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Effect of Stem Cell Injections on Osteoarthritis-related Structural Outcomes: A Systematic Review

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ABSTRACT. ***Objective.*** To systematically review the evidence for the efficacy of mesenchymal stem cell (MSC) injections in improving osteoarthritis (OA)-related structural outcomes.

Methods. Ovid Medline and EMBASE were searched from their inceptions to April 2020 using MeSH terms and key words. Independent reviewers extracted data and assessed methodological quality. Qualitative evidence synthesis was performed due to the heterogeneity of interventions and outcome measures.

Results. Thirteen randomized controlled trials (phase I or II) were identified: 10 in OA populations and 3 in populations at risk of OA, with low (n = 9), moderate (n = 3), or high (n = 1) risk of bias. Seven studies used allogeneic MSCs (4 bone marrow, 1 umbilical cord, 1 placenta, 1 adipose tissue), 6 studies used autologous MSCs (3 adipose tissue, 2 bone marrow, 1 peripheral blood). Among the 11 studies examining cartilage outcomes, 10 found a benefit of MSCs on cartilage volume, morphology, quality, regeneration, and repair, assessed by magnetic resonance imaging, arthroscopy, or histology. The evidence for subchondral bone was consistent in all 3 studies in populations at risk of OA, showing beneficial effects. Sixteen unpublished, eligible trials were identified by searching trial registries, including 8 with actual or estimated completion dates before 2016.

Conclusion. Our systematic review of early-phase clinical trials demonstrated consistent evidence of a beneficial effect of intraarticular MSC injections on articular cartilage and subchondral bone. Due to the heterogeneity of MSCs, modest sample sizes, methodological limitations, and potential for publication bias, further work is needed before this therapy is recommended in the management of OA.

Key Indexing Terms: cartilage, intraarticular injection, stem cells, subchondral bone

Osteoarthritis (OA) causes disability, impaired quality of life, and significant financial burden[1,2]. Current treatment modalities, including analgesics, nonsteroidal antiinflammatory drugs, opiates, intraarticular injections of steroids and hyaluronans, and physical therapies[3,4,5], only alleviate symptoms with short-term, small-to-moderate effects[6]. No drugs have shown enough of an effect on slowing structural progression of OA to be approved as disease-modifying OA drugs[7].

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Adult mesenchymal stem cells (MSCs) are multipotent, undifferentiated cells that can be isolated from bone marrow, adipose tissue, muscle, or synovium, and readily culture expanded without undergoing differentiation[8]. MSCs have been investigated as a promising treatment for OA due to their ability to differentiate into cartilage, bone, adipose, tendon, and other cells of the mesenchymal lineage, and their antiinflammatory and immunomodulatory activities[8,9,10,11]. While the use of MSCs has gained momentum in recent decades, their potential as a treatment for OA remains unclear, as studies have shown that few stem cells survive after injection[12,13,14], and there is a lack of data on the long-term safety and efficacy from larger clinical trials[15,16,17].

Several systematic reviews that focus on patient-reported outcomes have shown the safety and effectiveness of intraarticular MSC injections in improving pain and function in OA[17,18,19,20,21,22,23,24]. While previous studies on stem cell therapy are based on moderate numbers of participants, the effect of MSCs on patient-reported outcomes is critical information for clinical decision-making and future research. A number of clinical trials have examined the effect of MSCs on OA-related structural outcomes[25–37]. A recent systematic review that included 6 clinical trials of knee OA demonstrated beneficial effects of MSCs on improving radiological, histological, and arthroscopic outcomes, but all studies had high risk of bias and large clinical

heterogeneity[17]. Normal joints, established OA, and end-stage OA are on the same continuum, and preclinical diseases, such as focal chondral defect, partial meniscectomy, and anterior cruciate ligament injury, identify those at risk of OA in whom therapies such as MSC may be beneficial. Therefore, we systematically reviewed the evidence for the efficacy of stem cell injections in improving structural outcomes of the knee, hip, and spine in individuals with OA or at risk of OA, specifically focusing on OA-related structural outcomes assessed objectively in studies with a control group.

MATERIALS AND METHODS

Our systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines[38].

Search strategy. Ovid Medline and EMBASE databases were searched from their inceptions to April 2020 using MeSH terms and keywords to identify studies examining the effect of stem cell injections on joint structures (Table 1). Searches were limited to human and English-language studies. The references of identified manuscripts were searched for additional studies.

Study selection. Two authors (initial search: RV and LC; updated search: JF and YW) independently reviewed records to assess the eligibility of studies by title, abstract, and full text, using a 3-stage determination method according to the inclusion and exclusion criteria (Table 1). Any disagreement between the 2 authors was resolved by discussion.

Data extraction and synthesis. Two authors (JG and JF) extracted data on target population; sex, age, and number of study participants; type, source, and immunophenotypic characterization of stem cells; route of administration; number of injections; outcome measures; duration of follow-up; source of funding; and effect of stem cell injections on structural outcomes. Qualitative synthesis was performed due to the heterogeneity in interventions and outcome measures.

Risk of bias assessment. Two authors (SMH and YW) independently assessed the risk of bias using the Cochrane Collaboration tool for assessing risk of bias in randomized trials[39]. This tool covers 6 domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Studies were assessed as "high," "low," or "unclear" risk of bias for each item, with an overall risk of bias being scored as "low," "moderate," or "high"[17] (Supplementary Table 1, available from the authors on request). The agreement between the 2 authors was 86%. Differing assessments were discussed to get a consensus.

Search of trial registers and registries for unpublished studies. One author (YW) searched trial registers and registries for clinical trials with "completed" or "unknown" status that were eligible for our current systematic review but not published: US National Institutes of Health Trial Register (www.ClinicalTrials.gov), World Health Organization International Clinical Trials Registry Platform (apps.who.int), European Union Clinical Trial Register (www.clinicaltrialsregister.eu), Australian New Zealand Clinical Trials Registry (www.anzctr.org.au), and International Standard Randomized Controlled Trial Number registry (www.isrctn.com).

