Systematic Review

Regenerative Potential of Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis and Chondral Defects: A Systematic Review and Meta-analysis

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Purpose: To perform a systematic review and meta-analysis evaluating the effects of mesenchymal stem cells (MSCs) on cartilage regeneration and patient-reported pain and function. **Methods:** A systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using a PRISMA checklist. The Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, PubMed (2008-2019), EMBASE (2008-2019), and MEDLINE (2008-2019) were queried in July 2019 for literature reporting use of stem cells to treat knee osteoarthritis or chondral defects. Data describing administered treatment, subject population, injection type, duration of follow-up, pain and functional outcomes, and radiographic and magnetic resonance imaging findings were extracted. Risk of bias was assessed using the Downs and Black scale. Meta-analyses adjusted for random effects were performed, calculating pooled effect sizes in terms of patient-reported pain and function, cartilage quality, and cartilage volume. **Results:** Twenty-five studies with 439 subjects were identified. There was no significant difference in pain improvement between MSC treatment and controls (pooled standardized mean difference [SMD] = 0.23, $P = .30$). However, MSC treatment was significantly favored for functional improvement (SMD = 0.66, $P < .001$). There was improvement in cartilage volume after MSC treatment (SMD = 0.84, $P < .001$). Regarding cartilage quality, meta-analysis resulted in a small, nonsignificant effect size of 0.37 (95%, −0.03 to 0.77, $P = .07$). There was risk for potential bias among included studies, with 17 (68%) receiving either a grade of "poor" or "fair." **Conclusions:** The pooled SMD from meta-analyses showed statistically significant effects of MSC on self-reported physical function but not self-reported pain. MSCs provided functional benefit only in patients who underwent concomitant surgery. However, this must be interpreted with caution, as there was substantial variability in MSC composition and mode of delivery. MSC treatment provided significant improvement in cartilage volume but not cartilage quality. Preliminary data regarding therapeutic properties of MSC treatment suggest significant heterogeneity in the current literature, and risk of bias is not negligible. **Level of Evidence:** II, Systematic Review and Meta-analysis

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Osteoarthritis (OA) is one of the most frequent reasons for adult medical office visits and one of the most common causes of joint pain and disability, with more than 30 million symptomatic adults in the United States.[1] The health care cost of OA continues to grow due to increased patient longevity and the increasing prevalence of obesity. In 2013, the combined cost of medical care and lost wages due to OA exceeded $300 billion.[2,3] Currently, the mainstays of nonoperative treatment include activity modification, physical therapy, nonsteroidal anti-inflammatory drugs, and intra-articular injections of corticosteroid or hyaluronic acid. Unfortunately, none of these treatment options slow or reverse the progression of cartilage degeneration.

Mesenchymal stem cells (MSCs) have been extensively studied as a promising solution to alleviate symptomatic knee OA through pleiotropic effects on the local environment.[4] Attractive therapeutic properties of MSCs include immunosuppressive activity, multilineage potential, and a simple growth process in vitro.[5] MSCs also exhibit paracrine effects, which may impart therapeutic benefit even in the absence of tissue-specific differentiation.[6] Several meta-analyses have evaluated the efficacy of MSCs in the treatment of OA and chondral defects, focusing on the impact of MSCs on psychometric measures of pain and physical function.[7-10] Although these studies help validate the use of stem cells for clinical use, limited research has investigated the effect of MSCs on structural cartilage changes in this population. Furthermore, the potential for bias in assessing MSC effect on cartilage regeneration is likely to be high due to heterogeneity in study methodologies and treatment response due to challenges in blinding and randomization.

Multiple metrics have been described to evaluate cartilage quality and quantity, including the magnetic resonance observation of cartilage repair tissue (MOCART),[11] whole-organ magnetic resonance imaging score,[12] and T2 mapping values.[13] A recent meta-analysis reported the effect of MSC treatment on cartilage volume and quality; however, this study only analyzed changes in cartilage morphology in MSC treatment groups alone.[8]

Therefore, the purpose of this study is to perform a systematic review and meta-analysis evaluating the effects of MSCs on cartilage regeneration and patient-reported pain and function. It was hypothesized that treatment of knee OA and chondral defects with MSCs would result in significant improvements in patient-reported pain and function, with limited improvement in cartilage regeneration (i.e., cartilage volume and quality) relative to controls.

Methods

Article Identification and Selection

This study was conducted in accordance with the 2009 Preferred Reporting Items for Systematic Review and Meta-Analysis statement (Fig 1).[14] The Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, PubMed (2008-2019), EMBASE (2008-2019), and MEDLINE (2008-2019) were queried in July 2019 for literature reporting on the use of stem cells to treat OA or chondral defects of the knee. Database queries were performed using the following Boolean search terms: knee AND osteoarthritis AND cartilage AND (stem cells OR stromal cells OR transplantation). Inclusion criteria were all studies with level of evidence I or II concerning stem cell use in treating OA or knee chondral defects. Studies that were level of evidence 3 or greater were excluded. We excluded studies investigating effects of stem cell treatments without adequate number of cell counts (i.e., bone marrow aspirate concentrate). In addition, we excluded studies with inadequate study design, blinding, or randomization. Two investigators (B.M. and E.M.P.) independently screened articles sequentially based on title, followed by abstracts, and finally full text, when appropriate (Fig 1). Full-text articles were reviewed if further assessment of inclusion and exclusion criteria was required. All references from included studies were screened to identify additional articles absent from the primary query. Systematic review registration was submitted in July 2019 for review by the PROSPERO International prospective registrar of systematic reviews.

Outcome Measures and Data Extraction

The primary outcomes evaluated in this systematic review were (1) self-reported pain, (2) self-reported physical function, and (3) structural changes in articular cartilage (i.e., cartilage volume and quality) assessed via magnetic resonance imaging (MRI). A customized spreadsheet including a modified information extraction table was created to record all relevant data from the included studies, including publication information, study design (i.e., prospective cohort studies, nonrandomized comparative studies, and randomized controlled trials [RCTs]), level of evidence, treatment, subject population, treatment details, duration of follow-up, pain and functional outcome measures, and radiographic and MRI findings. All data was analyzed qualitatively using descriptions of study methods, results, and conclusions. Articles reporting outcomes using multiple pain and function scales were assessed according to the psychometric outcome hierarchy detailed previously in the literature.[8,15-17]

Risk of Bias Assessment

Two investigators (B.M. and E.M.P.) independently assessed risk of bias using the Downs and Black scale.[18] Disagreements between raters were resolved by consensus. To summarize, this numerical scale is composed of 27 questions, including quality of reporting (10 questions), external validity (3 questions), internal validity (bias and confounding, 13 questions),

