al[40] (2016)	Retrospective Cohort	2	48	Control: 53 PRF: 53 PRP: 52	NR	4 ± 2.7	24, 60	Injectable	1) MFx + PRP 2) MFx + PRF	MFx
13	Stanish et al[53] (2013)	RCT	1	80	Control: 37.2 Interv: 35.1	Control: 25.2 Interv: 27	Control: 1.95 ± 1.35 Interv: 2.32 ± 1.43	1, 3, 6, 12	Scaffold	MFx + BST-CarGel polymer + whole blood	MFx
14	Nguyen et al[39] (2017)	RCT	1	30	Control: 58.2 Interv: 58.6	NR	NR	6, 12, 18	Injectable	MFx + SVF	MFx

[a]BM, bone marrow; BMI, body mass index; BMAC, bone marrow aspirate concentrate; BST, bioscaffold technology; HA, hyaluronic acid; HTO, high tibial osteotomy; Interv, intervention; MFx, microfracture; MSC, mesenchymal stem cell; NR, not reported; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; RCT, randomized controlled trial; SVF, stromal vascular fraction.

TABLE 4
Breakdown of Injectable and Scaffolding Orthobiologic Augmentation in Interventional Groups Included in the Systematic Review[a]

Injectable Augmentation		Scaffolding Augmentation	
BMAC (TachoSil; Takeda Pharma A/S)	1	Atelocollagen + Thrombin + Fibrin (CartiFill; Sewon Cellontech)	2
MSCs (BM-d) (Takara Bio Inc)	1	Biomembrane cover (Artifilm; Regenprime Co, Ltd)	1
MSCs (BM-d) + HA (Invitrogen)	1	BST-CarGel polymer (BST-CarGel; Smith & Nephew)	1
MSCs (adipose-d) + Fibrin (Sigma)	1	BST-CarGel polymer + whole blood (BST-CarGel; Smith & Nephew)	1
PRF + PRP (Vivostat PRF System)	1	HA-based scaffold (Hyalofast; Anika Therapeutics)	1
PRP (Magellan Autologous Platelet Separator; Medtronic Biologic Therapeutics and Diagnostics)	1		
SVF (Lipogems; Lipogems International SpA) (ADSC Extraction Kit; GeneWorld)	2		

[a]adipose-d, adipose derived; BMAC, bone marrow aspirate concentrate; BM-d, bone marrow derived; BST, bioscaffold technology; HA, hyaluronic acid; MSC, mesenchymal stem cell; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; SVF, stromal vascular fraction.

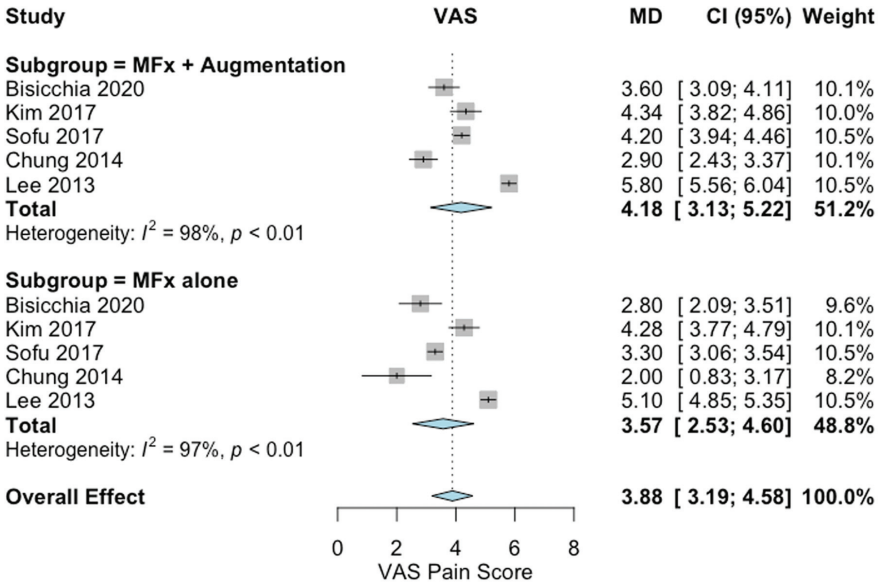

Figure 2. Meta-analysis for comparing the mean improvement of visual analog scale (VAS) pain scores from preoperative to postoperative scores in patients (n = 196) undergoing isolated microfracture (MFx) versus MFx + augmentation. MD, mean difference.

