Intra-articular Injection of Autologous Adipose-Derived Stem Cells or Stromal Vascular Fractions: Are They Effective for Patients With Knee Osteoarthritis?

A Systematic Review With Meta-analysis of Randomized Controlled Trials

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Background: Intra-articular injection of adipose-derived stem cells, which are divided into adipose-derived mesenchymal stem cells (ASCs) and adipose-derived stromal vascular fractions (ADSVFs), has been reported to be a viable treatment modality for knee osteoarthritis (OA); however, its efficacy remains limited.

Purpose: This study aimed to provide comprehensive information about the efficacy and safety of intra-articular injections of autologous ASCs and ADSVFs without adjuvant treatment in patients with knee OA.

Study Design: Meta-analysis; Level of evidence, 1.

Methods: A systematic search of the MEDLINE, Embase, Web of Science, and Cochrane Library databases was performed to identify randomized controlled trials (RCTs) that evaluated the efficacy and safety of intra-articular injections of autologous ASCs or ADSVFs without adjuvant treatments compared with placebo or hyaluronic acid in patients with knee OA. Clinically, the 100-mm visual analog scale for pain relief and the Western Ontario and McMaster Universities Osteoarthritis Index for functional improvement were implemented. Radiologically, cartilage status was assessed using magnetic resonance imaging (MRI). Procedure-related knee pain, swelling, and adverse events (AEs) were evaluated for safety. Additionally, we performed subgroup analyses comparing ASCs versus ADSVFs. Methodological quality was assessed using the modified Coleman Methodology Score (mCMS).

Results: A total of 5 RCTs were included in this study. Based on the meta-analysis, ASCs or ADSVFs showed significantly better pain relief at 6 months ($Z = 7.62$; $P < .0001$) and 12 months ($Z = 7.21$; $P < .0001$) and functional improvement at 6 months ($Z = 4.13$; $P < .0001$) and 12 months ($Z = 3.79$; $P = .0002$), without a difference in procedure-related knee pain or swelling compared with controls. Although a meta-analysis with regard to cartilage improvements was not performed owing to heterogeneous MRI assessment, 3 studies reported significantly improved cartilage status after the injection. No serious AEs associated with ASCs or ADSVFs were reported. Subgroup analyses showed similar efficacy between ASC and ADSVF treatments. The median mCMS was 70 (range, 55-75).

Conclusion: For patients with knee OA, intra-articular injection of autologous ASCs or ADSVFs without adjuvant treatment showed remarkable clinical efficacy and safety at short-term follow-up. Some degree of efficacy has been shown for cartilage regeneration in knee OA, although the evidence remains limited. Further RCTs that directly compare ASCs and ADSVFs are needed.

Keywords: adipose-derived stem cells; adipose tissue; knee osteoarthritis; mesenchymal stem cell; stromal vascular fraction

Knee osteoarthritis (OA) is a highly prevalent degenerative joint disorder that affects patients' quality of life.[12,25,40] OA is a progressive disease characterized by an imbalance between degeneration and regeneration that limits the knee cartilage potential for self-regeneration owing to the avascular nature of cartilage.[19,41,42] The

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eventual treatment for severe OA with intractable symptoms is surgery, such as knee arthroplasty; however, several concerns exist regarding surgery, such as comorbidities, surgical complications, and revision issues.[3,9,21,22,37,43,44] Various nonoperative treatments, including anti-inflammatory medications, physical therapy, and intra-articular (IA) injections of corticosteroids or hyaluronic acid (HA), have been used to manage knee OA symptoms and to delay surgery.[4,35] However, these modalities are palliative and not disease-modifying treatments to address the irreversible damage to cartilage and the associated structural abnormalities.[12,50]

Recently, cell-based therapies have gained attention as a disease-modifying treatment, and mesenchymal stem cells (MSCs) are particularly interesting, given their potential properties of regeneration, multilineage differentiation, and immunomodulatory capacity.[13,32,39] Although MSCs are commonly extracted from the bone marrow, adipose tissue, synovium, and umbilical cord, adipose tissue has become an attractive option owing to its easy accessibility and abundance.[19,41,50] Although the superiority of MSC chondrogenic potential is still debated,[17] several studies have reported that the application of MSCs from adipose tissue to patients with knee OA showed better clinical improvements than injections from other sources.[19,48]

Adipose-derived mesenchymal stem cells (ASCs) and adipose-derived stromal vascular fractions (ADSVFs) are common sources of MSCs from the adipose tissue, and their procurement depends on culture with cell expansion and heterogeneity in cells.[13,46,50] Many systematic reviews and meta-analyses have assessed the efficacy of MSCs, including those from adipose tissue, but most studies erroneously and confusingly used the terms *ASC* and *ADSVF* and otherwise were heterogeneous in terms of autologous or allogenic MSCs, adjuvant treatments, delivery methods, and level of evidence (LOE) of included studies.[8,13,17,19,35,41,48] In this regard, the results of systematic reviews and meta-analyses are still inconsistent with regard to the efficacy of MSCs from adipose tissue.[8,13,17,19,35,41,48]

Therefore, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to provide comprehensive information about the efficacy and safety of autologous ASC or ADSVF IA injection without adjuvant treatments in patients with knee OA. We also indirectly compared the efficacy of ASC and ADSVF use through subgroup analyses. The primary purpose of the current study was to use meta-analysis to assess the efficacy (including pain relief, functional improvement, and cartilage change using magnetic resonance imaging [MRI] assessment) and safety of ASC and ADSVF treatment.

METHODS

Literature Search

This systematic review and meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines,[36] and the protocol for review was registered with the International Prospective Register of Systematic Reviews (PROSPERO, registration no. CRD42021226770). Two independent reviewers (J.-H.K. and M.-S.K.) systematically searched for articles using the PubMed (MEDLINE), Embase, Cochrane Library, and Web of Science databases from study inception to December 17, 2020, using an a priori search strategy. The following keywords were used in the search: "knee joint," "osteoarthritis," "adipose derived mesenchymal stem cell," "adipose derived culture expanded mesenchymal stem cell," "adipose derived stem cell," "stromal vascular fraction," and "adipose tissue stromal vascular fraction" aided by the use of Boolean operators "AND" or "OR." The bibliographies of the initially retrieved studies were manually cross-checked to find additional, relevant articles that could have been missed by electronic searches. No language restrictions were imposed.