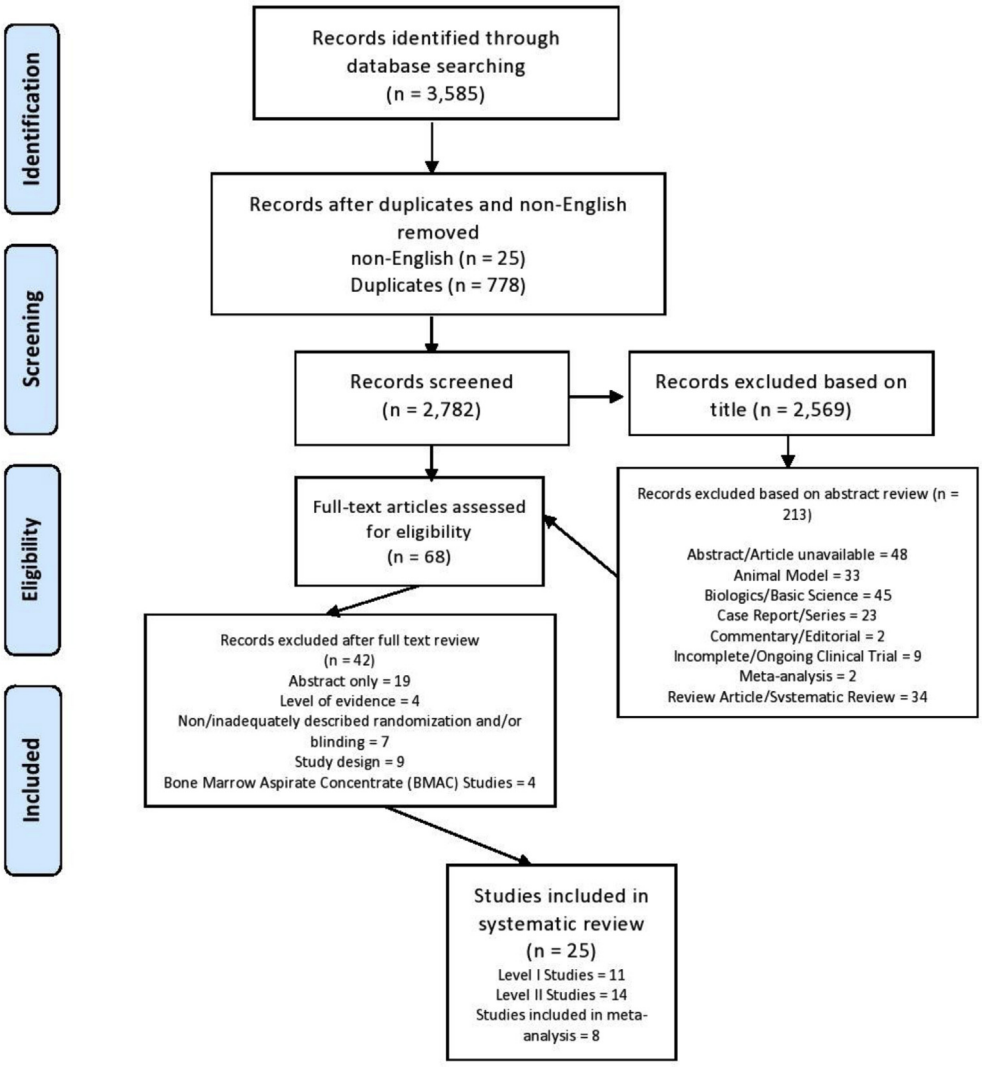

Fig 1. PRISMA diagram outlining steps included in the systematic review of queried articles. (PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis.)

and statistical power (1 question). Originally, the score was of 32 possible points with the statistical power question having a maximum of 5 points. However, in accordance with previous studies, a simplified scale was used in which statistical power received a maximum of 1 point if sufficiently powered to detect a meaningful difference.[19-21] The modified Downs and Black scale was used to assign each included article a categorical grade of "excellent" (24-28 points), "good" (19-23 points), "fair" (14-18 points), or "poor" (<14 points).[22]

Statistical Analysis

For the meta-analyses, pooled estimates of effect sizes were calculated using a random effects model for the primary outcomes of self-reported pain and physical function, and cartilage structural changes. Standardized mean differences (SMD) and 95% confidence interval (CI) were used to assess outcome improvement from baseline to the longest follow-up time point, comparing subjects receiving MSCs and controls. For outcomes measured with different assessment tools, such as self-reported physical function and cartilage quality, individual studies in the meta-analyses were grouped according to scoring metric.[8] The magnitude of the SMD was assessed according to Cohen's d estimate.[23] To summarize, <0.5, 0.5-0.8, and >0.8 correspond to small, medium, and large effect sizes, respectively. Considering the clinical interpretation of SMD is often ambiguous, mean differences in change (pre-to-post delta score) between MSC and control cohorts for the primary outcomes were also calculated and compared to established values of minimum clinically important difference (MCID). Study heterogeneity was assessed with I-squared (I^2) tests. Furthermore, sensitivity analyses were performed to explore the effects of MSC administration through computation of pooled SMD for outcome data from studies with MSC administered via injection and MSC administered concomitantly with a

Table 1. Summary of Included Level I Studies

			Study Group					Control Group						
Study	Level of Evidence	K-L Inclusion	Knees, n	Mean Age, y	M/F	Treatment (Dose)	Donor	Knees, n	Mean age, y	M/F	Treatment (Dose)	Objective Evaluation of MRI	Follow-Up	Downs and Black (Score, Grade)
Akgun et al.[25]	I (RCT)	Grade III-IV	14	32.3 ± 7.9	4/3	Matrix-induced MSC	Auto	7	32.7 ± 10.4	4/3	m-ACI	No	6, 12, 24 mo	19, Good
Gupta et al.[26]	I (RCT)	Grade I-III	40*	56.1 ± 7.7*	12/28*	BD-MSC	Allo	20*	55.8 ± 6.8*	3/17*	–	No	12 mo	18, Fair
Goncars et al.[27]	I (RCT)	Grade II-III	28	53.44	15/13	–	Auto	31	58.55	10/21	–	No	12 mo	13, Poor
Hashimoto et al.[28]	I (RCT)	Grade I-III	7	42.6	3/4	Cell-t group	Auto	4	46.3	4/0	Placebo	Yes	48 wk	15, Fair
Koh et al.[29]	I (RCT)	Grade I-II	21	54.2 ± 2.9	5/16	MSC-PRP	Auto	23	52.3 ± 4.9	6/17	PRP only	No	24.6 mo	21, Good
Koh et al.[30]	I (RCT)	Grade I-II	40	–	14/26	MFX + ADSCs	Auto	40	–	16/24	MFX only	No	27.4 mo	18, Fair
Kuah et al.[31]	I (RCT)	Grade I-III	16	52.6	8/2	ADMSC (3.9 million)	Allo	4	55 ± 10.42	1/3	Placebo	No	12 mo	21, Good
Lee et al.[32]	I (RCT)	Grade II-IV	12	62.2 ± 6.5	3/9	ADMSC (1.0×10^8)	Allo	12	63.2 ± 4.2	3/9	Saline	Yes	6 mo	22, Good
Lu et al.[33]	I (RCT)	Grade I-IV	26	55.03	3/23	ReJoin MPC treatment (AD with cell suspension)	Auto	26	59.64	3/23	HA	Yes	12 mo	20, Good
Turajane et al.[34]	I (RCT)	Grade II-III	40†	55.15†	13/27†	AAPBSC + GFA + HA + MSC	Auto	20	54.7	6/14	HA alone	No	1 and 6 mo	18, Fair
Wong et al.[35]	I (RCT)	–	28	53	13/15	HTO + BD-MSC (1.5×10^7)	Auto	28	49	14/14	HTO	Yes	6, 12, 24 mo	19, Good
Vega et al.[36]	I (RCT)	Grade II-IV	15	57	13/17	BM-MSC (40×10^6)	Allo	15	–	–	HA	No	12 mo	13, Poor
Wakitani et al.[37]	I (RCT)	–	12	–	–	BM-MSC	Auto	12	–	–	Cell-free controls	No	16 mo	9, Poor

AAPBSC, autologous-activated peripheral blood stem cell; AD, adipose derived; ADMSC, adipose-derived mesenchymal stem cells; ADSC, adipose-derived stem cells; Allo, allograft; Auto, autograft; BD-MSC, bone marrow-derived mesenchymal stem cells; GFA, growth factor addition; HA, hyaluronic acid; HTO, high tibial osteotomy; K-L, Kellgren-Lawrence, m-ACI, matric-induced autologous chondrocyte implantation; M/F, male/female, MFX, microfracture; MPC, mesenchymal progenitor cell; MRI, magnetic resonance imaging, MSC, mesenchymal stem cell; MSC-PRP, mesenchymal stem cells-platelet rich plasma; RCT, randomized controlled trial.

*Study group: cohort 1: (low dose) N = 10, 58.1(8.2), 3/7 (mid-dose) N = 10, 57.3(9.5), 2/8; cohort 2: (high dose) N = 10, 55.0 (6.7) 2/8 (very high) N = 10, 54.0 (6.7) 5/5; control group: cohort 1: n = 10, 54.9 (8.3), 0/10; cohort 2: n = 10, 56.7 (5.2) 3/7.

†Group 1: n = 20, 54.9, 10/10, group 2: n = 20, 55.4 3/17.