RESULTS

Study selection. Figure 1 shows the breakdown of the study selection. After removal of duplicates, 1250 articles were screened. Full text was reviewed for 32 studies, with 14 eligible studies identified (13 on knee, 1 on spine). No additional articles were found after searching the references of published research or review articles. A study on degenerative disc disease[40] was further excluded since a single study precludes a comparison with other studies and lacks the robustness to draw any reliable conclusion.

Description of included studies. Table 2 provides an overview of the 13 studies published between 2013 and 2019; all were phase I or II randomized controlled trials[25–37]. Three studies originated from Australia[31,32,35], 2 from Spain[28,30], and a single study each from Malaysia[25], Singapore[26], USA[27], India[29], Chile[33], Iran[34], South Korea[36], and China[37]. The mean ages of participants ranged from 26 to 66 years and percentage of men ranged 10–71%. Ten studies included patients with knee OA, defined using the Kellgren-Lawrence grading scale[28,29,30,32–37] or criteria not clearly specified[26]. Other studies examined patients with International Cartilage Repair Society (ICRS) grade 3–4

Table 1. Search terms, and inclusion and exclusion criteria.

Search Terms[a]		
Injection	Stem Cell	Joint Structure or Osetoarthritis
injections or intramuscular injections or spinal injections or intraarticular injections or intravenous injections or bolus injection	stem cell or mesenchymal stromal cells or mesenchymal cell or bone marrow or bone marrow cell	osteoarthritis or knee or knee joint or knee osteoarthritis or gonarthrosis or knee ligament or knee ligament injury or knee ligament surgery or knee cruciate ligament or knee arthritis or knee arthroscopy or knee meniscus or knee surgery or knee injury or knee meniscus rupture or hip or hip joint or hip contracture or hip osteoarthritis or coxarthrosis or hip arthroscopy or hip injury or hip surgery or spine or spine osteoarthritis or thoracic spine or thoracolumbar spine or lumbosacral spine or spine injury or lumbar spine or cervical spine or spine surgery
Inclusion Criteria		
Studies assessing the outcome of interest (i.e. joint structures or OA), and the exposure of interest of injection of stem cells comprising mesenchymal stromal cells, mesenchymal cell, bone marrow or bone marrow cell were included.		
Exclusion Criteria		
Case reports, case series, conference abstracts, review articles, or studies without a comparison group were excluded. Studies examining cell concentrates, such as stromal vascular fraction, bone marrow aspirate concentrate, and adipose tissue injections (fat grafts), were excluded.		

[a] Searches were limited to human and English-language studies. OA: osteoarthritis.