Study Selection

Two reviewers (J.-H.K. and M.-S.K.) independently screened the titles and abstracts of the retrieved articles; full manuscripts were reviewed if the abstract provided insufficient data for study inclusion. Any disagreement was resolved by consensus or consultation with another author (K.-I.K). Studies were included in the current study if they met the PICOS (patients, intervention, comparison, outcome, and study design) criteria[27] (Table 1). The exclusion criteria consisted of (1) conference abstracts; (2) clinical trial abstracts; (3) insufficient statistics or inability to reproduce statistics; (4) animal study or in vitro study; (5) allogenic cell therapy; (6) concomitant treatments, such as platelet-rich plasma (PRP), high-tibial osteotomy (HTO), or cartilage repair procedures, and biologic adjuvants, such as fibrin; (7) comparison group of other cell-based therapy or PRP; and (8) LOE 2, 3, 4, or 5. No minimum follow-up period was required for inclusion, because few RCTs existed and all had short-term follow-up.

Assessment of Literature and Methodological Quality

The literature quality was assessed using the LOE determined by 2 reviewers (J.-H.K. and M.-S.K.) based on

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TABLE 1
Inclusion and Exclusion Criteria Based on PICOS[a]

PICOS	Inclusion Criteria	Exclusion Criteria
Population	Patients with knee osteoarthritis	Animal study or in vitro study
Intervention	Intra-articular injection of autologous stromal vascular fraction or culture-expanded mesenchymal stem cells from adipose tissue	Adjuvant treatments such as platelet-rich plasma, cartilage repair procedures, or high-tibial osteotomy Allogenic cell therapy Biologic adjuvants such as fibrin
Comparison	Placebo or control group	Other cell-based therapy or platelet-rich plasma
Outcome	Patient-reported outcome measure (function and pain); magnetic resonance imaging; adverse effect	
Study design (level of evidence)	1	2, 3, 4, or 5

[a]PICOS, population, intervention, comparison, outcome, study design.

previously published criteria.[31] The methodological quality was assessed by 2 reviewers (J.-H.K. and M.-S.K.) based on the modified Coleman Methodology Score (mCMS).[6,7] This score evaluates the included studies for items such as inclusion criteria, sample size calculation, randomization, follow-up, patient analysis, blinding, similarity in treatment, treatment description, group comparability, outcome assessment, description of rehabilitation protocol, clinical effect measurement, and the number of patients treated. The mCMS ranges from 0 to 100 for grading the quality of studies. The grading was considered as follows: a score of >85 was excellent; 70-84, good; 55-69, fair; and ≤ 54, poor.[7] Any disagreement was resolved by consensus or consultation with the other author (K.-I.K).

Assessment of Risk of Bias

The Cochrane Handbook for Systematic Reviews of Interventions was used to evaluate the risk of bias in the included RCTs.[15] This risk assessment was based on the following types of bias: selection, performance, detection, and attrition. Two reviewers (J.-H.K. and M.-S.K.) independently assessed the studies, and any discrepancies in scores between the 2 reviewers were resolved by discussion or consultation with the other author (K.-I.K).

Data Extraction

The same reviewers independently collected available data from the included studies, and any disagreement was resolved by discussion or consultation with the third author. The basic characteristics of the study (author, year of publication, country of investigation, sample size, and LOE), details of patient characteristics (mean age, sex, mean body mass index, lower limb alignment, follow-up duration, and OA grading of involved patients), and details of cell therapy from adipose tissue (entity of cells, control group, delivery methods, culture with cell expansion, cell count, and adipose donor site) were collected. In addition, inclusion and exclusion criteria of included studies were collected. For outcome measurements, pain (100-mm visual analog scale [VAS] score), function (total Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] score), MRI assessment (cartilage improvement or structural change), and safety (procedure-related pain or swelling, adverse events [AEs], and serious AEs [SAEs]) were considered and extracted to a predefined data form. For missing data, we tried to contact the author of the article first; if this failed, we calculated the missing values from other available data using formulas in the Cochrane Handbook for Systematic Reviews of Interventions.[15] The cell type was determined according to a consensus statement regarding nomenclature by the International Society of Cellular Therapy.[2] Cellular therapy from adipose tissue was classified as that using ASCs and ADSVFs.

Statistical Analysis

The primary outcomes of this systematic review were the efficacy of MSC-based therapy from adipose tissue, namely ASCs or ADSVFs, with respect to pain relief, functional improvement, cartilage, or structural change on MRI assessment, and the safety of this therapy. If possible, a meta-analysis was performed to show the standardized mean difference (SMD) with 95% CI for continuous variables and the risk ratio with 95% CI in dichotomous variables. If a meta-analysis was not possible because of a lack of variables, a qualitative description of the outcome was performed. A subgroup analysis was performed to indirectly compare ASCs and ADSVFs with SMD and standardized variance, which were calculated from the weighted estimate, standard error, and sample size of each cohort using a logit model.[20,47] Publication bias was not assessed because it was not considered necessary if there were <10 studies in a comparison.[15] Heterogeneity was assessed by estimating the proportion of between-study inconsistencies because of actual differences between studies using the I^2 statistic.[34] A fixed-effects meta-analysis model was performed to pool outcomes across the included studies. Forest plots were used to show outcomes, pooled estimate of effect, and an overall summary effect of each study and were constructed using RevMan (Version 5.4; The Cochrane Collaboration) and