Table 2. Summary of Included Level II Studies

			Study Group					Control Group						
Study	Level of Evidence	K-L Inclusion	Knees, n	Mean Age, y	M/F	Treatment (Dose)	Donor	Knees, n	Mean Age, y	M/F	Treatment (Dose)	Objective Evaluation of MRI	Follow-Up	Downs and Black (Score, Grade)
Al-Najar et al.[38]	II (NRCS)	Grade II/III	13	50	6/7	1×10^6	Auto	–	–	–	–	Yes	24 mo	11, Poor
Chahal et al.[39]	II (NRCS)	Grade III-IV	12	40-65 (range)	–	BM-MSC (1×10^6, 10×10^6, 50×10^6)	Auto	–	–	–	–	Yes	12 mo	12, Poor
Jo et al.[40]	II (NRCS)	Grade lII-IV	18*	62.3 ± 7.1*	3/15*	AD-MSC*	Auto	–	–	–	–	Yes	6 mo	16, Fair
Kim et al.[41]	II (NRCS)	Grade I-II	17	57.7	8/9	AD-MSC w/ scaffold	Auto	37	57.5	14/23	MSC no scaffold	No	28.6 mo	15, Fair
Kim et al.[42]	II (NRCS)	Grade III-IV	50	59.2	16/34	HTO + AD-MSC	Auto	50	58.3	16/34	HTO	No	12.7 mo	16, Fair
Pers et al.[43]	II (NRCS)	Grade III-IV	18†	64.7 ± 4.8	8/10†	AD-SVF†	Auto	–	–	–	–	Yes	1 wk and 3, 6 mo	14, Fair
Park et al.[44]	II (NRCS)	Grade III	7	58.7 ± 15.4	2/5	Umbilical blood-MSC	Allo	–	–	–	–	No	24 wk	14, Fair
Spasovski et al.[45]	II (NRCS)	–	9	–	–	AD-MSC ($0.5\text{-}1 \times 10^7$)	Auto	–	–	–	–	No	18 mo	10, Poor
Song et al.[46]	II (NRCS)	Grade 0-IV	18	–	–	AD-MSC (1×10^7, 2×10^7, 5×10^7)	Auto	–	–	–	–	No	96 wk	22, Good
Kim et al.[47]	II (SAPS)	Grade I-II	24	57.9	11/9	AD-MSC	Auto	–	–	–	–	Yes	27.9	16, Fair
Koh et al.[48]	II (SAPS)	Grade I-III	25	54.2 ± 9.3	8/17	MSC + PRP + debridement (1.89×10^6)	Auto	25	54.4 ± 11.3	8/17	PRP + arthroscopy	No	16.4 mo	19, Good
Kim et al.[49]	II (SAPS)	Grade I-II	40	59.2 ± 3.3	14/26	MSC + PRP or fibrin scaffold	Auto	–	–	–	–	No	28.6 mo	16, Fair

ADMSC, adipose-derived mesenchymal stem cells; AD-SVF, adipose derived stromal vascular fraction; Allo, allograft; Auto, autograft; BM-MSC, bone marrow-derived mesenchymal stem cell; HTO, high tibial osteotomy; K-L, Kellgren-Lawrence; M/F, male/female; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; NRCS, nonrandomized comparative studies; PRP, platelet-rich plasma; SAPS, single-arm prospective study.

*Study group: n = 3, 63 (8.6), 1/2, low dose; n = 3, 63 (6.6), 0/3, mid dose; n = 12, 61 (6.2) 2/10, high dose; AD-MSC (low dose 1.0×10^7, mid dose 5.0×10^7, high dose 1.0×10^8).

†Study group: n = 6, 63.2 (4.1), 3/3, low dose; n = 6, 65.6 (8.1) 3/3, mid dose; n = 6, 65.2 (2.3) 2/4, high dose; AD-SVF injection (low dose: 2×10^6, mid dose: 10×10^6, high dose: 50×10^6 cells).

Table 3. Cell Therapy Descriptions for All Included Studies

Study	Source Site	Collection Technique	Initial V olume	Source	Cell Type	No. of Cells ($\times 10^6$)	Injection Site/ Technique	Delivery Solution	Qualitative Cell Characterization, CD markers	Successive Injections
Akgun et al.[25]	Synovia	From femoral condyles	5-mm cartilage chip	Auto	MSC	~8	NR	Implantation via mini-arthrotomy	CD105+, CD73+, CD90+, CD45−, CD34−, CD14−, CD79a-, HLA−DR−	None
Gupta et al.[26]	BMA	NR	In 15 mL PLASMA-LYTE A	Allo	BM-MSC	200	Lateral midpatellar	IMP injection followed by 2 mL HA	CD73+, CD105+, CD90+, CD166+, CD34−, CD45−, CD133−, CD14−, CD19−, HLA−DR−	None
Goncars et al.[27]	BMA	NR	45 mL of into heparin-treated syringes	Auto	BM-MNC	NR	NR	5-10 mL saline injected + MNCs	CD34+, CD45+	None
Hashimoto et al.[28]	BMA	From PSIS	30-40 mL	Auto	BM-MSC	NR	MFX of cartilage lesion	Suspended in 2.4 mL HA	CD44+, CD105+	None
Koh et al.[29]	Adipose	Tumescent liposuction	120 mL for injection, 20 for lab analysis	Auto	MADNC	48.3	Medial, arthroscopic guidance	In 3 mL PRP after arthroscopy, before HTO	CD90+, CD105+, CD45−, CD34−, CD14−	None
Koh et al.[30]	Adipose	Liposuction	NR	Auto	ADSC	NR	MFX 3-4 mm apart	SVF + MSC implanted into each well on cartilage lesion surface	CD90+, CD105+, CD34−, CD14−	None
Kuah et al.[31]	Adipose	NR	NR	Allo (1 donor)	AD-MSC	3.9, 6.7	NR	Intra-articular injection	NR	None
Lee et al.[32]	Adipose	Tumescent Lipoaspiration	20 mL adipose tissue	Auto	AD-MSC	100	US-guided intra-articular injection	MSCs in 3 mL of saline	CD31, CD34, CD35, CD73, CD90	None
Lu et al.[33]	Adipose	Liposuction	NR	Auto	AD-MPC	50	NR	~2.5 mL AD-MPC intra-articular injection	Profile of cultures conformed to ISCT criteria	Additional injection at wk 3, sham injections at wk 1 and 2
Turajane et al.[34]	Peripheral Blood	Leukapheresis and hG-CSF	3 mL, with portion frozen for intra-articular injection	Auto	AA-PBSC	1.0-1.3	Arthroscopic debridement and drillings of 2 mm	3 mL AAPBSC injected + 2 mL GFA concentrate from PRP + hG-CSF	CD34+, CD105+	One weekly injection for 3 wk

(continued)