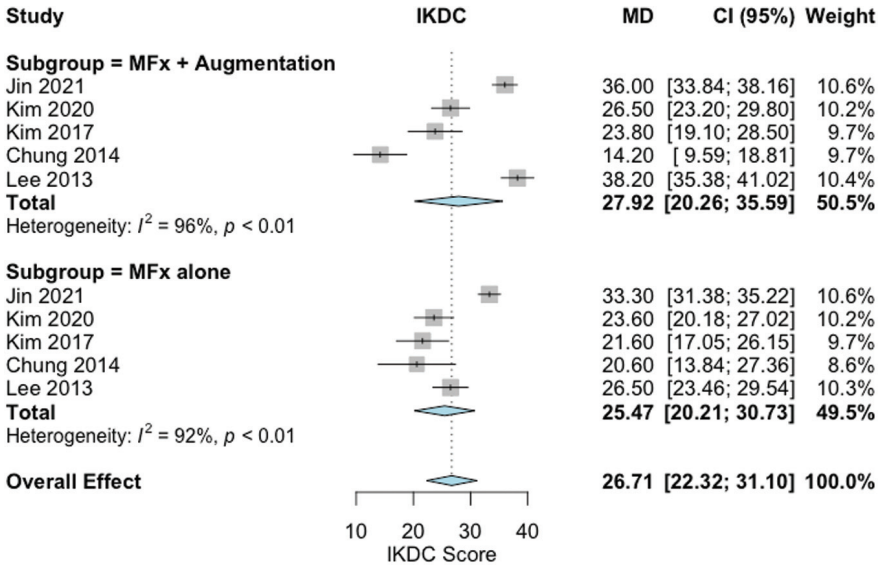

Figure 3. Meta-analysis for comparing the mean improvement of International Knee Documentation Committee (IKDC) scores from preoperative to postoperative scores in patients (n = 293) undergoing isolated microfracture (MFx) versus MFx + augmentation. MD, mean difference.

AEs were appreciated in patients undergoing isolated MFx (16.7%; n = 59/355) versus those treated with MFx + augmentation (16.4%; n = 65/397) (P = .93) (Table 5).

DISCUSSION

The main findings of this investigation were that MFx + augmentation resulted in significant differences in mean improvements in the Lysholm score and radiographic MOCART scores when compared with isolated MFx, without significant differences in improvements in VAS, IKDC, and WOMAC scores. No significant difference in the reported incidence of postoperative complications or AEs was appreciated when comparing patients undergoing isolated MFx versus MFx + augmentation.

No significant differences in VAS, IKDC, or WOMAC scores were appreciated when comparing patients undergoing isolated MFx versus MFx + augmentation. While isolated MFx represents the traditional first-line treatment

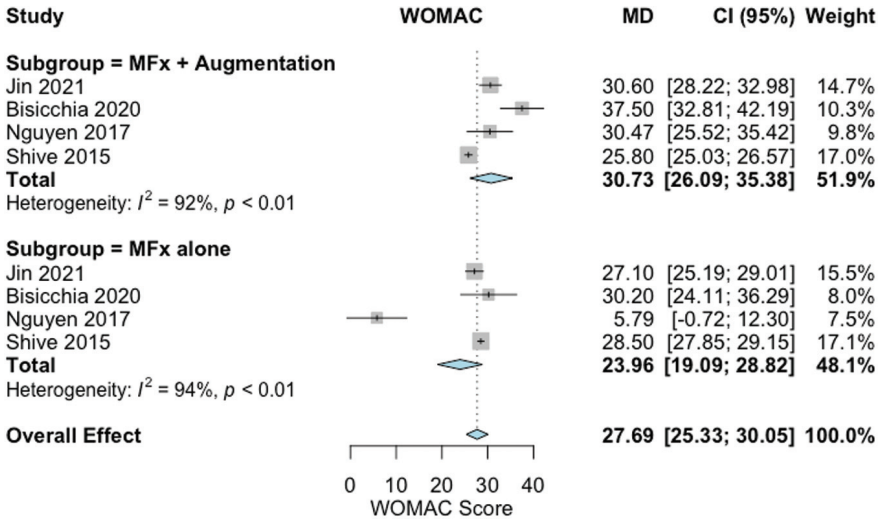

Figure 4. Meta-analysis for comparing the mean improvement of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores from preoperative to postoperative scores in patients (n = 221) undergoing isolated microfracture (MFx) versus MFx + augmentation. MD, mean difference.