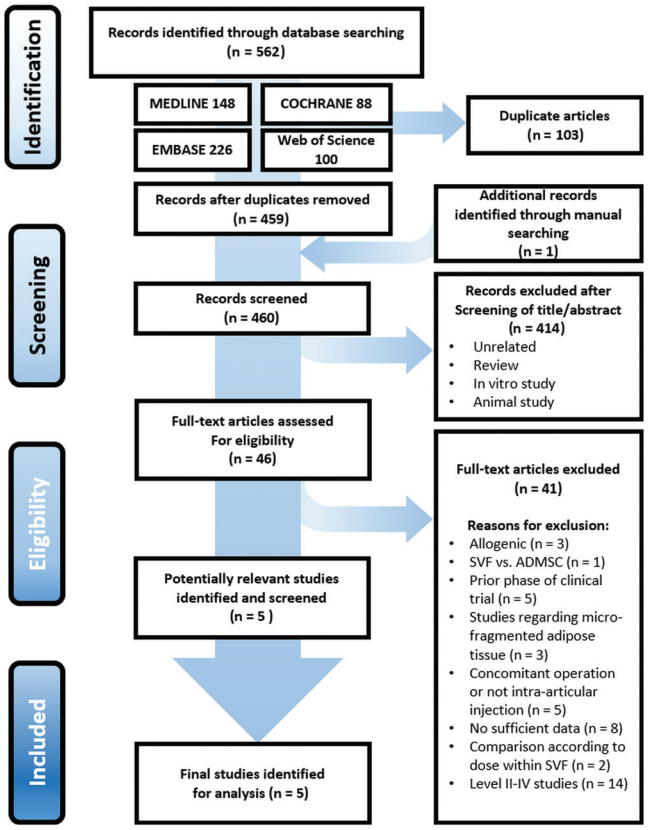

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for identification and selection of studies. ADMSC, adipose-derived mesenchymal stem cell; SVF, stromal vascular fraction.

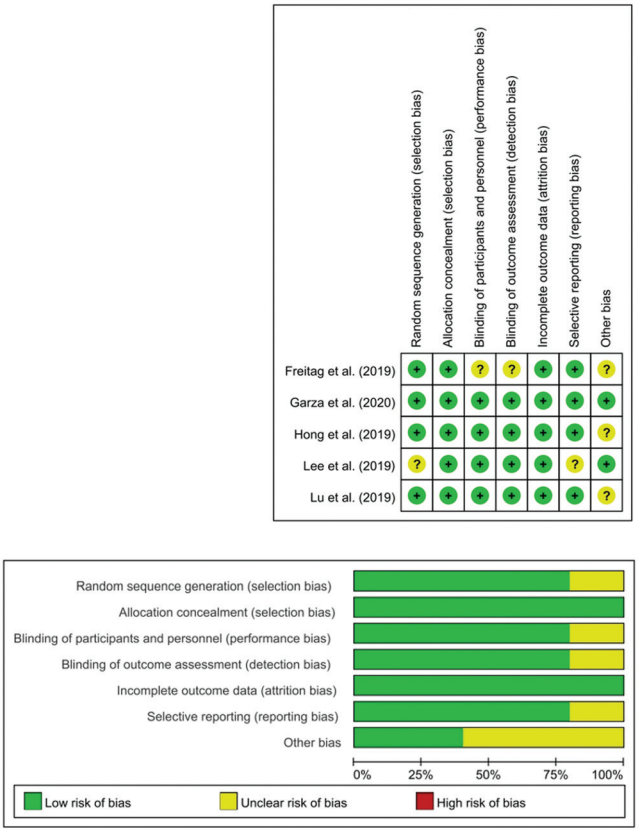

Figure 2. Risk of bias assessment of the included studies, involving a risk of bias graph and summary.

Open Meta-Analyst (http://www.cebm.brown.edu/open-meta). Statistical significance was set at $P < .05$.

RESULTS

Identification of Studies

The initial electronic search yielded 562 studies, and 1 study was identified from an additional manual search. After removal of 103 duplicates, 460 studies remained. We excluded 414 studies after reading the title or abstract, and 41 studies were excluded after a full-text review. Finally, 5 RCTs were included in this systematic review (Figure 1).

Study Characteristics

Of the 5 RCTs, 3 studies compared ASC treatment versus no injection[10] and placebo,[26,30] and 2 studies compared ADSVF treatment versus placebo[11] and HA.[16] A total of 177 knees with OA were included, with a mean patient age of 56.8 ± 9.0 years. Follow-up was conducted for up to 6 months in 1 RCT[26] and 12 months in 4 RCTs.[10,11,16,30] All knees ranged from I to III on the Kellgren-Lawrence grading scale, with the exception of 1 knee that was grade IV. Details of the study characteristics, patient characteristics, and therapy protocol are presented in Table 2. Inclusion and exclusion criteria of included studies are presented in Appendix Table A1 (available in the online version of this article).

Assessment of Literature and Methodological Quality and Risk of Bias

All of the 5 studies[10,11,16,26,30] included had LOE 1. Regarding mCMS for quality assessment, no study was of excellent quality, whereas 3 studies[11,26,30] were of good quality and 2 studies[10,16] were of fair quality (Table 2). The median mCMS was 70 (range, 55-75). The included studies showed a low risk of bias, and there was no high risk of bias in the properties evaluated (Figure 2).

Pain Improvement (100-mm VAS)

In total, 4 studies reported 100-mm VAS scores at 6 months, and the total mean improvement was significantly higher in the overall study groups than in the controls (SMD, 1.06; 95% CI, 1.19-2.02; I^2 = 85%; Z = 7.62;

TABLE 2
Details of Studies on Osteoarthritis Treatment Using Autologous Adipose Tissue[a]

Characteristics	Freitag[10] (2019)	Garza[11] (2020)	Hong[16] (2019)	Lee[26] (2019)	Lu[30] (2019)
Country	Australia	USA	China	South Korea	China
Level of evidence	1	1	1	1	1
Sample size, n					
Study	20	26	16	12	26
Control	10	13	16	12	26
Age, y, mean ± SD					
Study	54.7 ± 10.2	60.0 ± 9.8	51.0 ± 6.0	62.2 ± 6.5	55.0 ± 9.2
Control	51.5 ± 6.1	57.1 ± 9.1	53.0 ± 11.0	63.2 ± 4.2	59.6 ± 6.0
Sex, male:female, n					
Study	11:9	15:11	3:13	3:9	3:23
Control	1:9	7:6	3:13	3:9	3:23
Body mass index, mean ± SD					
Study	31.0 ± 5.6	28.2 ± 4.2	26.3 ± 1.8	25.3 ± 4.9	24.3 ± 3.0
Control	25.2 ± 3.4	27.1 ± 2.7		25.4 ± 3.0	24.3 ± 2.6
Lower limb alignment	<5° varus or valgus for inclusion criteria	NR	NR	NR	Mean varus 1.4° for ASC Mean varus 0.4° for control group
Follow-up, mo	1, 3, 6, 12	1.5, 3, 6, 12	1, 3, 6, 12	3, 6	6, 12
Kellgren-Lawrence grade	II, III	II, III	II, III	II, III, IV[b]	I, II, III
Entity of cells	ASC	ADSVF	ADSVF	ASC	ASC
Control	No injection	Placebo (lactated Ringer solution)	HA	Placebo (normal saline)	HA
Delivery method	IA ± second IA under US at 6 mo	IA under US	IA under arthroscopy	IA under US	Direct IA twice at 0 and 3 wk
Culture and cell expansion	Passage 2	No	No	Passage 3	Passage 4
No. of cells ($\times 10^7$)	10	1.5, 3.0	0.8	10	5
Adipose donor site	Abdomen	Abdomen	Abdomen	Abdomen	Abdomen
Modified Coleman Methodology Score	55	70	67	73	75