Table 3. Continued

Study	Source Site	Collection Technique	Initial V olume	Source	Cell Type	No. of Cells ($\times 10^6$)	Injection Site/ Technique	Delivery Solution	Qualitative Cell Characterization, CD markers	Successive Injections
Wong et al.[35]	BMA	NR	49 mL (median)	Auto	BM-MSC	14.6	NR	0.5-1 mL autologous serum + 2 mL HA	CD73+, CD90+, CD105+, CD14-, CD20−, CD34−, CD45−	2 doses of 2 mL HA at weekly intervals
Vega et al.[36]	BMA	Multiple repeated aspiration (2-4 mL BMA) under iliac spine	80 mL	Allo	BM-MSC	40	Medial parapatellar	Suspended in Ringer lactate at 5×10^6 cells/mL	Profile of cultures conformed to ISCT criteria for MSCs	None
Wakitani et al.[37]	BMA	Both sides of iliac crest ~2 cm from ASIS	10 mL embedded in 2 mL of acid soluble collagen	Auto	BM-MSC	10	Medial Parapatellar	Cell-gel composite put on abraded area of knee	NR	None
Al-Najar et al.[38]	BMA	Multiple small aspirations from iliac crest	35-40 mL	Auto	BM-MNC	30.5	Lateral tibiofemoral	BM-MSCs suspended in 5 mL NS	Profile of cultures conformed to ISCT criteria for MSCs	2 injections given 1 mo apart
Chahal et al.[39]	BMA	PSIS	50 mL, with 25 mL collected for generating autologous serum	Auto	BM-MSC	30	NR	US-guided intra-articular injection	CD73, CD90, CD19, CD34, CD45, CD105, HLADR, CD14	None
Jo et al.[40]	Adipose	Liposuction	NR	Auto	AD-MSC	10, 50	Mesial portal of the knee	ADMSCs in 3 mL of saline injected	CD31, CD34, CD45, CD73, CD90	None
Kim et al.[41]	Adipose	Tumescent liposuction	140 mL, with 120 mL used for injection and 20 mL for analysis	Auto	AD-MSC	3.9	Arthroscopic implantation	Articular cartilage lesion filled with MSCs (group 1), Fibrin glue + thrombin/ fibrinogen solution (group 2)	CD90+, CD105+, CD14−, CD34−,	None
Kim et al.[42]	Adipose	Tumescent liposuction	NR	Auto	AD-MSC	4.26	Medial, arthroscopic guidance	NR	CD90+, CD105+, CD14−, CD34−	None
Pers et al.[43]	Adipose	Liposuction	10 g aliquots of adipose tissue	Auto	AASC	0.20	US-guided injection	5 mL single intra-articular dose of ASCs	CD90+, CD73+, CD105+, CD45−, CD14−, CD34−	None

(continued)

Table 3. Continued

Study	Source Site	Collection Technique	Initial V olume	Source	Cell Type	No. of Cells ($\times 10^6$)	Injection Site/ Technique	Delivery Solution	Qualitative Cell Characterization, CD markers	Successive Injections
Park et al.[44]	Human umbilical cord blood	From umbilical veins at time of neonatal delivery	NR	Auto	hUCB-MSC	5.0	Holes made at cartilage defect site of femoral condyle	MSCs Implanted in drill holes of lesions	Profile of cultures conformed to ISCT criteria for MSCs	None
Spasovski et al.[45]	Adipose	Small incision under local anesthesia	5 mL	Auto	AD-MSC	5-10	NR	MSC loaded into 2 mL syringes and injected into affected joint	CD34, CD45, CD73, CD90, CD105	None
Song et al.[46]	Adipose	Liposuction	NR	Auto	ha-MSCs	10, 20, 50	Medial portal under US guidance	3 mL cell suspension into both knee joints	CD90+, CD73+, CD49d+, CD14−, CD34−, CD45−, HLA-DR	3 injections at wk 0, and wk 3 and 6 after liposuction
Kim et al.[47]	Adipose	Liposuction	140 cc, with 120 cc used for implantation and 20 cc for cell analysis	Auto	AD-MSC	4.4	Under arthroscopic guidance after arthroscopic fluid extracted	Cell-thrombin-fibrinogen suspension applied using probe, coated at cartilage lesion surface	CD14, CD34, CD90, CD105	None
Koh et al.[48]	Adipose	Adipose tissue harvest from skin at arthroscopic lateral portal	9.2 g (6.9-11.2 g range)	Auto	MADNC	1.89	Lateral approach, upper pole of patella	In 3 mL PRP	NR	Two 3 mL PRP on days 7 and 14
Kim et al.[49]	Adipose	Tumescent liposuction	NR	Auto	ADMSC	4.01	Injection via arthroscopic guidance	MSCs + 3 mL PRP	CD90+, CD105+, CD34−, CD14−	None

AAPBSC, autologous-activated peripheral blood stem cell; AD-MPC, adipose derived mesenchymal progenitor cell; AD-MSC, adipose-derived mesenchymal stem cell; ADSC, adipose-derived stem cell; Allo, allograft; Auto, autograft; BMA, bone marrow aspirate; BM-MNC, bone marrow mononuclear cell; BM-MSC, bone marrow mesenchymal stem cell; GFA, growth factor addition; HA, Hyaluronic acid; ha-MSC, human adipose-derived mesenchymal stem cell; hG-CSF, granulocyte colony stimulating factor; HTO, high tibial osteotomy; hUCB-MSC, human umbilical cord blood-derived mesenchymal stem cell; IMP, investigational medicinal product; ISCT, International Society of Cell & Gene Therapy; MADNC, mixed adipose-derived nucleated cell; MFX, Microfracture; MNC, mononuclear cell; MSC, mesenchymal stem cell; NR, not recorded; NS, normal saline; PRP, platelet-rich plasma; SVF, stromal vascular fraction, US, ultrasound.

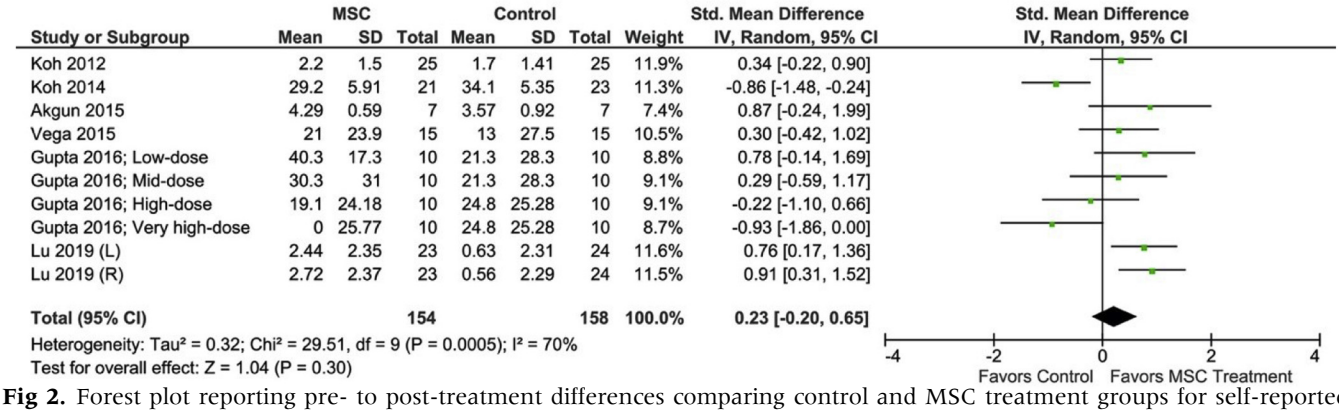

Fig 2. Forest plot reporting pre- to post-treatment differences comparing control and MSC treatment groups for self-reported knee pain, including the summary estimate (center of diamond) and 95% CI (width of diamond) at furthest follow-up. Means and SD are reported as numeric values on the VAS. (CI, confidence interval; IV, inverse variance; MSC, mesenchymal stem cell; SD, standard deviation; VAS, visual analog scale.)

surgical intervention (as this could act as a confounding factor). Statistical analyses were performed using Review Manager 5 (The Nordic Cochrane Center, Copenhagen, Denmark).[24]

Results

Study Characteristics

The database query yielded a total of 3585 studies, of which 25 studies satisfied all prespecified inclusion criteria. Because of extensive cross referencing and confirmation that no study data were replicated in included studies, there was no potential for duplicate data on the same patients across studies. Study characteristics of all studies, including those not used for meta-analyses, are described in Tables 1 and 2.[25-49] Of the 25 included level I and II studies, 3 (12%) had a single-arm, prospective design, 9 (36%) had a nonrandomized comparative study design, and 13 (52%) were RCTs. Dose-escalation studies were categorized as RCTs or nonrandomized comparative studies depending on study design. A total of 489 subjects across the included studies received MSC treatment for OA or chondral defects of the knee. The mean age of treatment subjects was 54.4 ± 7.2 years (range, 29.0-77.0 years). Seventeen studies (65%) included control arms, with a reported mean age of 53.4 ± 7.1 years (range, 18.0-70.0 years). Seventeen studies reported sex distributions for the treatment group (n = 440), with 269 female treatment