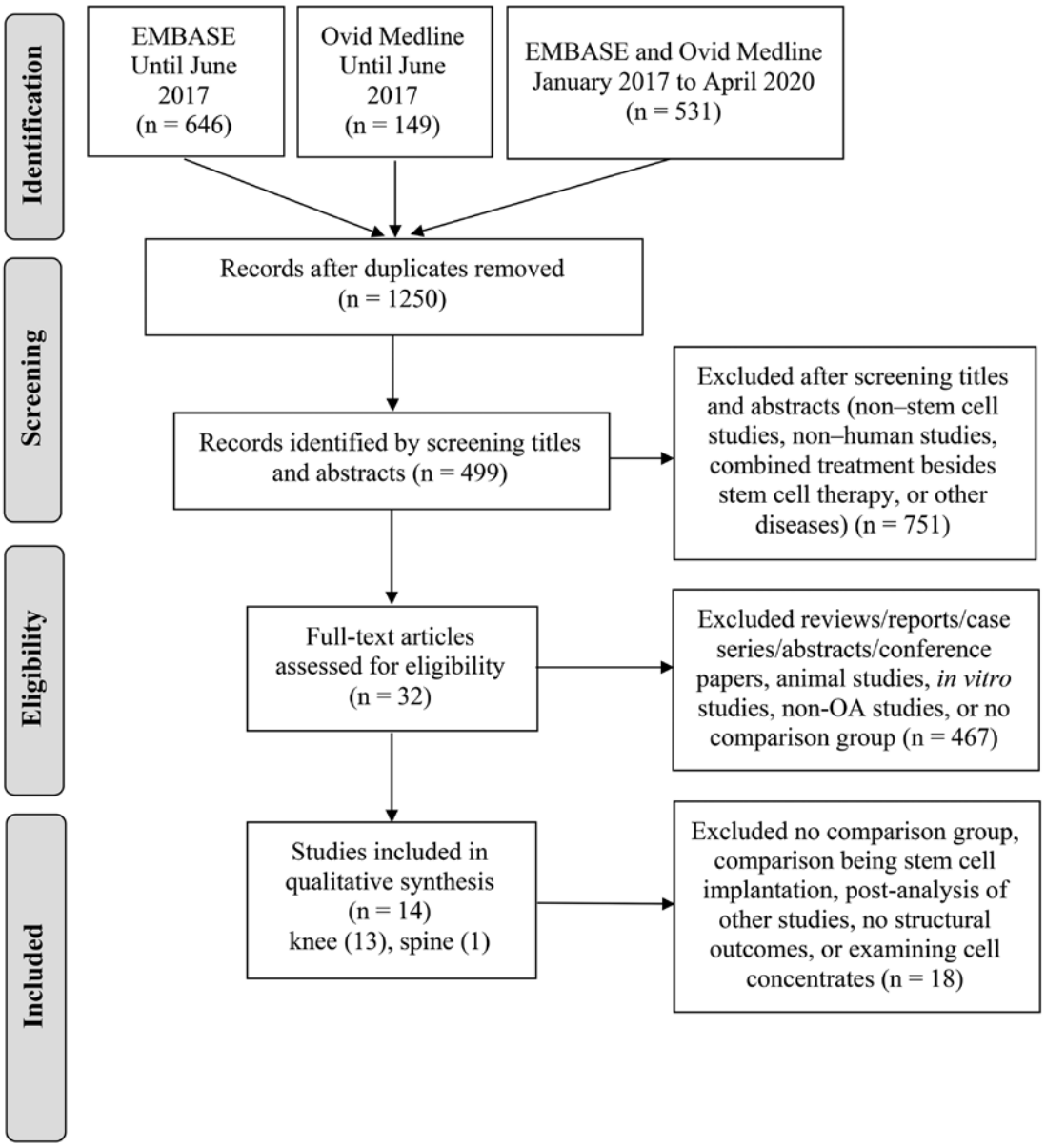

Figure 1. PRISMA flow diagram of included articles. PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses.

cartilage lesions[25], partial meniscectomy[27], or unilateral anterior cruciate ligament injury[31]. The follow-up was at 6 months[34,36], 12 months[26,28,29,30,32,33,35,37], 18 months[25], or 24 months[27,31]. Six studies were funded by companies[27,29,31,32,35,36], 4 studies by governments[25,28,30,34], 1 study by a company and government[37], and 2 studies did not report the funders[26,33].

Interventions. Stem cells were sourced through allogeneic or autologous method. Seven studies used allogeneic MSCs, derived from bone marrow[27,28,29,31], umbilical cord[33], placenta[34], or adipose tissue[32]. Six studies used autologous MSCs, derived from adipose tissue[35,36,37], bone marrow[26,30], or peripheral blood[25]. Twelve trials performed immunophenotypic characterization of MSCs[25–31,33,34,35,36,37], reporting positive CD73, CD90, or CD105[26–30,33,34,35,37], and negative CD14, CD19, CD34, CD35, or HLA-D related (HLA-DR)[26–30,33,34,35,37]. One study reported positive CD105 and CD34[25]. Two studies did not report the details[31,36]. All stem cell treatment was administrated through intraarticular injection of varying doses. Eleven studies involved a single injection[26–36], with 2 studies also involving 2 injections at baseline and 6 months[33,35]. One study applied 8 injections[25]. One study involved 2 injections at 0 and 3 weeks[37]. Seven studies used a single dose group[25,26,28,31,34,36,37], 5 studies had 2 dose groups[27,30,32,33,35], and 1 study had 4 dose groups[29]. MSCs were suspended in different media, including hyaluronic acid (HA) only[25,26,31,37]; Plasma-Lyte A only[29]; normal saline only[34,35,36]; HA, human serum albumin, and Plasma-Lyte A[27]; Ringer lactate containing human albumin[28,30]; or saline with AB plasma[33]. One study did not report the suspension medium[32]. The control group received intraarticular injection of HA[25,26,27,28,30,31,33,37], normal saline[34,36], Plasma-Lyte A[29], or cell culture media and

Table 2. General characteristics of included studies.

First Author, Country, Yr, Trial Phase	Study Population, n (% Men)	Age of Study Participants, Yrs, Mean ± SD or Median (Range)	Source of Stem Cells	Immunophenotypic Characterization	Route of Administration and No. Injections	Outcome Measures	Duration of Follow-up, months	Source of Funding
Saw, Malaysia, 2013[25], phase II	49 (35) patients with ICRS grade 3 and 4 lesions of the knee who underwent arthroscopic subchondral drilling and abrasion chondroplasty	Stem cell group: 38 ± 7.33; HA group: 42 ± 5.91	Autologous peripheral blood stem cells	Positive CD45 and CD105	IA injection of the knee; injections: 8 (first 5 injections began at 1 week on a weekly basis; 3 additional injections administered beginning at 6 months at weekly intervals)	MRI: repaired cartilage signal, repaired lesion morphologic features, repaired cartilage fill, peripheral repaired cartilage integration, subchondral edema, and osseous overgrowth (max score of 12). Second-look arthroscopy with chondral core biopsy, histologic evaluation and grading using the ICRS II (max score of 1400)	18	The Ministry of Science, Technology and Innovation Technofund, Malaysia
Wong, Singapore, 2013[26], phase not specified	56 (48) patients with medial-compartment OA and genu varum who underwent arthroscopic microfracture and medial opening-wedge high tibial osteotomy	MSC group: 53 (range 36–54); HA group: 49 (range 24–54)	Autologous bone marrow–derived MSC	Positive CD73, CD90, and CD105; negative CD14, CD20, CD34, and CD45	IA injection of the knee; injections: 1	MRI: MOCART score	12	No funding reported
Vangsness, USA, 2014[27], phase I/II	55 (63) patients with a partial medial meniscectomy	Low-dose MSC group: 44.6 ± 9.82; high-dose MSC group: 45.6 ± 12.42; HA group: 47.8 ± 8.00	Allogeneic bone marrow–derived MSC	Positive CD105, CD73, CD29, CD44, CD71, CD90, CD106, CD120a, CD124, CD166; negative markers of hematopoietic lineages, CD14, CD34, and CD45	IA injection of the knee; injections: 1	MRI: meniscus regeneration: > 15% increase in meniscal volume; WORMS: cartilage degeneration, thickening, sclerosis of subchondral bone, osteophyte formation, and femoral or tibial edema	24	Osiris Therapeutics, Columbia, Maryland
Vega, Spain, 2015[28], phase I/II	30 (43) patients with KL grade 2–4 knee OA and chronic knee pain unresponsive to conservative treatments	MSC group: 56.7 ± 9.5; HA group: 57.3 ± 9.4	Allogeneic bone marrow–derived MSC	Strongly positive CD90 and CD166; moderately positive CD105, CD106 and kinase insert domain receptor; negative CD34, CD45 and HLA-DR	IA injection of the knee; injections: 1	MRI: articular cartilage quality assessed by quantitative T2 mapping	12	The Spanish Ministerio de Sanidad, Red de Terapia Celular of the Instituto de Salud Carlos III, Ministerio de Economia y Competitividad, and the Centro en Red de Medicina Regenerativa de Castilla y León

Table 2. Continued.