[a]ADSVF, adipose-derived stromal vascular fraction; ASC, adipose-derived stem cell; HA, hyaluronic acid; IA, intra-articular injection; NR, not reported; US, ultrasonography.
[b]One patient with Kellgren-Lawrence grade IV was included in the control group.

$P < .0001$) (Figure 3A). Furthermore, in the subgroup analysis for study groups, significantly larger improvements in the 100-mm VAS were also noted in the ASC (SMD, 1.32; 95% CI, 0.88-1.76; $I^2 = 72\%$; $Z = 5.87$; $P < .0001$) and ADSVF (SMD, 3.64; 95% CI, 2.47-4.82; $Z = 6.06$; $P < .0001$) groups than in the controls.

A total of 3 studies reported a 100-mm VAS improvement at 12 months, and the total mean improvement was significantly higher in the overall study groups than in the controls (SMD, 1.65; 95% CI, 1.20-2.10; $I^2 = 82\%$; $Z = 7.21$; $P < .0001$) (Figure 3B). Furthermore, in the subgroup analysis for study groups, significantly higher improvements in the 100-mm VAS score were noted in the ASC (SMD, 1.37; 95% CI, 0.87-1.87; $I^2 = 80\%$; $Z = 5.35$; $P < .0001$) and ADSVF (SMD, 2.81; 95% CI, 1.80-3.82; $Z = 5.45$; $P < .0001$) groups than in the controls.

Function Improvement (Total WOMAC Score)

In total, 4 studies reported a total WOMAC score at 6 months, and the total mean improvement was significantly higher in the overall study groups than in the controls (SMD, 0.75; 95% CI, 0.39-1.11; $I^2 = 64\%$; $Z = 4.13$; $P < .0001$) (Figure 4A). Furthermore, in the subgroup analysis for study groups, significantly higher improvements in the total WOMAC score were noted in the ASC (SMD, 0.65; 95% CI, 0.24-1.05; $I^2 = 72\%$; $Z = 3.12$; $P = .002$) and ADSVF (SMD, 1.09; 95% CI, 0.35-1.83; $Z = 2.90$; $P = .004$) groups than in the controls at 6 months.

We found that 3 studies reported total WOMAC score improvement, and the total mean improvement was significantly larger in the overall study groups than in the controls (SMD, 0.83; 95% CI, 0.40-1.26; $I^2 = 87\%$; $Z = 3.79$; $P = .0002$) (Figure 4B). Furthermore, in the subgroup analysis for study groups, significantly higher improvements in the total WOMAC score were noted in the ASC (SMD, 0.67; 95% CI, 0.19-1.14; $I^2 = 92\%$; $Z = 2.76$; $P = .006$) and ADSVF (SMD, 1.60; 95% CI, 0.57-2.63; $Z = 3.05$; $P = .002$) groups than in the controls at 12 months.

MRI Outcome (Cartilage or Structural Change)

All included studies reported MRI outcomes in terms of cartilage or structural changes after IA injection of ASCs or ADSVFs. A meta-analysis could not be performed owing to heterogeneity in the methods of assessment and a lack of studies. Details of the MRI assessment are shown in Table 3.

Among the 5 studies, 3 studies reported significantly better changes in cartilage status in the ASC or ADSVF