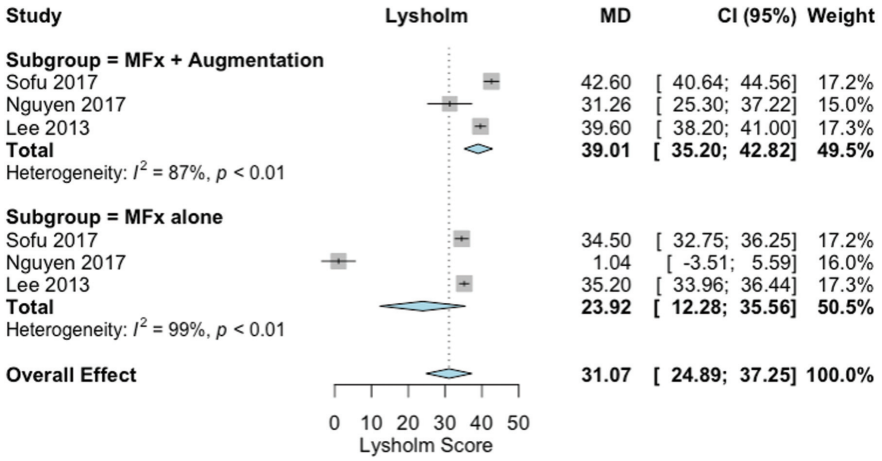

Figure 5. Meta-analysis for comparing the mean improvement of Lysholm scores from preoperative to postoperative scores in patients (n = 122) undergoing isolated microfracture (MFx) versus MFx + augmentation. MD, mean difference.

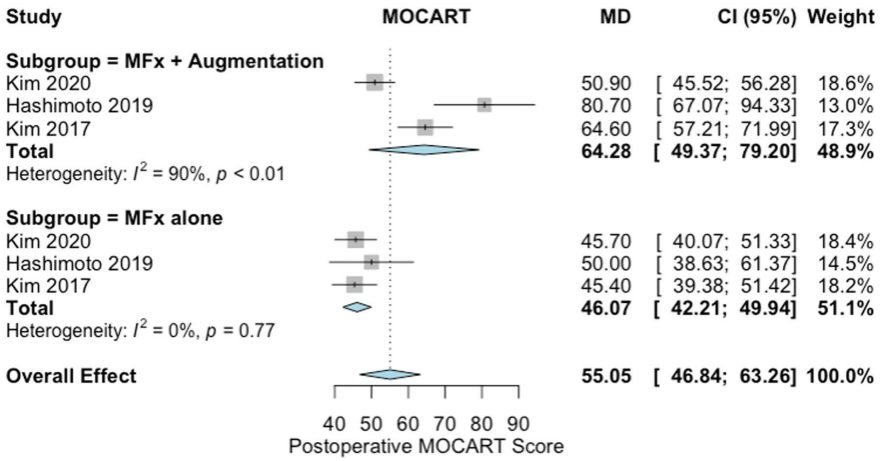

Figure 6. Meta-analysis for comparing the mean postoperative MOCART (magnetic resonance observation of cartilage repair tissue) in patients (n = 128) undergoing isolated microfracture (MFx) versus MFx + augmentation. MD, mean difference.

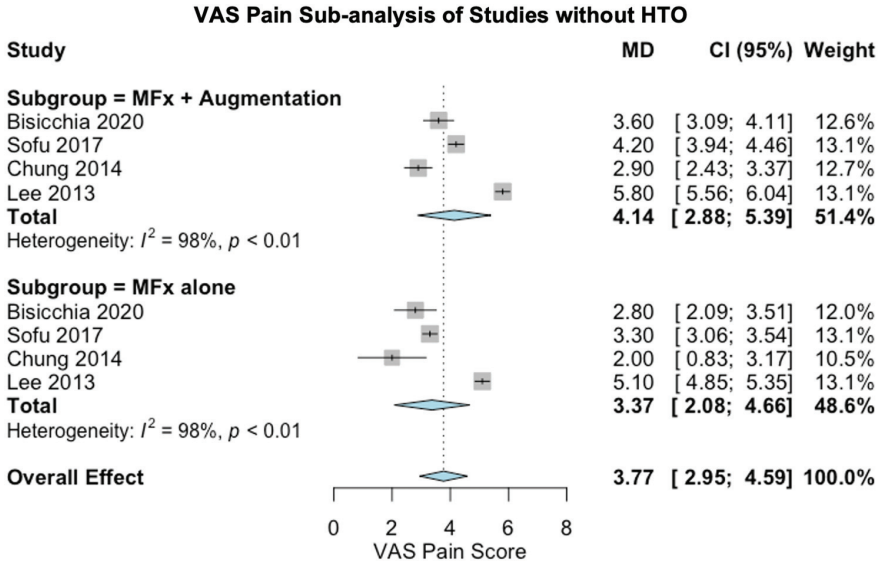

Figure 7. Meta-analysis for comparing the mean improvement of visual analog scale (VAS) pain scores from preoperative to postoperative scores in patients (n = 168) undergoing isolated microfracture (MFx) versus MFx + augmentation in studies without high tibial osteotomy (HTO). MD, mean difference.