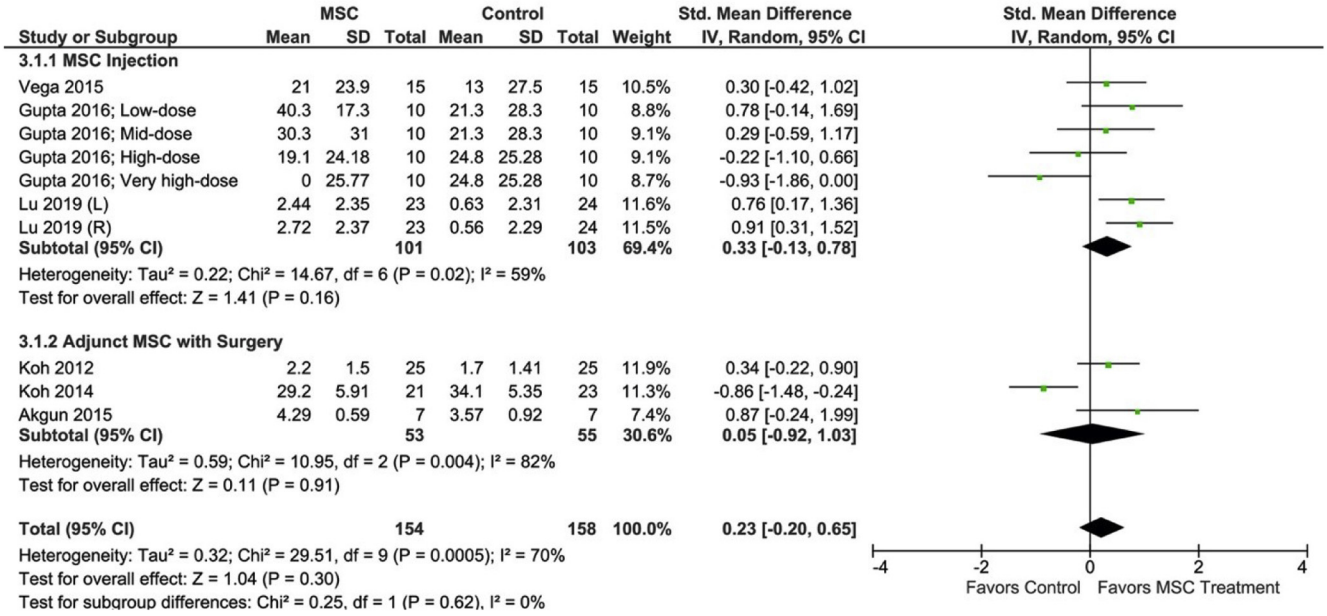

Fig 3. Forest plot reporting pre- to post-treatment differences comparing studies that administered MSC via injection only versus MSC administration in conjunction with a surgical adjunct, including the summary estimate (center of diamond) and 95% CI (width of diamond) at furthest follow-up. Means and SDs are reported as numeric values on the VAS. (CI, confidence interval; IV, inverse variance; MSC, mesenchymal stem cell; SD, standard deviation; VAS, visual analog scale.)

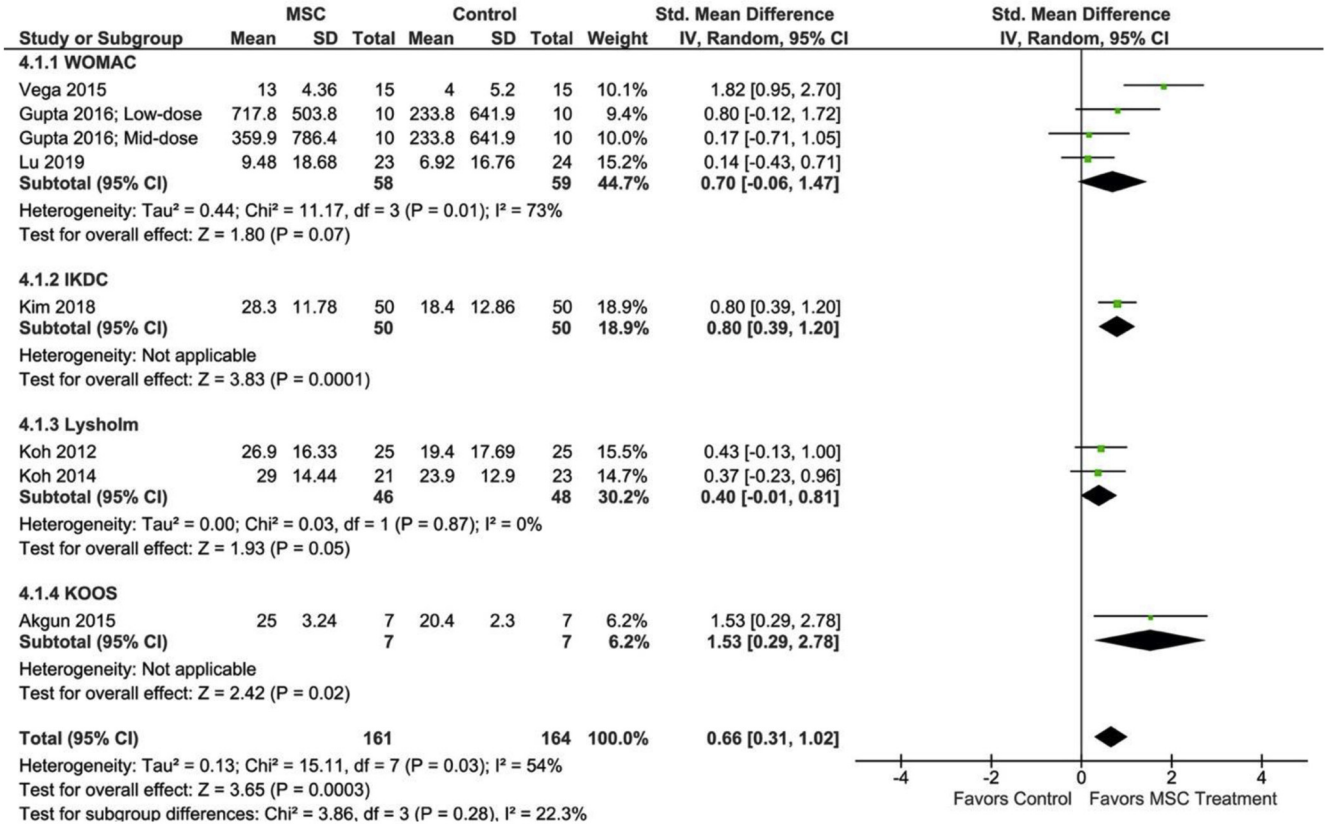

Fig 4. Forest plot reporting pre- to post-treatment changes comparing control and MSC treatment groups for self-reported physical function, including summary estimates (center of diamond) and 95% CI (width of diamond) at furthest follow-up. Means and SDs are reported according to each respective PRO scoring scale. (CI, confidence interval; IKDC, International Knee Documentation Committee; IV, inverse variance; KOOS, Knee Injury and Osteoarthritis Outcome Score. MSC, mesenchymal stem cell; PRO, patient-reported outcome; SD, standard deviation; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Index.)

subjects (61%). Fourteen studies reported sex for the control group (n = 320), with 216 female subjects (68%). Radiographic grading of knee OA using the Kellgren–Lawrence scale was reported in 22 studies (85%) with included Kellgren–Lawrence grades of 0-VI, with variable exclusion criteria across studies. Overall length of final follow-up ranged from 1 week to 100 months with a mean of 8.3 years. Treatments implemented in study groups included autologous and allogenic intra-articular MSC injection,[26,27,28,30-32,36-9,41,43-46,49-51] matrix-induced MSC implantation,[25] MSC with platelet-rich plasma (PRP),[29,48,49] high tibial osteotomy (HTO) with MSC injection,[19,42] MSC implantation on fibrin glue scaffold,[49] and cell-based biologics.[26,33] Descriptions of cell therapies used in all included studies are listed in Table 3.