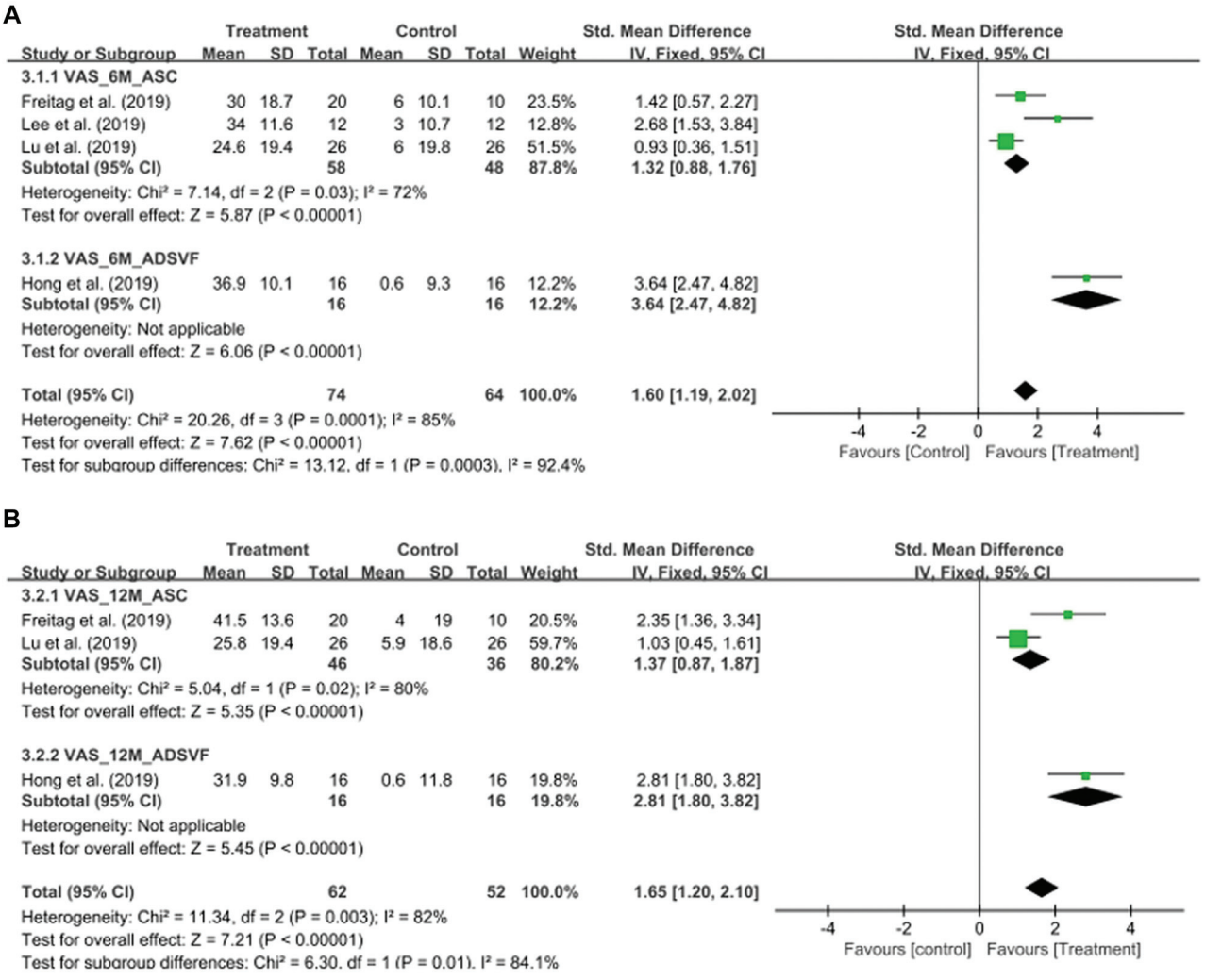

Figure 3. Forest plots of the included studies showing improvement in the 100-mm visual analog scale (VAS) score at (A) 6 months and (B) 12 months after intra-articular injection of adipose-derived stem cells (ASCs) or adipose-derived stromal vascular fractions (ADSVFs) compared with controls. Squares represent the mean difference in outcomes, with the size of the square being proportional to the sample size. IV, inverse variance; Std, standard.

groups than in the controls,[16,26,30] whereas 2 studies reported no significant change.[10,11]

Among the 3 studies on ASC treatment, 1 study reported no significant difference compared with the control based on MRI osteoarthritis knee score (MOAKS).[10] Another study reported a significantly increased cartilage defect size in the control group compared with no significant change in the ASC group at 6 months,[26] and yet another reported significantly increased cartilage volume change at 6 and 12 months in the ASC group compared with the control group.[30]

Among 2 studies of ADSVF treatment, 1 study reported that ADSVFs significantly improved the Whole-Organ Magnetic Resonance Imaging Score (WORMS) and magnetic resonance observation of cartilage repair tissue (MOCART) score at 6 and 12 months compared with the control group,[16] whereas no difference was reported in the change of cartilage thickness and Outerbridge classification between the ADSVF and control groups after treatment at 6 or 12 months.[11]

Safety

Procedure-related knee pain or swelling was reported in all included studies at 46% and 46.7% in the treatment and control groups, respectively. The pooled estimate of risk ratio was 1.02 (95% CI, 0.77-1.33; I^2 = 52%; Z = 0.11), with no significant difference (P = .91) (Figure 5).

Details of AEs in the included studies are shown in Table 4; no SAEs of ASC or ADSVF treatment were reported in the included studies. Only 1 patient in the HA group had an infection at 2 months and consequently underwent arthroscopic debridement.[30]