First Author, Country, Yr, Trial Phase	Study Population, n (% Men)	Age of Study Participants, Yrs, Mean ± SD or Median (Range)	Source of Stem Cells	Immunophenotypic Characterization	Route of Administration and No. Injections	Outcome Measures	Duration of Follow-up, months	Source of Funding
Gupta, India 2016[29], phase II	60 (25) patients with symptomatic radiographic knee OA (KL grade 2–3)	Cohort 1: MSC dose level 1: 58.1 ± 8.2, MSC dose level 2: 57.3 ± 9.5 Placebo 1: 54.9 ± 8.3 Cohort 2: MSC dose level 3: 55.0 ± 6.7, MSC dose level 4: 54.0 ± 6. Placebo 2: 56.7 ± 5.2	Allogeneic bone marrow–derived MSC	Positive CD73, CD105, CD90 and CD166; negative CD34, CD45, CD133, CD14, CD19 and HLA-DR	IA injection of the knee; injections: 1	Radiograph, no details provided; MRI, WORMS: cartilage signal and morphology, marginal osteophytes, subarticular bone marrow abnormality, subarticular cysts, subarticular bone attrition, menisci, cruciate ligaments	12	Stempeutics Research Pvt Ltd, Bangalore
Lamo-Espinosa, Spain 2016[30], phase I/II	30 (63) patients with diagnosed knee OA and KL grade ≥ 2	Low-dose MSC group: 65.9 (IQR 59.5–70.6); high-dose MSC group: 57.8 (IQR 55.0–60.8); HA group: 60.3 (IQR 55.1–61.1)	Autologous bone marrow–derived MSC	Positive CD90, CD73 and CD44; negative CD34 and CD45	IA injection of the knee; injections: 1	Radiograph: joint space width; MRI, WORMS: number and location of the lesions, cartilage thickness, signal intensity, subchondral bone alternation and volume	12	Instituto de Salud Carlos III
Wang, Australia, 2017[31], phase Ib/IIa	17 (71) patients with unilateral anterior cruciate ligament injury and subject to a reconstruction within 6 months but with no visual evidence of articular cartilage lesions	Stem cell + HA group: 26.0 ± 3.6; HA group: 26.9 ± 10.3	Allogeneic bone marrow–derived mesenchymal precursor cells	STRO-3$^+$ immunogenicity evaluated by anti-HLA panel reactive antibodies against class I and II HLA measured by flow cytometry	IA injection of the knee; injections: 1	Radiograph: joint space width; MRI: tibial cartilage volume and bone area	24	Mesoblast Ltd
Kuah, Australia 2018[32], phase I	20 (60) patients with KL grade 1–3 knee OA with moderate-to-severe pain	MSC 3.9M group: 50.8 ± 7.29; MSC 6.7M group: 55.0 ± 5.15; Placebo group: 55.0 ± 10.42	Allogeneic adipose-derived MSC	Not reported	IA injection of the knee; injections: 1	MRI: tibial cartilage volume, tibial bone area, semiquantitative assessment of cartilage defects and bone marrow lesions	12	Regeneus Ltd
Matas, Chile, 2019[33], phase I/II	29 (45) patients with symptomatic knee OA (KL grade 1–3), without meniscal rupture	MSC single-dose group: 56.1 ± 6.8; MSC repeated-dose group: 56.7 ± 4.1; HA group: 54.8 ± 4.5	Allogeneic umbilical cord–derived MSC	Positive CD73, CD90 and CD105; negative CD45, CD34, and HLA-DR	IA injection of the knee; injections: 1 (baseline); 2 (baseline and 6 months)	MRI: WORMS score (14 items, 0–332 points), articular cartilage score, meniscal integrity score	12	No funding reported
Khalifeh Soltani, Iran, 2019[34], phase I/II	20 (10) patients with symptomatic knee OA (KL grade 2–4)	MSC group: 57.5 yrs; control group: 55.8 yrs	Allogeneic placenta-derived MSC	Positive CD73, CD90, and CD105; negative CD34, CD45, and CD31	IA injection of the knee; injections: 1	MRI, magnetic resonance arthrography: cartilage thickness measured at 14 sites, synovial hypertrophy, spur, erosion, meniscus, and anterior cruciate ligament injury	6	The National Institute for Medical Research Development
Freitag, Australia, 2019[35], phase II	30 (53) patients with unilateral symptomatic knee OA (KL grade 2–3)	MSC 1-injection group: 54.6 ± 6.3; MSC 2-injection group: 54.7 ± 10.2; control group: 51.5 ± 6.1	Autologous adipose-derived MSC	Positive CD90, CD73 and CD105; negative CD14, CD19, CD34, and CD45	IA injection of the knee; injections: 1 (baseline); 2 (baseline and 6 months)	MRI, MRI OA Knee Score: bone marrow lesions and cysts, articular cartilage, osteophytes, synovitis, meniscus, periarticular features	12	Magellan Stem Cells and Melbourne Stem Cell Centre
Lee, South Korea, 2019[36], phase IIb	24 (25) patients with knee OA (KL grade 2–4), pain intensity on VAS ≥ 4/10 for at least 12 weeks	MSC group: 62.2 ± 6.5, control group: 63.2 ± 4.2	Autologous adipose-derived MSC	Tested for CD31, CD34, CD45, CD 73, CD 90	IA injection of the knee; injections: 1	Radiograph: KL grade, joint space width; MRI: size and depth of cartilage defects	6	R-Bio Co Ltd

Table 2. Continued.