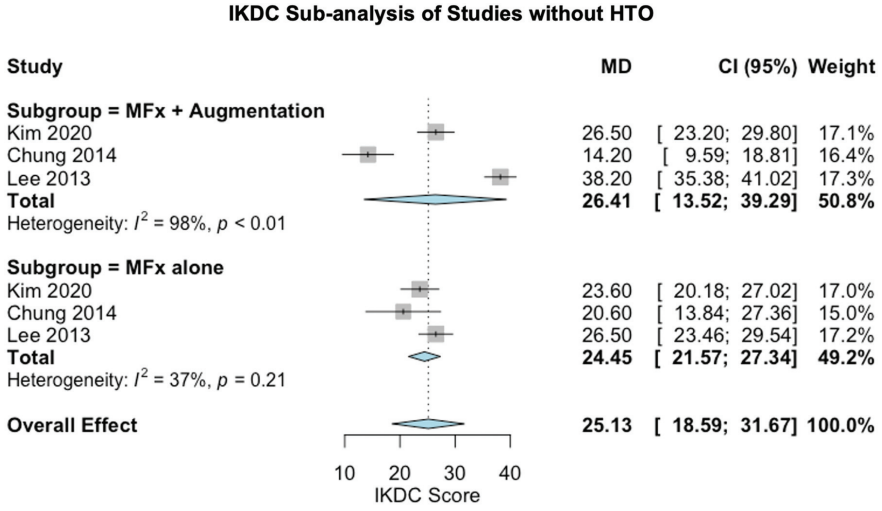

Figure 8. Meta-analysis for comparing the mean improvement of International Knee Documentation Committee (IKDC) scores from preoperative to postoperative scores in patients (n = 174) undergoing isolated microfracture (MFx) versus MFx + augmentation in studies without high tibial osteotomy (HTO). MD, mean difference.

for focal articular cartilage treatment, concerns remain regarding repair tissue durability and integrity, leading to increased interest in augmentation techniques.[32,37,45,50,51] Gobbi and Whyte[13] demonstrated that MFx + HA provided better clinical outcomes and more durable cartilage repair 5 years after surgery when compared with isolated MFx, while Krych et al,[30] Saris et al,[44] and Solheim et al[52] provided further evidence confirming the deteriorating outcomes after isolated MFx. Meanwhile, Gudas et al[16] conducted a prospective study further confirming poor results of isolated MFx technique at 10 years' follow-up, reporting failures in 38% (n = 11/29) of patients, defined by the need for reoperation within 10 years because of symptoms arising from the primary defect. As such, further investigations evaluating MFx + augmentation outcomes at long-term follow-up are warranted to better understand the clinical benefit of augmentation techniques when compared with MFx alone.

Lysholm scores were significantly superior in patients undergoing MFx + augmentation when compared with patients undergoing isolated MFx. This statistical difference also reached the minimal clinically important difference (MCID). The MCID was previously reported to be 10.1 for Lysholm scores in cartilage repair procedures,

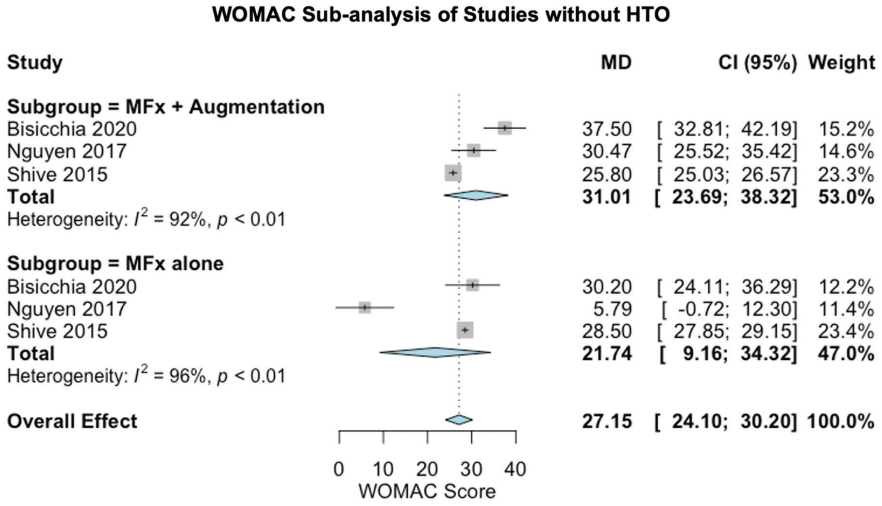

Figure 9. Meta-analysis for comparing the mean improvement of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores from preoperative to postoperative scores in patients (n = 130) undergoing isolated microfracture (MFx) versus MFx + augmentation in studies without high tibial osteotomy (HTO). MD, mean difference.