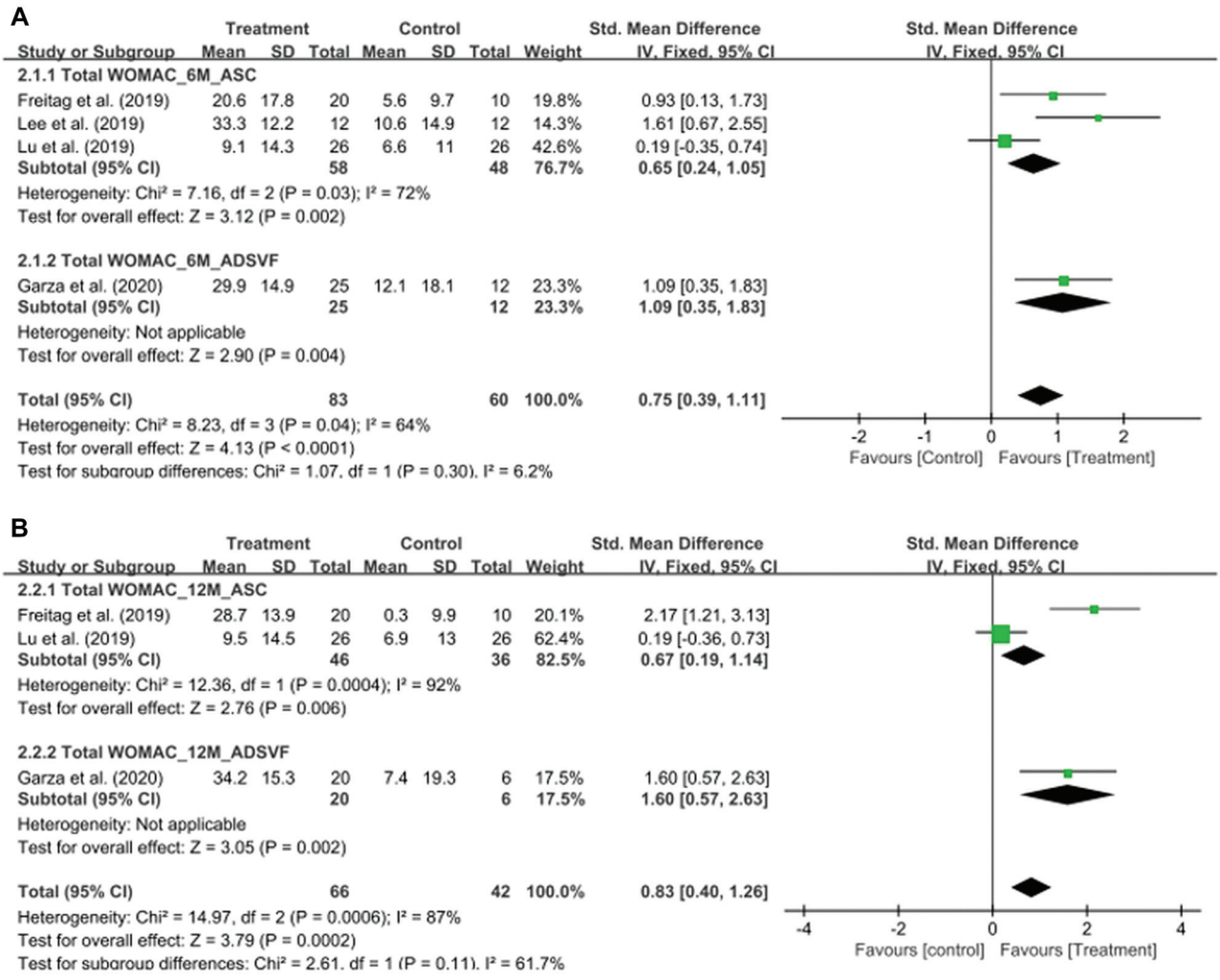

Figure 4. Forest plots of the included studies showing improvement in total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at (A) 6 months and (B) 12 months after intra-articular injection of adipose-derived stem cells (ASCs) or adipose-derived stromal vascular fractions (ADSVFs) compared with controls. Squares represent the mean difference in outcomes, with the size of the square being proportional to the sample size. IV, inverse variance; Std, standard.

Subgroup Analysis (ASC vs ADSVF)

No significant differences were found between ASC and ADSVF treatments regarding improvement of VAS or total WOMAC scores at 6 and 12 months (Table 5). However, limited evidence remains owing to heterogeneous individual conditions and low statistical power.

DISCUSSION

The principal findings of this meta-analysis were that ASC or ADSVF treatments had advantages over placebo or HA with respect to pain and functional improvement at 6 and 12 months without a significant difference in procedure-related knee pain or swelling. However, ASCs or ADSVFs had limited evidence for cartilage repair using MRI evaluation in the current review. No SAEs were reported after ASC or ADSVF IA injection. In addition, a subgroup analysis revealed similar efficacy in pain and functional improvement between ASCs and ADSVFs, although a direct comparison is necessary for the future.

This meta-analysis revealed that autologous ADMSC injection induced significant pain relief at 6 and 12 months compared with placebo or HA injection. All ASC and ADSVF groups in the included studies showed significant differences in pain improvement after treatment and between the treatment and control groups. The mean improvement of VAS ranged from 24.6 to 36.9 at 6 months and from 25.8 to 41.5 at 12 months in the ASC or ADSVF groups, whereas the mean improvement of VAS ranged from 0.6 to 6 at 6 months and from 0.6 to 5.9 at 12 months in the control groups. Freitag et al[10] showed that pain improvement above the minimal clinically important difference (MCID) on VAS at 12 months was 94.4% in the ASC group but 40% in the control group. Recent meta-

TABLE 3
MRI Assessment of Cartilage Regeneration on Osteoarthritis[a]

Lead Author (Year) Cell Type	Assessment	MRI Protocol	F/U, mo	Cartilage Pathology		Overall Results of Cell Therapy
				Study	Control	
Freitag[10] (2019) ASC	MOAKS	1.5-T or 3.0-T standard sequence (PDFS)	12	Improved: 1/19 (5.3%) No change: 14/19 (73.7%) Progression: 4/19 (21.0%)	Improved: 0/9 (0%) No change: 3/9 (33%) Progression:6/9 (67%)	Tended to be better in the ASC group than in the control group, but not significant Modified disease progression
Garza[11] (2020) ADSVF	Cartilage thickness (change)	1.5-T or 3.0-T with standard sequence	6	–0.2 mm	+ 0.5 mm	No difference
			12	–0.1 mm	+ 0.8 mm	No change after treatment
	Outerbridge grade (change)		6	0	0	
			12	0	0	
Hong[16] (2019) ADSVF	WORMS	3.0-T with standard sequence (PDFS)	6	Improved: 7.8 (cartilage), 11.4 (total)	Deteriorated: 2.6 (cartilage), 12.8 (total)	Significant improvement in the study group at 6 and 12 months
			12	Improved: 12.0 (cartilage), 15.4 (total)	Deteriorated: 4.1 (cartilage), 15.5 (total)	Significant deterioration in the control group at 6 and 12 months
	MOCART score		6	Complete: 12.5% Hypertrophy: 31.25% Incomplete: >50%: 25% <50%: 18.65% SB exposure: 12.5% Total: 54.1 ± 11.6	Complete: 0% Hypertrophy: 6.25% Incomplete: >50%: 12.5% <50%: 25.0% SB exposure: 56.25% Total: 19.4 ± 9.6	Significant improvement in the study group at 12 months Deterioration in the control group at 6 and 12 months
			12	Complete: 31.25% Hypertrophy: 37.5% Incomplete: >50%: 12.5% <50%: 12.5% SB exposure: 6.25% Total: 62.8 ± 8.2	Complete: 0% Hypertrophy: 6.25% Incomplete: >50%: 12.5% <50%: 18.75% SB exposure: 62.5% Total: 19.1 ± 7.8	
Lee[26] (2019) ASC	Cartilage defect size (change)	3.0-T with standard sequence (PDFS)	6	+ 2.4 ± 14.5 mm^2	+ 35.6 ± 58.8 mm^2	No significant change in the ASC group; the defect size was significantly increased in the control group Significant difference in the degree of change between the 2 groups ASC treatment was better than placebo
Lu[30] (2019) ASC	Cartilage volume (change)	3.0-T with standard sequence (PDFS)	6	Significantly increased in the right knee	Significantly decreased in the left tibia	Significant difference in the left tibia and right femur (ASC treatment was better than HA)
			12	Significantly increased in both femurs	No significant change	Significant difference in both femurs ASC treatment was better than HA

[a]ADSVF, adipose-derived stromal vascular fraction; ASC, adipose-derived stem cell; F/U, follow-up; HA, hyaluronic acid; MOCART, magnetic resonance observation of cartilage repair tissue; MOAKS, MRI Osteoarthritis Knee Score; MRI, magnetic resonance imaging; PDFS, proton density fat saturated; SB, subchondral bone; WORMS, Whole-Organ Magnetic Resonance Imaging Score.