First Author, Country, Yr, Trial Phase	Study Population, n (% Men)	Age of Study Participants, Yrs, Mean ± SD or Median (Range)	Source of Stem Cells	Immunophenotypic Characterization	Route of Administration and No. Injections	Outcome Measures	Duration of Follow-up, months	Source of Funding
Lu, China, 2019[37], phase IIb	53 (11.5) patients with knee OA (ACR criteria; KL grade 1–3) and pain	Mesenchymal progenitor cell group: 55.03 ± 9.19; HA group: 59.64 ± 5.97	Autologous adipose-derived mesenchymal progenitor cells	Positive CD90, CD73, CD29 and CD49d; negative actin, CD14, CD34, CD45 and HLA-DR	IA injection of the knee; injections: 2 (0 and 3 weeks)	MRI: knee cartilage volume (femur, tibia, and patella)	12	The Cellular Biomedicine Group and the National Key Research and Development Program of China

ACR: American College of Rheumatology; HA: hyaluronic acid or hyaluronan; ICRS: International Cartilage Repair Society; KL: Kellgren-Lawrence; IA: intraarticular; MOCART: Magnetic Resonance Observation of Cartilage Repair Tissue; MRI: magnetic resonance imaging; MSC: mesenchymal stem cell; OA: osteoarthritis; STRO: Stromal precursor antigen; VAS: visual analog scale; WORMS: whole-organ magnetic resonance imaging score

cryopreservative[32]. One study used standard care as the control[35] (Table 3).

Assessment of structural outcomes. Structural outcomes were the primary outcome in 4 studies[25,27,30,34] and the secondary outcome in 9 studies[26,28,29,31,32,33,35–37] (Supplementary Table 2, available from the authors on request). Knee structure was assessed in 8 studies by magnetic resonance imaging (MRI) only[26,27,28,32,33,34,35,37], 4 studies by both MRI and radiograph[29,30,31,36], and 1 study by MRI and second-look arthroscopy with chondral core biopsy[25]. Articular cartilage outcomes were cartilage volume/thickness[31,32,34,37], cartilage defects[32,35,36], cartilage quality[28,33], cartilage repair[25,26], meniscal volume[27], and meniscal pathology[35], assessed using MRI, and cartilage repair, assessed using validated arthroscopy grading systems[25]. Subchondral bone outcomes were tibial bone area[31,32], bone marrow lesions[25,32,35], and subchondral bone sclerosis and osteophyte formation[27,34,35], assessed by MRI. Composite MRI scores of multiple features were assessed using the Whole-Organ Magnetic Resonance Imaging Score (WORMS)[27,29,30,33], MRI Osteoarthritis Knee Score[35], or a scoring system developed for morphological evaluation[25]. Radiograph outcome was either joint space width[30,31,36] or not specified[29].

Risk of bias assessment. The overall risk of bias was low in 9 trials[25,27,29,30,32–35,37], moderate in 3 trials[26,31,36], and high in 1 trial[28] (Table 4). The study population and research question were clearly defined and participants and personnel were blinded in all the studies. Some studies did not have adequate allocation concealment[26,28,33,36] or complete outcome data[25,27,28,31]. Some studies had unclear risk of bias for random sequence generation[28,31,36], blinding of outcome assessment[29], or selective reporting as they were not registered in trial registries[26].

Effect of MSCs on articular cartilage outcomes. Eight studies examined cartilage volume, quality, regeneration, and repair in OA populations[26,28,32,33,34,35,36,37] (Table 3). Wong, *et al* showed significantly better Magnetic Resonance Observation of Cartilage Repair Tissue score and more prevalent cartilage coverage (complete and > 50%), as well as complete integration of regenerated cartilage in the intervention group compared with the control group after 1 year[26]. Vega, *et al* found a significant decrease in poor cartilage index in the intervention group but not the control group, with improvement against baseline score not significantly different between the 2 groups at 12 months[28]. Kuah, *et al*'s study showed no significant decrease in lateral tibial cartilage volume in the Progenza 3.9M group but a significant cartilage loss in the control group after 12 months[32]. Khalifeh Soltani, *et al* showed increased cartilage thickness in the intervention group but no significant change in the control group over a 24-week period; no significant change in meniscus lesions was seen in either group[34]. Freitag, *et al* found significantly reduced progression of cartilage loss in those treated with 2 MSC injections (11%), compared with those treated with 1 MSC injection (30%) or controls (67%) at 12 months[35]. Lee, *et al* demonstrated a significant increase in cartilage defect size in the control group but not in the MSC group at 6 months[36]. Lu, *et al* found a significant increase in knee cartilage volume at

Table 3. Effect of stem cell injections on joint structural outcomes.