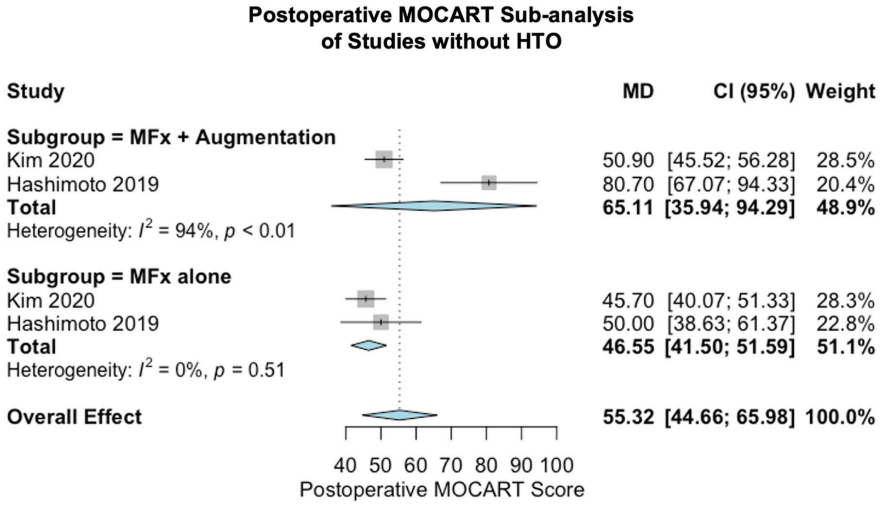

Figure 10. Meta-analysis for comparing the mean postoperative MOCART (magnetic resonance observation of cartilage repair tissue) in patients (n = 100) undergoing isolated microfracture (MFx) versus MFx + augmentation in studies without high tibial osteotomy (HTO). MD, mean difference.

while the difference observed in our meta-analysis was substantially greater[23] (15.18). The observed differences in the Lysholm score over the follow-up period are meaningful, as this PRO has been validated as an excellent tool for the assessment of cartilage repair surgery at 1 to 6 years postoperatively.[23,48] The Lysholm score assesses improvements in pain and physical function, which are the most clinically meaningful endpoints assessing function after the treatment of articular cartilage lesions.[42] Specifically, this survey emphasizes specific activities and movements as well as a strong consideration for symptoms, including swelling, pain, and instability.[6] Relative to the WOMAC and KOOS scores, the Lysholm survey includes an additional instability subsection and reduces the weight placed on the pain portion of the survey.[6] On the other hand, the WOMAC survey assesses challenges with activities of daily living and requests responses to activities that are not uniformly performed by all patients (ie, "taking a bath"). It also places a disproportionate weight on simple physical tasks, which Collins et al[6] argue is reason to conclude that this outcome score is not validated in patients who may have a higher level of physical activity, such as someone undergoing a cartilage restoration procedure. Furthermore, the WOMAC survey places more weight on pain as compared with the Lysholm survey and also includes a stiffness component that may not be relevant in patients undergoing arthroscopic MFx procedures.[6] Although the confidence of this conclusion

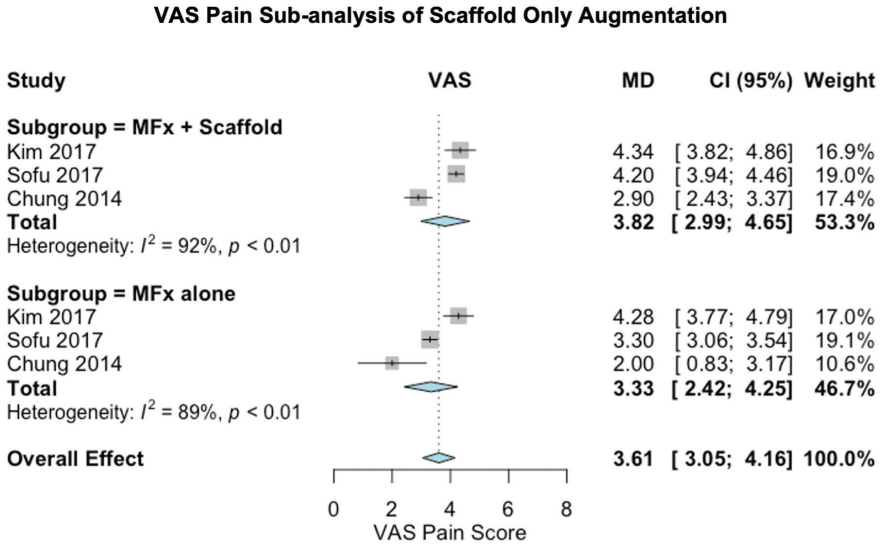

Figure 11. Meta-analysis for comparing the mean improvement of visual analog scale (VAS) pain scores from preoperative to postoperative scores in patients (n = 107) undergoing isolated microfracture (MFx) versus MFx + scaffold augmentation. MD, mean difference.