Risk of Bias Assessment

The Downs and Black score and categorical grade for the included studies are displayed in Tables 1 and 2. The mean total score for all 25 studies was 16.3 ± 3.7 (range, 9-22); 9.2 ± 1.5 for quality of reporting, 3.7 ± 1.0 for internal validity (bias), 3.2 ± 1.6 for internal validity (confounding), and 0.2 ± 0.4 for statistical power. None of the included studies received points in terms of external validity due to an inadequate discussion of generalizability. Of the 25 studies, 6 (24%) received a categorical grade of "poor," 11 (44%) studies were "fair," 8 (32%) studies were "good," whereas no studies attained a grade of "excellent." The mean score stratified by study design was 17.0 ± 1.7 for single-arm, prospective studies; 14.4 ± 3.5 for nonrandomized, comparative studies; and 17.4 ± 3.8 for RCTs. There were no statistically significant differences between the stratified group means as determined by one-way analysis of variance ($F = 1.87$, $P = .18$). The primary potential sources of bias for non-RCTs were lack of randomization, lack of a priori power analysis or insufficient power to detect a statistical difference, and inadequate blinding of subjects and study staff to the intervention assignment.

Outcome Measures

Self-Reported Knee Pain

Nine studies assessed the effect of MSC treatment on knee pain via the visual analog scale (VAS). Of these, 6 studies (10 data sets, n = 312) compared improvement between MSC treatment and control groups. The mean

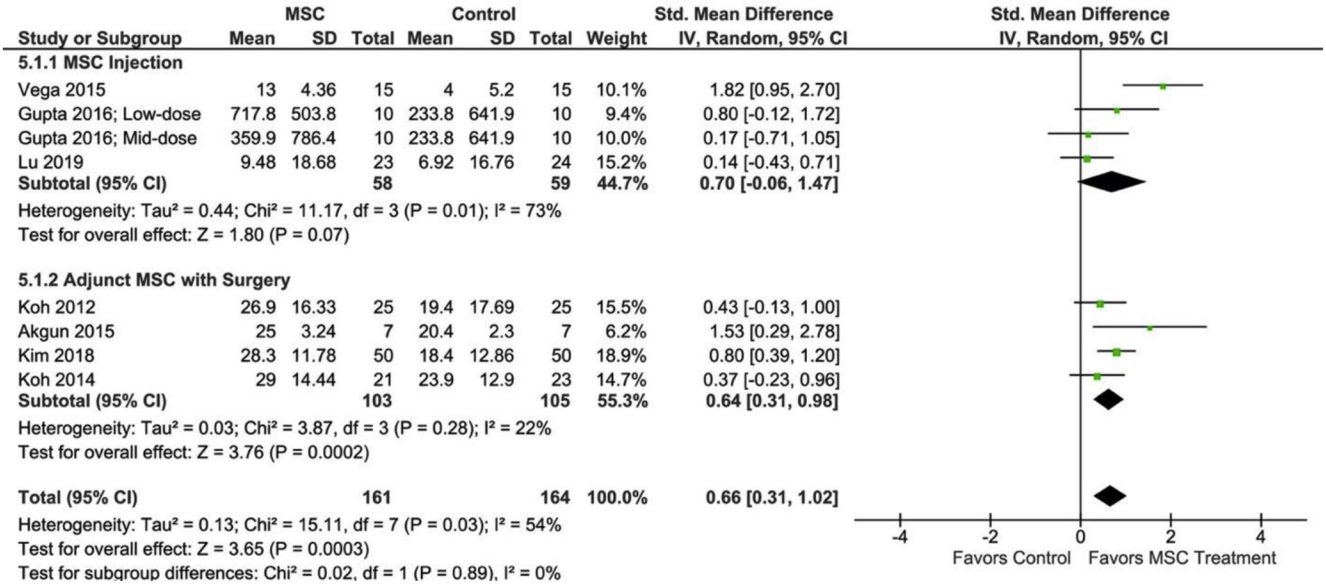

Fig 5. Forest plot reporting pre- to post-treatment differences comparing studies that administered MSC via injection only versus with a surgical adjunct for self-reported physical function, including summary estimates (center of diamond) and 95% CI (width of diamond) at furthest follow-up. Means and SDs are reported according to each respective PRO scoring scale. (CI, confidence interval; IV, inverse variance; MSC, mesenchymal stem cell; PRO, patient-reported outcome; SD, standard deviation.)

follow-up time for these 6 studies was 16.9 ± 6.0 months (range, 12-24.4 months). Considering all 6 studies, the meta-analysis resulted in a pooled SMD of 0.23 (95% CI, −0.20 to 0.65) (Fig 2). However, this value was not statistically significant ($P = .30$), indicating no significant difference in pain improvement between MSC treatment and control groups. Estimates of effect sizes were moderately heterogenous ($I^2 = 70\%$).

To investigate whether effect size and heterogeneity estimates vary based on surgical intervention, a subanalysis stratifying studies based on whether studies administered MSC via injection only versus with a surgical adjunct (i.e., surgical administration of MSC or MSC administration with concomitant surgical procedure) was performed. The mean follow-up time of studies assessing MSC injection (12.0 ± 0 months) and MSC as surgical adjunct (21.7 ± 4.3 months) was significantly different ($P = .02$). Study heterogeneity decreased in the MSC injection subgroup ($I^2 = 59\%$) but increased slightly in the MSC surgical adjunct cohort ($I^2 = 82\%$). Subanalysis resulted in a SMD 0.33 (95% CI −0.13 to 0.78, $P = .16$) and 0.05 (95% CI −0.92 to 1.03, $P = .91$), respectively (Fig 3). The test for subgroup differences in SMD was not significant ($P = .62$).

Self-Reported Physical Function

Twenty-two studies reported functional outcome scores, with 7 studies and 8 data sets comparing functional improvement between MSC treatment (n = 161) and control (n = 164) cohorts. Self-reported physical function questionnaires included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) functional score, International Knee Documentation Committee (IKDC) score, Lysholm scores, and Knee

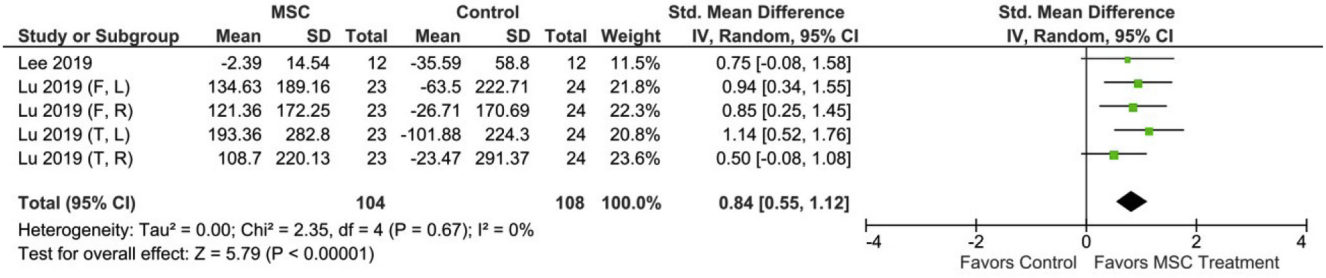

Fig 6. Forest plot reporting pre- to post-treatment changes comparing control and MSC treatment groups for cartilage volume, including a summary estimate (center of diamond) and 95% CI (width of diamond) at final follow-up. Means and SDs are reported in millimeters cubed (mm^3). (CI, confidence interval; F, femoral; IV, inverse variance; L, left leg. MSC, mesenchymal stem cell; R, right leg; SD, standard deviation; T, total.)