First Author, Country, Yr	Stem Cells	Control	Structural Outcome	Results			
				Outcome Measure	Intervention	Control	*P*
Populations with OA							
Wong, Singapore, 2013[26]	MSC 14.6M + HA 2 mL (n = 28)	HA 2 mL (n = 28)	Articular cartilage	MOCART Score (evaluation of cartilage repair)	62.32 ± 17.56	43.21 ± 13.55	< 0.001
				Cartilage coverage, n (%)	9 (32) complete coverage; 10 (36) > 50% coverage	0 complete coverage; 4 (14) > 50% coverage	< 0.001
				Complete integration of regenerated cartilage, n (%)	17 (61)	4 (14)	< 0.001
Vega, Spain, 2015[28]	MSC 40M (n = 15) suspended in Ringer lactate solution containing 0.5% human albumin and 5 mM glucose	HA 60 mg (n = 15)	Articular cartilage	Cartilage quality (T2 mapping): PCI	Significant decrease ($P < 0.05$)	Nonsignificant decrease ($P > 0.05$)	NR
				PCI improvement plotted against baseline score, slope of line (efficiency of treatment)	0.69	0.28	> 0.05
Gupta, India, 2016[29]	25M (n = 10), 50M (n = 10), 75M (n=10), 150M (n=10); suspended in Plasma-Lyte A	Plasma-Lyte A 15 mL (n = 20)	Composite MRI score	WORMS score	6 months 25M: 67.5 ± 20.5 50M: 77.9 ± 41.2 75M: 71.4 ± 20.9 150M: 62.0 ± 17.7 12 months 25M: 66.1 ± 19.2 50M: 78.0 ± 41.1 75M: 67.0 ± 20.9 150M: 60.6 ± 15.7	74.9 ± 22.4 69.9 ± 14.3 74.9 ± 22.5 72.3 ± 15.2	0.55 0.74 0.53 0.06
			Radiograph	Variables not presented	No clinically meaningful change (data not presented)	No clinically meaningful change (data not presented)	NR
Lamo-Espinosa, Spain, 2016[30]	10M (n = 10), 100M (n = 10); suspended in Ringer lactate buffer containing 1% human albumin	HA 60 mg (n = 10)	Composite MRI score	Improvement in WORMS score	10M: median 2.5 (IQR –3 to 25) 100M: median –4 (IQR –22 to 2); 25% of patients had an improvement of 22 points	Median –0.5 (IQR –16 to 15)	NR
			Radiograph	Reduction in joint space width	10M: median 0 (IQR 0 to 3) 100M: median 0 (IQR –1 to 2)	Median –4 (IQR –18 to 0), $P = 0.05$	NR
Kuah, Australia, 2018[32]	Progenza (PRG), 3.9M (n = 8), 6.7M (n = 8); suspension medium not reported	Cell culture media and cryopreservative (n = 4)	Articular cartilage	Change in tibial cartilage volume	3.9M: Medial –1.5% (95% CI –6.7 to 3.6) Lateral 0.4% (95% CI –2.0 to 2.7) 6.7M: Medial –3.5% (95% CI –8.7 to 1.8) Lateral –3.5% (95% CI –5.8 to –1.2)	Medial –1.7% (95% CI –8.8 to 5.3) Lateral –5.0% (95% CI –8.8 to –1.3)	0.96 0.02 0.69 0.48
				Cartilage defects	Very few changes	Very few changes	NR
			Subchondral bone	Change in tibial bone area	3.9M: Medial 2.0% (95% CI –0.0 to 4.0) Lateral –0.2% (95% CI –3.1 to 2.7) 6.7M: Medial –1.0% (95% CI –3.1 to 1.1) Lateral –2.0% (95% CI –4.9 to –0.9)	Medial 1.4% (95% CI –1.6 to 4.3) Lateral –0.2% (95% CI –4.0 to 3.6)	0.71 0.99 0.21 0.44
				Bone marrow lesions	Very few changes	Very few changes	NR

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Table 3. Continued.

First Author, Country, Yr	Stem Cells	Control	Structural Outcome	Results			
				Outcome Measure	Intervention	Control	*P*
Matas, Chile, 2019[33]	20M MSCs in 3 mL of saline with 5% AB plasma; single dose group: MSCs at baseline and placebo (5% AB plasma in 3 mL of saline) at 6 months (n = 9); repeated dose group: MSCs at baseline and 6 months (n = 9)	3 mL of HA at baseline and 6 months (n = 8)	Articular cartilage	Articular cartilage score	6 months Repeated dose: 21.3 ± 14.1 Single dose: 22.4 ± 10.8 12 months Repeated dose: 21.3 ± 13.8 Single dose: 23.1 ± 10.2	16.7 ± 14.5 16.8 ± 14.5	0.28 0.30
				Meniscal integrity score	6 months Repeated dose: 2.7 ± 2.1 Single dose: 0.9 ± 1.2 12 months Repeated dose: 2.7 ± 2.1 Single dose: 0.9 ± 1.2	1.7 ± 1.6 1.7 ± 1.6	0.13 0.13
				WORMS score	6 months Repeated dose: 40.6 ± 21.4 Single dose: 46.6 ± 18.1 12 months Repeated dose: 40.5 ± 23.9 Single dose: 41.5 ± 14.3	33.2 ± 25.7 33.6 ± 26.3	0.30 0.15
				Composite MRI score			
Khalifeh Soltani, Iran, 2019[34]	10 mL of MSCs, 50–60M (n = 10)	10 mL of normal saline (n = 10)	Articular cartilage	Magnetic resonance arthrography: cartilage thickness	Increased in ~10% of total knee joint areas — superior medial patella maximum ($P = 0.013$), middle medial patella maximum ($P = 0.025$), and tibial compartment, lateral minimum ($P = 0.011$)	No significant change	NR
				Meniscus lesions	Stable 100%	Stable 100%	NR
			Subchondral bone	Spur	Stable 90%	Stable 100%	NR
				Erosion	Stable 40%	Stable 60%	NR
Freitag, Australia, 2019[35]	100M MSCs suspended in injectable sterile isotonic (0.9%) normal saline to a total of 3 mL; 1-injection group (n = 10, baseline); 2-injection group (n=10, baseline and 6 months)	Ongoing conventional conservative management (n = 10)	Articular cartilage	Progression of cartilage loss, n (%)	1-injection: 3 (30) 2-injection: 1 (11)	6 (67)	0.04
				Progression of meniscus pathology, n (%)	1-injection: 1 (10) 2-injection: 0 (0)	1 (11)	0.60
			Subchondral bone	Extension of osteophyte formation, n (%)	1-injection: 5 (50) 2-injection: 1 (11)	5 (56)	0.11
				Progression of bone marrow lesions, n (%)	1-injection: 3 (30) 2-injection: 5 (56)	3 (33)	0.47
Lee, South Korea, 2019[36]	100M MSCs in 3mL 0.9% saline (n = 12)	3 mL of 0.9% saline (n = 12)	Articular cartilage	Change in cartilage defect size, mm^2	2.39 ± 14.54 ($P = 0.5803$)	35.61 ± 58.80 ($P = 0.0049$)	0.005
			Radiograph	Kellgren-Lawrence grade	No significant change	No significant change	NR
				Joint space width	No significant change	No significant change	NR
Lu, China, 2019[37]	50M mesenchymal progenitor cells combined with cell suspension solution (~2.5 mL) injected at 0 and 3 weeks. Sham injection at 1 and 2 weeks (n = 26)	2.5 mL sodium HA injected at 0, 1, 2, and 3 weeks (n = 26)	Articular cartilage	Change in total articular cartilage volume	6 months Left: 17.25 ± 394.23 mm^3 ($P = 0.8431$ vs baseline) Right: 77.81±155.37 mm^3 ($P = 0.0327$ cf. baseline) 12 months	Left: −54.00±227.21 mm^3 ($P = 0.2666$ cf. baseline) Right: −10.15 ± 201.59 mm^3 ($P = 0.8115$ cf. baseline)	> 0.05 > 0.05