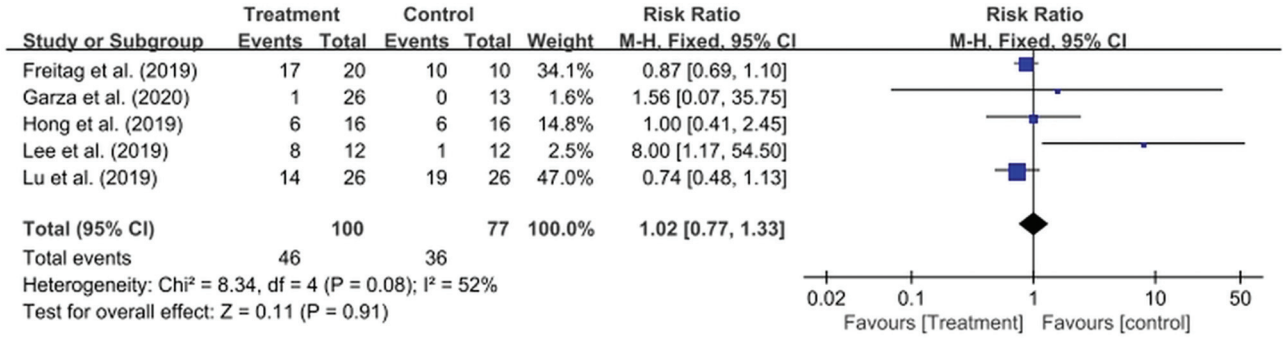

Figure 5. Forest plots of the included studies showing procedure-related knee pain or swelling after intra-articular injection of adipose-derived stem cells (ASCs) or adipose-derived stromal vascular fractions (ADSVFs) compared with controls. Squares represent the mean difference in outcomes, with the size of the square being proportional to the sample size. IV, inverse variance; M-H, Mantel-Haenszel.

TABLE 4
Adverse and Serious Adverse Events in the Included Studies[a]

Lead Author (Year) Cell Type	Study Sample Size	Adverse Events	Serious Adverse Events
Freitag[10] (2019) ASC	20	None: 15%. Mild: 55%. Moderate: 20%. Severe: 10% had pain and swelling for 4 weeks and observed an effect on their usual daily activity.	None
Garza[11] (2020) ADSVF	26	3 patients (11.5%) had minor adverse events. 1 patient reported knee swelling, and 2 patients reported possible bacterial growth; however, none was due to an infection.	None
Hong[16] (2019) ADSVF	16	4 patients (25%) had abdominal pain. 6 patients (37.5%) had pain and swelling in knee joints. All of these events were resolved by pain medication.	None
Lee[26] (2019) ASC	12	10 patients (83%) in the ASC group and 7 patients (58%) in the control group had adverse events. 8 patients (66.75%) in the ASC group had treatment-related adverse events, including arthralgia in 6 patients and joint effusion in 2 patients. All of these events were resolved by pain medication.	None
Lu[30] (2019) ASC	26	Similar proportion between the ASC (73.1%) and the HA (55.9%) groups. The most common symptoms were pain and swelling of the injection site. Spontaneous relief within 7 days without special treatment.	None for the ASC group 1 for the HA group (infection 2 months after injection)

[a]ADSVF, adipose-derived stromal vascular fraction; ASC, adipose-derived stem cell; HA, hyaluronic acid.

TABLE 5
Weighted Standard Mean Differences of Outcomes After Subgroup Analysis Comparing ASC and ADSVF Treatment[a]

Outcome or Subgroup	No. of Studies	Standardized Mean Difference (Standardized Variance)	95% CI	Significance
Improvement of 100-mm VAS score at 6 mo (ASC vs ADSVF)	4	–0.325 (0.080)	–0.881 to 0.231	No significance
Improvement of 100-mm VAS score at 12 mo (ASC vs ADSVF)	3	0.042 (0.085)	–0.527 to 0.611	No significance
Improvement of total WOMAC score at 6 mo (ASC vs ADSVF)	4	–0.200 (0.057)	–0.067 to 0.270	No significance
Improvement of total WOMAC score at 12 mo (ASC vs ADSVF)	3	–0.277 (0.072)	–0.804 to 0.250	No significance

[a]ADSVF, adipose-derived stromal vascular fraction; ASC, adipose-derived stem cell; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

analyses showed a significant pain reduction at 6 and 12 months after the administration of MSCs from adipose tissue,[8,14,19,48] although Jeyaraman et al[19] reported that no difference was noted in pain improvement at 12 months between the treatment and control groups. The inconsistent results and differences compared with our meta-analysis may be because previous studies included allogenic MSCs and adjuvant surgeries for HTO and microfracture, which could not fully reflect the efficacy in pain reduction by ASCs or ADSVFs alone. As mentioned above, we demonstrated that ASCs or ADSVFs significantly improved 100-mm VAS scores at 6 and 12 months compared with placebo or HA. With these points in mind, IA autologous ASC or ADSVF injections without any additional treatments would be an attractive option for pain relief in knee OA at 12 months.

The results of this review revealed that ASC or ADSVF injections led to a significant functional improvement in the total WOMAC score at 6 and 12 months compared with placebo or HA injection. Of the 5 included studies, 4 studies reported a significant improvement after treatments and better improvement compared with controls in the total WOMAC score at 6 and 12 months. Lu et al[30] showed that the difference in the improvement at 6 and 12 months did not reach statistical significance between ASCs (31.7% and 28.5%, respectively) and HA (20.2% and 20.7%, respectively). However, those investigators reported that ASC treatment was superior to HA in terms

of improvement in quality of life because ASC treatment showed a significantly better improvement than HA on the 36-Item Short Form Health Survey. In total, 2 of the included studies reported improvement above MCID in the total WOMAC score: Garza et al[11] showed that 62% of their ADSVF group and 38% of their placebo group had a WOMAC score above MCID at 6 months, whereas Freitag et al[10] showed that 94.4% of their ASC group and 20% of their placebo group were above MCID at 12 months. Further, 4 included studies showed that a significant difference started to appear after 3 months because the control groups had worsened or experienced no change.[10,11,16,26] According to recent systematic reviews and meta-analyses, controversy remains regarding functional efficacy of ASCs or ADSVFs,[8,13,14,17,19,35,48] which results from heterogeneity of the inclusion criteria of these reviews. Adjuvant treatments, such as cartilage repair, HTO, or other adjuvant cell therapies, including PRP, may affect the results because these procedures also enhance functional scores in addition to the MSC treatments.[1,13,20,23] Based on our findings, this review suggests that IA autologous ASC or ADSVF injections can be a viable therapeutic option to achieve functional improvement in patients with knee OA.