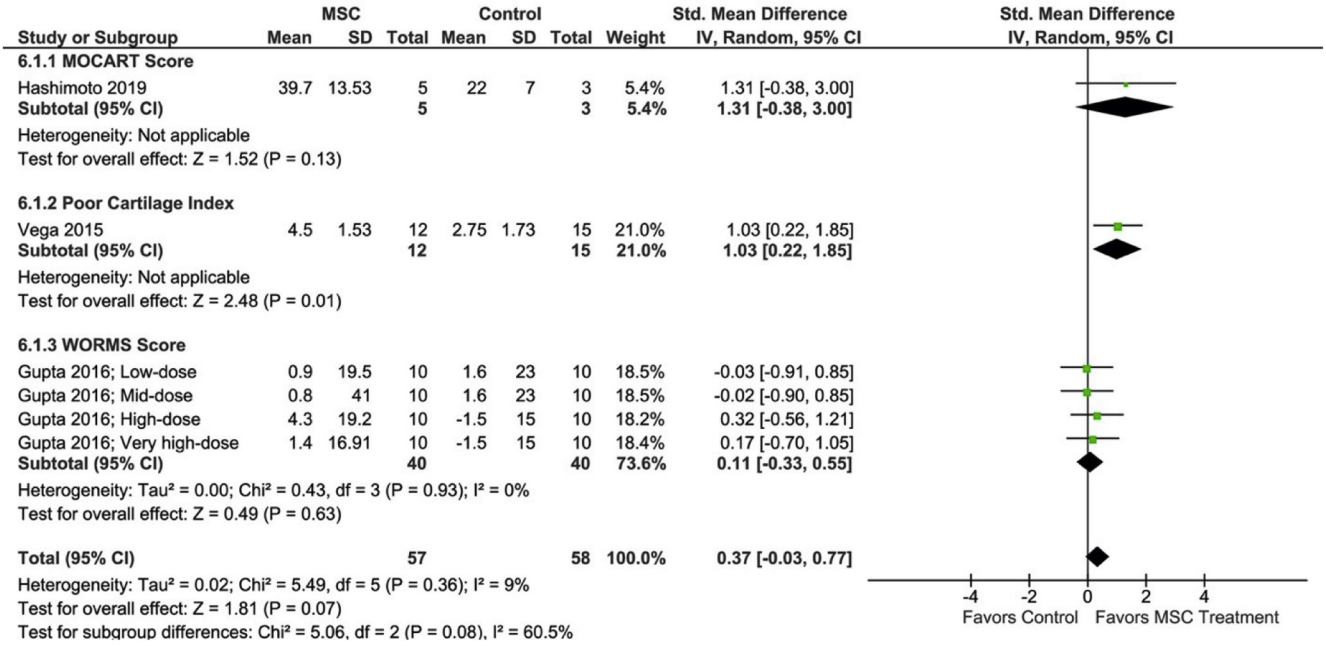

Fig 7. Forest plot reporting pre- to post-treatment changes comparing control and MSC treatment groups for cartilage quality, including summary estimates (center of diamond) and 95% CI (width of diamond) at final follow-up. Means and SDs are reported according to each respective scoring scale. (CI, confidence interval; IV, inverse variance; MOCART, magnetic resonance observation of cartilage repair tissue; MSC, mesenchymal stem cell; SD, standard deviation; VAS, visual analog scale; WORMS, whole-organ magnetic resonance imaging score.)

Injury and Osteoarthritis Outcome Score (KOOS). The mean follow-up time for these 6 studies was 20.0 ± 9.9 months (range, 12.0-38.8 months). When we combined all 7 studies, the meta-analysis resulted in a pooled SMD of 0.66 (95% CI 0.31-1.02), significantly favoring MSC treatment groups ($P < .001$) (Fig 4). This statistical value corresponds to a mean difference in pre-to-post score change of 11.4 (95% CI, −0.98 to 24.0) in the WOMAC functional outcome (0-100 points); 11.8 (95% CI 5.7-17.6) in the IKDC score (0-100 points); 8.2 (95% CI, −0.2 to 16.5) in the Lysholm score (0-100 points); and 4.0 (95% CI 0.8-7.3) in the KOOS activities of daily living (ADL) subscale. The estimate of heterogeneity among the 6 included studies was moderate ($I^2 = 54\%$).

Similar to the subanalysis performed for the VAS pain scale, stratification and subanalysis of studies that administered MSC via injection only versus with a surgical adjunct was performed (Fig 5). The mean follow-up period was not significantly different between the subgroups ($P = .05$). Within the MSC injection subgroup, functional benefits were nonsignificant (pooled SMD: 0.70, 95% CI −0.06 to 1.47, $P = .07$) and moderate heterogeneity ($I^2 = 64\%$) was observed. In contrast, functional benefits among adjunct MSC with surgery cohorts significantly favored MSC (pooled SMD 0.64, 95% CI 0.31-1.02, $P < .001$) without significant heterogeneity ($I^2 = 22\%$). The test for subgroup differences in SMD was not significant ($P = .89$).

Structural Changes in Articular Cartilage

Five studies reported changes in cartilage volume following MSC treatment.[32,33,38,46,50] Two studies with 5 data sets assessed improvement in cartilage volume between MSC treatment (n = 104) and controls (n = 108).[32,33] Mean follow-up in these studies was 9.0 ± 4.2 months. Meta-analysis yielded a pooled SMD of 0.84 (95% CI 0.55-1.12) that significantly favored MSC treatment ($P < .001$) (Fig 6). This statistical value corresponds to a mean difference of 2940 mm^3 (95% CI 1925-3920 mm^3) and 1764 mm^3 (95% CI 1155-2352 mm^3) in total and femoral cartilage volume, respectively.

Regarding cartilage quality, 3 studies investigated improvement between MSC treatment (n = 57) and controls (n = 58).[26,28,36] Mean follow-up for these studies was 11.0 ± 0.6 months. Meta-analysis resulted in a small effect size of 0.37 (95%, −0.03 to 0.77) that favored MSC treatment, but was not statistically significant ($P = .07$) (Fig 7). Estimates of heterogeneity among the included studies was low ($I^2 = 9\%$).

Discussion

The main findings of the current study are as follows: (1) the majority of studies reported improvements in patient-reported pain and physical function following MSC interventions; however, meta-analyses found that only self-reported physical function significantly improved relative from controls; (2) MSC treatment

results in significant improvement in cartilage volume, but not cartilage quality, relative to controls; and (3) there is limited evidence in the current literature to support MSC-induced cartilage regeneration.

Patient-Reported Outcomes

There was significant variability in patient-reported pain improvement between MSC and control groups. Consequently, meta-analysis failed to demonstrate superior improvement in postoperative pain relative to controls. A previous systematic review concluded that MSC treatment resulted in significantly improved VAS pain scores at 24 months.[10] Another meta-analysis reported pain improvement at 24 months that significantly favored MSC treatment.[7] However, these studies reported improvements in pain relative to baseline, rather than differential improvement in the MSC treatment group versus matched controls. Because the analyses in the current study included matched-control groups, the conclusions potentially have greater validity and applicability, despite their significant variability.

One potential factor implicated in the efficacy of MSCs for pain mitigation and analgesia is dose—response. Previous studies have demonstrated differences in pain response depending on MSC concentration and dose. Gupta et al.[26] reported improved outcomes in pain measurement scores in the low-dose group (25 million cells), but no improvement in the greater-dose groups. They proposed that a dose of 25 million cells may be optimal with the 2 mL of hyaluronic acid used as supportive matrix. Second, they proposed that the 25-million-cell dose group may be optimal for the limited intra-articular space in the knee joint. Gupta et al.[26] also postulated that MSC doses greater than 25 million cells may cause cell aggregation due to high cell concentration or insufficient knee joint space, consequently causing cell death. In addition, greater doses of MSCs may potentially cause MSCs behave as M1-type cells with a proinflammatory response, compared with lower MSC doses that may be the ideal cell concentrations giving rise to an M2-type MSC with an immunosuppressive/anti-inflammatory response.[52] Finally, a limitation highlighted in Gupta et al.[26] was the unblinding of patients after 6 months follow-up, which could have influenced subjective patient-reported outcome measures evaluating pain.