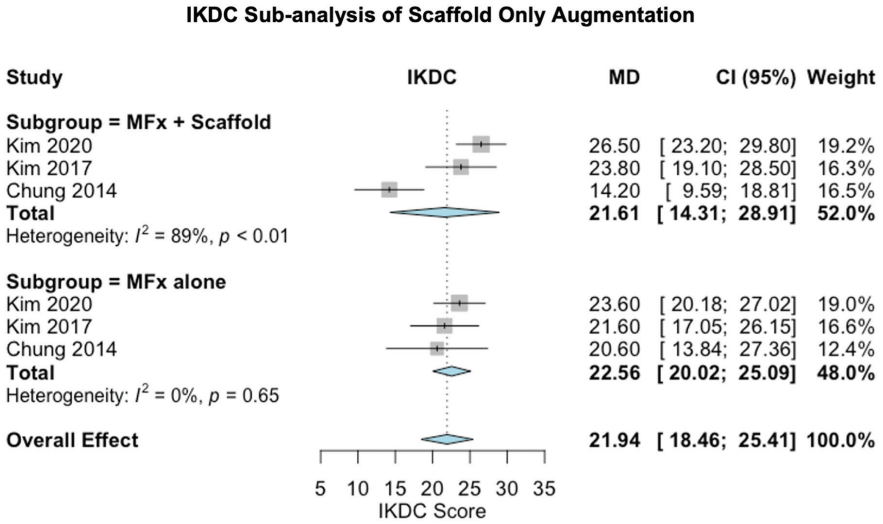

Figure 12. Meta-analysis for comparing the mean improvement of International Knee Documentation Committee (IKDC) scores from preoperative to postoperative scores in patients (n = 153) undergoing isolated microfracture (MFx) versus MFx + scaffold augmentation. MD, mean difference.

(superior Lysholm scores) may be limited by the relatively few number of studies included in the meta-analysis, our analysis was still able to include 3 studies, which is routinely regarded as a sufficient number of studies to conduct a meta-analysis. These findings are consistent with 2 previous systematic reviews that similarly reported improvement in Lysholm scores when MFx treatment was augmentation.[1,55]

Patients undergoing MFx + augmentation also possessed improved magnetic resonance imaging (MRI) outcomes based on MOCART scores when compared with patients undergoing isolated MFx. Although the confidence of this conclusion may also be limited by the inclusion of only 3 studies in this meta-analysis, it was the most we could include based on our inclusion/exclusion criteria. Moreover, MRI is considered the gold standard in evaluating the structural integrity of the repair after cartilage restoration.[24,34,36,48] However, in a systematic review and meta-analysis by de Windt et al,[8] the authors concluded that strong evidence showing a reliable correlation between MRI parameters and clinical outcomes after chondral restoration is lacking. Out of the 32 studies that they included, only 9 studies reported any correlation between MRI morphologic evaluation and clinical outcomes. For

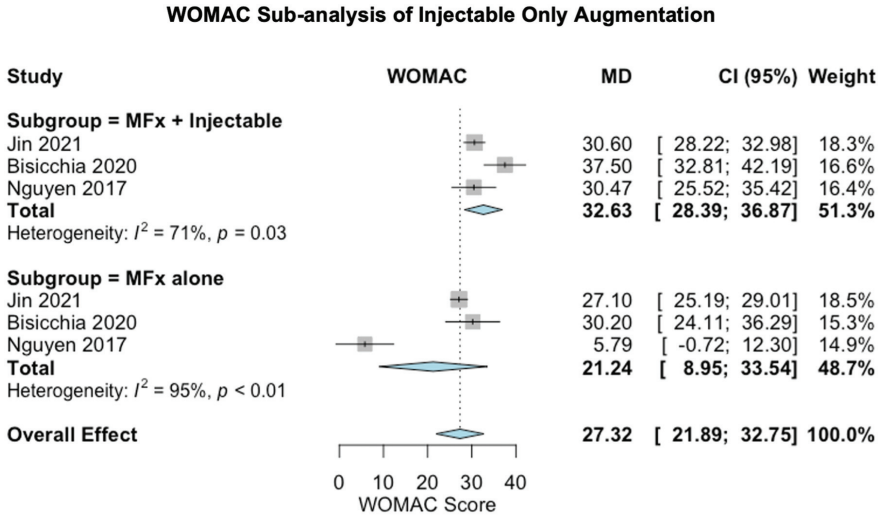

Figure 13. Meta-analysis for comparing the mean improvement of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores from preoperative to postoperative scores in patients (n = 171) undergoing isolated microfracture (MFx) versus MFx + injectable augmentation. MD, mean difference.