Table 3. Continued.

First Author, Country, Yr	Stem Cells	Control	Structural Outcome	Outcome Measure	Results: Intervention	Results: Control	Results: *P*
Lu, China, 2019[37] (continued)					Left: 193.36 ± 282.80 mm^3 (P = 0.0042 cf. baseline)	Left: −101.88 ± 224.30 mm^3 (P = 0.034 cf. baseline)	< 0.001
					Right: 108.70 ± 220.13 mm^3 (P = 0.0307 cf. baseline)	Right: −23.47 ± 291.37 mm^3 (P = 0.70 cf. baseline)	> 0.05
				Change in femoral cartilage volume over 12 months	Left: 134.63 ± 189.16 mm^3	Left: −63.50 ± 222.71 mm^3	0.009
					Right: 121.36 ± 172.25 mm^3	Right: −26.71 ± 170.69 mm^3	0.004
Populations at risk of OA							
Saw, Malaysia, 2013[25]	Stem cell 8 mL + HA 2 mL (n = 25)	HA 2 mL (n = 24)	Articular cartilage	Arthroscopy: histologic grading using ICRS II score	1066	957	0.02
				Flush morphologic features, n (%)	38 (68)	32 (54)	NR
				Good repaired cartilage fill, n (%)	46 (82)	35 (59)	NR
				No-gap cartilage integration, n (%)	44 (79)	35 (59)	NR
			Subchondral bone	Moderate to severe subchondral edema, n (%)	1 (2)	6 (10)	NR
			Composite MRI score	Morphological grading	9.9	8.5	0.01
Vangsness, USA, 2014[27]	Group A (n = 18): 50M, Group B (n = 18): 150M; suspended in 2 mL (20 mg) of sodium hyaluronate, human serum albumin (1.2%), and Plasma-Lyte A	Sodium hyaluronate (n = 19)	Articular cartilage	Significant (> 15%) increase in meniscal volume, n (%)	6 months Group A: 1 (6), P = 0.472 (vs control) Group B: 1 (6), P = 0.486 (vs control)	0	Overall: 0.54
					12 months Group A: 4 (24), P = 0.04 (vs control) Group B: 1 (6), P = 0.486 (vs control)	0	Overall: 0.02
					2 yrs Group A: 3 (18), P = 0.103 (vs control) Group B: 0, P = 1.00 (vs control)	0	Overall: 0.03
				Articular cartilage degeneration at 1 yr, n (%)	Group A: 2 (11) Group B: 2 (11)	1 (5)	NR
			Subchondral bone	Subchondral sclerosis and osteophyte formation	Group A and B: 6%	21%	NR
Wang, Australia, 2017[31]	75M MPC suspended in 2 mL sodium hyaluronate (n = 11)	Sodium hyaluronate 2 mL alone (n = 6)	Articular cartilage	Annual tibial cartilage volume change	6 months Medial 0.7 ± 5.9% Lateral −1.4 ± 5.3%	Medial −4.0 ± 3.9% Lateral −2.7 ± 4.4%	0.10 0.65
					12 months Medial 0.3 ± 6.3% Lateral −4.7 ± 3.4%	Medial −2.4 ± 3.1% Lateral −2.6 ± 2.5%	0.36 0.25
					24 months Medial −1.4 ± 4.2% Lateral −3.7 ± 3.4%	Medial −3.3 ± 5.3% Lateral −0.8 ± 3.5%	0.54 0.22
			Subchondral bone	Rate of total tibial bone expansion	6 months 0.5 ± 2.4%	4.0 ± 2.3%	0.02
					12 months −1.2 ± 2.8%	1.7 ± 2.0%	0.09
					24 months −0.7 ± 1.5%	1.0 ± 1.1%	0.09

Table 3. Continued.

First Author, Country, Yr	Stem Cells	Control	Structural Outcome	Outcome Measure	Results		
					Intervention	Control	*p*
Wang, Australia, 2017[31] (continued)			Radiograph	Change in joint space width	6 months		
					Medial 0.06 (95% CI −0.25 to 0.38)	Medial −0.29 (95% CI −0.67 to 0.10)	0.17
					Lateral −0.41 (95% CI −0.81 to −0.02)	Lateral −0.14 (95% CI −0.61 to 0.33)	0.37
					12 months		
					Medial 0.24 (95% CI −0.09 to 0.56)	Medial −0.07 (95% CI −0.45 to 0.32)	0.25
					Lateral 0.18 (95% CI −0.23 to 0.58)	Lateral −0.64 (95% CI −1.11 to −0.17)	0.01
					18 months		
					Medial 0.76 (95% CI 0.44 to 1.09)	Medial 0.15 (95% CI −0.27 to 0.58)	0.03
					Lateral 0.43 (95% CI 0.04 to 0.83)	Lateral 0.31 (95% CI 0.83 to 0.22)	0.03
					24 months		
					Medial 0.69 (95% CI 0.31 to 1.07)	Medial 0.15 (95% CI −0.27 to 0.58)	0.07
					Lateral 0.25 (95% CI −0.22 to 0.72)	Lateral −0.51 (95% CI −1.03 to 0.02)	0.04

HA: hyaluronic acid; ICRS: International Cartilage Repair Society; IQR: interquartile range; MOCART: Magnetic Resonance Observation of Cartilage Repair Tissue; MPC: mesenchymal precursor cells; MRI: magnetic resonance imaging; MSC: mesenchymal stem cell; NR: not reported; OA: osteoarthritis; PCI: poor cartilage index; WORMS: whole-organ magnetic resonance imaging score.