The efficacy of ASCs or ADSVFs in cartilage regeneration remains unclear in this systematic review. A quantitative meta-analysis could not be performed because the included studies evaluated cartilage change using different methods, such as the WORMS, MOAKS, and MOCART scores; the Outerbridge classification; and cartilage thickness, cartilage defect area, and cartilage volume using MRI. Thus, we describe the qualitative MRI results of cartilage changes in Table 3, which shows that among the 5 studies, 3 studies[16,26,30] showed that cartilage change was significantly better in the ASC or ADSVF groups compared with controls, 1 study[10] showed a tendency for better cartilage changes in ASC treatment compared with placebo without statistical significance, and 1 study[11] showed no significant differences between the 2 study groups. Recent systematic reviews have reported that the efficacy of MSCs for cartilage repair has limited evidence, which is consistent with our results.[8,13,17,33,48] Despite the limited evidence on cartilage regeneration, many clinical studies have suggested that MSCs, including ASCs and ADSVFs, have potential efficacy for cartilage regeneration in patients with knee OA.[16,18,24,26,30,49] Therefore, we believe that more high-quality, well-designed studies with long-term follow-up and no adjuvant treatments are necessary to draw a conclusion concerning the efficacy of ASC or ADSVF treatments for cartilage regeneration in patients with knee OA.

Safety has been a concern for clinicians regarding the administration of MSCs.[5,38,49] Procedure-related knee pain and swelling are the most common side effects after IA injection therapies.[5,33,38] Our meta-analysis showed no difference in procedure-related pain or swelling between ASC or ADSVF groups and their controls, which is consistent with recent meta-analyses.[19,48] Minor discomfort and bruising were commonly noted at the lipoharvested site, although liposuction has shown a very low complication rate of approximately 0.1%.[45] Fortunately, all of these AEs resolved spontaneously or with pain relievers in a few days, and no SAEs were reported after ASC or ADSVF injection, although 1 patient had an infection with consequent surgery after HA injection. The results of recent systematic reviews were in accordance with our result that no SAEs, such as death, malignancy, or systemic reactions, that were definitely related to MSC injection were identified.[5,19,33,38,48] Based on this review, autologous IA ASC or ADSVF injection is a safe therapeutic option for patients with knee OA; however, as this evidence is limited to $\leq$1 year, long-term studies are warranted to guarantee confidence in the safety of ASC or ADSVF treatments.

ASCs and ADSVFs are commonly used types of MSC-based therapy from adipose tissue, but the terms used in previous clinical studies have been inconsistent and confusing.[13,17,50] Theoretically, ASCs are assumed to have higher potential efficacy than ADSVFs, but ASCs require time and costs for culture with cell expansion.[2,28,50] In contrast, ADSVFs are convenient because they are injected directly after tissue digestion and lavage of liberated cells, without cell-expansion culture; however, ADSVFs inevitably contain heterogeneous cells, including approximately only 9.2% MSCs, as well as hematopoietic, vascular, and stromal cells.[2,17,19,28,50] The current study also showed different cell concentrations, such as 0.8-3.0 $\times 10^7$ cells in the ADSVF group and 5-10 $\times 10^7$ cells in the ASC group. Recent reviews have reported comparable efficacy between the 2 methods,[17,19,29] whereas the only study that directly compared the 2 methods showed that ASCs outperformed ADSVFs in early improvement with less comorbidity.[50] Although our subgroup analyses were consistent with most reviews, these studies do not allow us to draw a conclusion about the efficacy between ASCs and ADSVFs because the indirect comparison had inherent statistical limitations. Rather, a direct comparison study may have stronger evidence than indirect comparisons suggesting the potential superiority of ASCs.[50] In addition, a higher number of MSCs tended to show advantageous long-term effects according to recent meta-analyses,[8,19] and the counted ADSVF cells in groups of the included studies were not only pure MSCs but also stromal vascular fraction (SVF) cells.[11,16] Thus, the current study has limited evidence to show the clinical efficacy of ASCs and ADSVFs. Further studies with direct comparison, longer-term follow-up, higher cell qualities, and identical cell counts are required to select the best strategy for this application.

This study has several limitations that need to be addressed. First, the number of studies and the sample sizes were small because we included studies that entailed strict designs (such as RCTs), autologous cells, patients without adjuvant treatments, and direct injections without transplantation to avoid heterogeneity. To the best of our knowledge, only 5 RCTs satisfying these inclusion strategies existed in 2020. Second, the heterogeneity in cell concentrations, passage of cell expansion, and control groups may have produced a potential risk of bias despite the strict inclusion criteria. Third, we were not able to perform a quantitative analysis of cartilage repair on MRI

assessment owing to the variety of imaging modalities; thus, we described a qualitative analysis, although this limited the evidence. Fourth, the short-term follow-up of the included studies does not guarantee the safety of cell-based therapy from adipose tissue; thus, high-quality studies with long-term follow-up are necessary to demonstrate the long-term efficacy and safety of this treatment. However, this meta-analysis included studies with strict and homogeneous conditions because we excluded possible confounders, such as allogenic sources, biologic adjuvants, and adjuvant treatments. This contributed to the strength of this study, which attempted to demonstrate the differential efficacy of ASCs or ADSVFs for the management of patients with knee OA. The current review demonstrates the interest in the scientific field for this nonoperative therapeutic approach, which may potentially contribute to the introduction of a new paradigm for the treatment of knee OA.

CONCLUSION

For patients with knee OA, intra-articular injection of autologous ASCs or ADSVFs without adjuvant treatment showed remarkable clinical efficacy and safety at a short-term follow-up. Some efficacy has been shown for cartilage regeneration in knee OA, although the evidence remains limited. Further RCTs that directly compare ASCs and ADSVFs are needed.

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