In contrast, the pooled results of patient-reported physical function showed significant improvement with MSCs. There are a number of potential explanations for this discrepancy and the lack of significant pain improvement, despite functional response. There is considerable variability in the included study protocols that could potentially contribute to these results. For example, patient factors including OA grade, lesion size, alignment, and comorbid conditions could affect patient-reported responses on pain and physical function. Treatment factors (i.e., MSC type, source site), administration technique, concomitant procedures (i.e., HTO or microfracture), and concomitant injections (i.e., hyaluronic acid, PRP) all contribute to the possible explanations for discrepant patient-reported pain and functional outcomes. Although this is difficult to standardize, future studies with uniform protocols should be repeated to establish the best method of administration of MSCs. Alongside uniform protocols, standardization of MSC preparation should be implemented in future studies. These study protocols emphasize the incredibly diverse patient populations and methodologies included in these studies, rendering it difficult to draw direct conclusions despite the high quality of evidence in each included study.

Due to inherent difficulties in interpretation of SMD in the clinical context, mean differences in change (pre-to-post delta) for functional outcome scores were calculated to determine if these values represented a clinically significant difference. The meta-analysis yielded a mean difference in change between MSC and controls of 11.4, 11.8, 8.2, and 4.0 points for WOMAC functional outcome, IKDC, Lysholm, and KOOS ADL, respectively. These scores exceeded established values of MCID for WOMAC physical function (MCID = 8.1-9.1)[53,54] and IKDC (MCID = 6.3-10.6),[53,55] but not KOOS ADL (MCID = 11.0)[55] at the 6-month postoperative time point. No studies examining knee OA or cartilage procedures have established MCID for the Lysholm score. These results suggest that treatment with MSC may confer functional benefits that are clinically significant and perceptible to patients; however, high risk for bias and a small number of studies qualifying for meta-analysis render this conclusion speculative, necessitating future corroborating research.

To address the inclusion of studies that implemented concomitant surgical procedures or surgically administered MSCs, 2 subanalyses stratifying studies based on whether MSCs were administered via injection versus with a surgical adjunct were performed. In terms of patient-reported pain, neither subgroup significantly favored MSC. The test for subgroup differences in SMD was also not significant, indicating that one method of MSC implementation is not superior to the other. Regarding patient-reported physical function, functional benefits were nonsignificant within the MSC injection subgroup. In contrast, functional benefits among adjunct MSC with surgery cohorts significantly favored MSC based on subanalysis. However, because the test for subgroup differences in SMD was not significant, there is insufficient evidence to broadly conclude that MSCs with surgical adjunct is superior to the MSC injection subgroup. These results must be interpreted with extreme caution, as there was there was substantial heterogeneity in the protocols implemented to control and treatment groups. For example, some studies administered MSC with PRP,[29,48,49] whereas others administered MSCs at

the time of surgery (HTO).[42,35] Furthermore, there was heterogeneity of concomitant procedures and adjunctive treatment. Koh et al.[29] divided enrolled patients into 2 groups: the control group would undergo HTO with PRP injection and the MSC treatment group would undergo HTO with PRP injection and MSC therapy. The presence of heterogeneity in these subanalyses further illustrates the notion that there are a variety of confounding variables proving difficult to isolate, thus necessitating the creation of standardized protocols for MSC administration.

Structural Changes in Articular Cartilage

The role of MSCs in cartilage restoration and regeneration is highly controversial. Based on our analysis, there remains limited evidence to support the effect of MSC treatment on cartilage restoration relative to control. This meta-analysis aimed to exclusively include studies reporting differential changes in cartilage quantity and quality between treatment and control groups.

Based on pooled studies investigating structural changes in cartilage volume, there was a significant increase in cartilage volume after MSC treatment compared with controls. This finding contradicts the results of a previous study that found no significant improvement in cartilage volume with MSC treatment.[8] Although this finding is promising and may suggest that MSC treatment may play a potential role in cartilage regeneration, several key questions remain. The proposed mechanism for this change is not clear, as this could be attributed to a direct progenitor effect or more likely a pleiotropic effect of MSCs. It is also not known whether this effect on cartilage volume is sustained beyond 1 year. Overall, this conclusion is limited by the short-term follow-up of the included studies. Future studies should be aimed at investigating MSC effect on cartilage volume at further timepoints beyond 1 year.

Regarding cartilage quality, there was no significant improvement when we compared MSC treatment and controls from baseline to final follow-up. However, when individually assessing the 3 studies eligible for meta-analysis, we found that 2 studies reported improvement between MSC treatment and control.[28,36] Hashimoto et al.[28] reported a significantly greater mean MOCART score in the MSC + microfracture group than in the control group (microfracture alone). In addition, Vega et al.[36] found that quantification of cartilage quality by T2 relaxation measurements showed a significant decrease in poor cartilage areas, with cartilage quality improvements in MSC-treated patients. In contrast, Gupta et al.[26] detected no significant difference in cartilage signal and morphology on MRI between MSC and controls. Gupta et al.[26] proposed multiple explanations for this finding. They postulated that the type of MSCs used may be different from one study to another, or that there were a limited number of patients included in the study's MRI analysis.[26] Despite the lack of statistical significance, the pooled SMD was small in size (0.37). These results are promising; however, it is still difficult to make generalizing conclusions about MSC effect on cartilage quality due to the paucity and variability of studies comparing improvement in cartilage quality relative to controls. The lack of studies containing a matched-cohort group highlights the necessity for future comparative studies with appropriate controls. More specifically, future studies conducted should compare MSC effect on cartilage regeneration between treatment and control groups.

Many included studies used the MOCART classification, which is one of the most frequently used MR scores for postoperative cartilage repair tissue evaluation.[11] Although this validated scoring tool offers many benefits, it does not allow for baseline comparison of cartilage quality. Future studies should implement knee MR scores that enable baseline measurements to allow for comprehensive comparison, such as the MRI Osteoarthritis Knee Score (MOAKS).[49] This knee MR score provides a semiquantitative analysis of knee OA[56] and includes evaluation of key variables such as area of cartilage loss and percentage of full-thickness cartilage loss at preoperative and final follow up time points.[49] Widespread implementation of MOAKS in analysis of MSC treatment would permit greater data collection of MSC effects on cartilage regeneration.

Cost-Analysis

Although cell therapies have been used more frequently in orthopaedic surgery compared with other specialties, there are still considerable barriers to commercial implementation. According to Davies et al.,[57] the most concerning barriers to adoption include cost-effectiveness and efficacy, followed by regulation, reimbursement, and safety. Specifically, orthopaedic surgeons surveyed identified "clinical trial methodologies" as a large barrier to implementation. Clinical trial methodologies were defined as the quality and rigor of clinical trial designs implemented. The growing popularity and desire for implementation of stem-cell therapies must be equally balanced with focused debate regarding cost-effectiveness and strong evidence-based justification for use in orthopaedic patients.

Risk of Bias

The Downs and Black scale is a well-established checklist that allows for assessment of a paper's methodological strengths and weaknesses. After completing Downs and Black Scores for all included studies, more than one-half of the studies received a categorical grade of "poor" or "fair" (68%). Consequently, while MSC treatment resulted in significant improvement in cartilage volume, but not cartilage quality (relative to controls), this must be interpreted judiciously in the context of high risk of bias. Future studies need to be conducted

not only with high-quality evidence, but with strong internal validity to help address the levels of bias seen in the included studies.

Limitations

The results of the current study should be interpreted in the context of a few limitations. First, there were a limited number of studies that qualified for our meta-analyses, as the studies were required to have matched-control group for comparison with the MSC-treated arm. There is also significant variability in the source, preparation, and concentration of currently used MSC products. These differences between studies can confound comparisons and limit conclusions that can be drawn. In addition, it is not clear how MSCs were typed, prepared, and processed in each study.

Conclusions

In conclusion, the pooled standard mean difference from meta-analyses showed statistically significant effects of MSC on self-reported physical function but not self-reported pain. MSCs provided functional benefit only in patients who underwent concomitant surgery. However, this must be interpreted with caution, as there was substantial variability in MSC composition and mode of delivery. MSC treatment provided significant improvement in cartilage volume, but not cartilage quality. Preliminary data regarding therapeutic properties of MSC treatment suggest significant heterogeneity in the current literature and risk of bias is not negligible.

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