TABLE 5
Complications Reported in Individual Studies Related to Intervention or Control Procedures[a]

Study (y)	Sample Size	Intervention	Adverse Events/Complications
Wong et al[56] (2013)	MFx – 28 Aug - 28	MSCs (BM-d) + HA	None
Hashimoto et al[18] (2019)	MFx – 4 Aug - 7	MSCs (BM-d)	1 hematoma in the knee joint (control group)
Jin et al[21] (2020)	MFx – 43 Aug - 48	BMAC	None
Kim et al[26] (2020)	MFx – 48 Aug - 52	Atelocollagen + Thrombin + Fibrin	None
Kim et al[27] (2017)	MFx – 14 Aug - 14	Atelocollagen + Thrombin + Fibrin	5 episodes of hypertrophy of repaired cartilage (intervention group)
Koh et al[28] (2016)	MFx – 40 Aug - 40	MSCs (adipose-d) + Fibrin	None
Bisicchia et al[3] (2020)	MFx – 20 Aug - 20	SVF	1 knee effusion 3 days postop (control group)
Chung et al[4] (2014)	MFx –12 Aug - 24	Biomembrane cover	None
Shive et al[47] (2015)	MFx – 26 Aug - 34	BST-CarGel polymer	54 AEs reported in 31 patients (13 in intervention group, 18 in control group); The most frequent AE was knee pain.
Sofu et al[49] (2017)	MFx – 24 Aug - 19	HA-based scaffold	1 cellulitis 6 days postop (intervention group) 3 persistent pain and early degenerative changes with planned total knee replacement (1 in intervention group; 2 in control group)
Lee et al[31] (2013)	MFx – 25 Aug - 24	PRP	None
Papalia et al[40] (2016)	MFx – 17 Aug - 31	PRP + PRF	None
Stanish et al[53] (2013)	MFx – 39 Aug - 41	BST-CarGel polymer + whole blood	76 AEs reported (40 in interventional group; 36 in control group); most frequent AEs were arthralgia, procedural pain, and nausea. 6 serious AEs were reported (5 in intervention group 1 in control group).
Nguyen et al[39] (2017)	MFx – 15 Aug. - 15	SVF	None

[a]adipose-d, adipose derived; AE, adverse event; Aug, augmentation; BMAC, bone marrow aspirate concentrate; BM-d, bone marrow derived; BST, bioscaffold technology; HA, hyaluronic acid; MSC, mesenchymal stem cell; Postop, postoperative; PRF, platelet-rich fibrin; PRP, platelet-rich plasma; SVF, stromal vascular fraction. Manufacturer details: MSC (BM-d) + HA (Invitrogen); MSC (BM-d) (Takara Bio Inc); BMAC (TachoSil; Takeda Pharma A/S); Atelocollagen + Thrombin + Fibrin (CartiFill; Sewon Cellontech); MSC (adipose-d) + Fibrin (Sigma); SVF; Biomembrane cover (Artifilm; Regenprime Co, Ltd); BST-CarGel polymer (BST-CarGel; Smith & Nephew); HA-based scaffold (Hyalofast; Anika Therapeutics); PRP (Magellan Autologous Platelet Separator; Medtronic Biologic Therapeutics and Diagnostics); PRP + PRF (Vivostat PRF System); BST-CarGel polymer + whole blood (BST-CarGel; Smith & Nephew); SVF (Lipogems; Lipogems International SpA) (ADSC Extraction Kit; GeneWorld).

example, the study by Kim et al[26] comparing isolated MFx with MFx + collagen scaffold augmentation found superior MOCART scores in the intervention group, while no differences in VAS pain, KOOS, IKDC, or Tegner activity scale scores were observed between the 2 groups at the final follow-up. Further investigations examining correlations between clinical improvements based on PROs and chondral healing based on MRI findings are necessary to better validate the utility of MRI outcomes on clinical improvement.

Previous studies have reported variable improvements in PROs when comparing patients undergoing isolated MFx versus MFx + augmentation. Arshi et al[1] reported significant improvements in IKDC, Lysholm, and VAS pain scores at a mean follow-up of 2 to 5 years in their systematic review of 18 studies comprising 625 patients undergoing MFx + augmentation with biological adjuvants versus MFx alone. However, a control group was reported in only 5 of the included studies. Moreover, when comparing MFx + augmentation to MFx alone, the authors noted in a subjective synthesis that 2 randomized controlled trials (RCTs) demonstrated significantly greater improvements in IKDC and KOOS scores after MFx + augmentation, with 2 other RCTs demonstrating comparable postoperative outcomes. Similarly, a systematic review and meta-analysis by Wen et al[55] evaluating 13 clinical trials, comprising a total of 635 patients, compared the efficacy and safety of isolated MFx versus MFx + augmentation. Comparable with the findings from our investigation, the authors reported no significant difference in IKDC, WOMAC, and VAS pain scores between the 2 groups. Moreover, the authors reported a statistically significant superiority in the MFx + augmentation group based on Lysholm ($P = .04$) and MOCART ($P < .01$) scores. As such, the heterogeneity of reported outcomes in the literature demonstrates the need for standardization of reporting measures to better evaluate the benefit of augmentation in patients with focal chondral defects undergoing MFx treatment.

The benefits of MFx + augmentation compared with isolated MFx may involve a variety of factors. In an RCT by Bisicchia et al,[3] the experimental group underwent augmented MFx with stromal vascular fraction, while the control group underwent isolated MFx. The authors reported lower VAS scores and superior WOMAC scores in the experimental group, hypothesizing that the improvement in outcomes was secondary to the anti-inflammatory effects of the stromal vascular fraction on the synovial membrane and the subchondral bone. Benefits with augmentation were maintained at 1-year follow-up, with the authors suggesting that the MSCs present in stromal vascular fraction may release cytokines and growth factors that induce a proliferative response from native chondrocytes and chondroblasts. A trial by Koh et al[28] examining the effects of adipose-derived MSCs on MFx reported statistically significant improvements at 24 months in the VAS ($P = .032$), KOOS Pain ($P = .034$), and KOOS Symptoms ($P = .005$) subscores as well as MOCART radiologic outcome scores ($P = .033$) when compared with isolated MFx. The authors proposed that the addition of MSCs may induce chondral repair, resulting in tissue comparable with native cartilage, being mechanically stable and less likely to deteriorate over time. Meanwhile, the multicenter RCT by Kim et al[26] evaluated the augmentation of MFx with a collagen scaffold versus isolated MFx. The authors reported significant improvements in VAS scores ($P = .047$) and higher postoperative MOCART scores ($P = .0377$) in the investigational group at 1-year follow-up, citing that the addition of the scaffold effectively mediated attachment of stem cells at the defect site, enhancing proliferation. Despite the reported benefits of orthobiologics and scaffold augmentation, further investigations are warranted to better understand the cellular and biologic processes responsible for repair enhancement when compared with isolated MFx treatment.

As described in this paper, a variety of different orthobiologic augmentation options are available on the market. Recently, Arthrex developed a BioCartilage allogenic extracellular scaffolding matrix technique that is combined with PRP and implanted into a MFx defect to treat focal cartilage defects.[5] A preliminary, prospective level 3 cohort study by Cole et al[5] enrolled 48 patients at 8 different institutions who underwent treatment for focal cartilage defects of the knee with the BioCartilage technique. At 2 years' follow-up, all function-related and joint-specific outcome scores (VAS, IKDC, KOOS, WOMAC, and Veterans RAND 12-Item Health), except for the Marx score, demonstrated a significant improvement as compared with the baseline. A similar particulated juvenile cartilage implant, DeNovo (Zimmer Biomet), has recently shown 85% survivorship at 5 years in knees. To date, the clinical data available on this new intervention have been limited to studies of cartilage defects in the ankle and surgical technical notes.[35,43] As such, the strict inclusion/exclusion criteria of our investigation limited the ability to include these 2 promising orthobiologic augmentation techniques.

This investigation is not without limitations. Because of the heterogeneity of reported outcomes, the authors were limited in the number of outcomes scores in which a meaningful statistical assessment could be performed. Additionally, because of the small number of studies with the necessary number of reported PROs, the analyses are likely underpowered. This also required us to combine scaffold and injectable augmentation interventions into 1 "augmentation" group, which introduces inherent bias as these 2 types of intervention are heterogeneous and may act on different pathways to enhance cartilage repair. Nonetheless, we attempted to address this limitation by conducting subanalyses separating injectable augmentation from scaffold augmentation, which did not change the conclusions. We suspect a bias in the reported outcomes, as several patients included in the analyses underwent concomitant procedures during MFx treatment, such as HTO, potentially confounding our data. However, a subanalysis of studies without HTO resulted in the same conclusions. Also, the duration of follow-up may not have been sufficient to assess differences in functional outcomes between isolated MFx and MFx + augmentation that may eventually develop. Last, the generalizability of the findings in this study is limited by the heterogeneity of surgical

techniques, patient characteristics, and the reporting of variable outcome measures.

CONCLUSION

Patients undergoing combined MFx + augmentation reported a significant difference in improvement in mean Lysholm and MOCART scores, without significant differences in improvements in VAS, IKDC, or WOMAC scores when compared with patients undergoing isolated MFx.

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