12 months in the MSC group, whereas the control group had a significant reduction in cartilage volume[37]. In contrast, Matas, *et al* found no significant difference in articular cartilage or meniscal integrity scores between the intervention and control groups over 6 or 12 months[33].

Three studies examined articular cartilage in populations at risk of OA[25,27,31] (Table 3). In Saw, *et al*'s study, a second look arthroscopy with chondral biopsy and histologic evaluation at 18 months after the initial surgery showed a significantly higher ICRS II score in the intervention group compared with the control group[25]. The intervention group scored 14% higher on flush morphologic features, 23% higher on good repaired cartilage fill, and 20% higher on no-gap integration than the control group at 18 months[25]. In the Vangsness, *et al* study, while no patients in the control group met the 15% threshold for increased meniscal volume, significant increase in meniscal volume was observed in 24% of patients treated with 50 million MSCs and 6% of patients treated with 150 million MSCs at 12 months[27]. At the 2-year follow-up, 18% of patients treated with 50 million MSCs had significant increase in meniscal volume that was not observed in the 150 million MSC group or control group, with no significant differences between either MSC or control groups[27]. Wang, *et al* found no significant difference in tibial cartilage volume loss at 6, 12, and 24 months between the intervention group treated with mesenchymal precursor cells (MPC) and the control group[31]. There was a trend in which the MPC group had a reduced rate of medial tibial cartilage volume loss over the first 6 months[31].

Effect of MSCs on subchondral bone outcomes. Three studies examined subchondral bone in OA populations[32,34,35] (Table 3). Freitag, *et al* found a nonsignificant trend of less extension of osteophyte formation over 12 months in patients receiving 2 MSC injections (11%), compared with those receiving 1 MSC injection (50%) or the control group (56%), with no significant difference in bone marrow lesions between groups[35]. Kuah, *et al* found no significant difference in the change in tibial bone area or bone marrow lesions among Progenza 3.9M, Progenza 6.7M, or control groups over 12 months[32]. Khalifeh Soltani, *et al* found no significant change in spur or erosion in either group over 24 weeks[34].

Three studies examined subchondral bone in populations at risk of OA[25,27,31] (Table 3). Wang, *et al* found a significantly reduced rate of tibial bone expansion in the MPC group compared with the control group over 6 months, with the trend maintained over 12 and 24 months[31]. Saw, *et al* found that moderate to severe edema was 2% in the intervention group vs 10% in the control group at 18 months[25]. In Vangsness, *et al*'s study, subchondral bone sclerosis and osteophyte formation were found in 6% of the MSC group and 21% of the control group at 1-year follow-up[27].

Effect of MSCs on composite MRI scores of the knee. Four studies examined composite MRI scores in populations with OA[29,30,33] and at risk of OA[25] (Table 3). Saw, *et al* found morphological MRI grading was significantly higher in the intervention group than the control group at 18 months[25]. Lamo-Espinosa, *et al*

Table 4. Assessment of risk of bias.

First Author, Country, Yr	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Overall Bias Assessment
Saw, Malaysia, 2013[25]	Low	Low	Low	Low	High	Low	Low
Wong, Singapore, 2013[26]	Low	Unclear	Low	Low	Low	Unclear	Moderate
Vangsness, USA, 2014[27]	Low	Low	Low	Low	Unclear	Low	Low
Vega, Spain, 2015[28]	Unclear	Unclear	Low	Low	Unclear	Low	High
Gupta, India, 2016[29]	Low	Low	Low	Unclear	Low	Low	Low
Lamo-Espinosa, Spain, 2016[30]	Low	Low	Low	Low	Low	Low	Low
Wang, Australia, 2017[31]	Unclear	Low	Low	Low	Unclear	Low	Moderate
Kuah, Australia, 2018[32]	Low	Low	Low	Low	Low	Low	Low
Matas, Chile, 2019[33]	Low	Unclear	Low	Low	Low	Low	Low
Khalifeh Soltani, Iran, 2019[34]	Low	Low	Low	Low	Low	Low	Low
Freitag, Australia, 2019[35]	Low	Low	Low	Low	Low	Low	Low
Lee, South Korea, 2019[36]	Unclear	Unclear	Low	Low	Low	Low	Moderate
Lu, China, 2019[37]	Low	Low	Low	Low	Low	Low	Low

found a median improvement of 4 points in WORMS score in the 100M MSC group at 12 months, with 25% of patients having an improvement of 22 points, and no improvement in either the 10M MSC or control group[30]. Studies by Gupta, *et al* and Matas, *et al* showed no significant differences in WORMS score between intervention and control group at 6 or 12 months[29,33].

Effect of MSCs on radiograph outcomes. Three studies assessed joint space width in populations with OA[30,36] and at risk of OA[31] (Table 3). Wang, *et al* showed a greater increase in joint space width at 12, 18, and 24 months in the MPC + HA group than in the HA alone group[31]. Lamo-Espinosa, *et al* found no significant change in joint space width in the MSC groups at 12 months, but a borderline reduction in the control group[30]. Lee, *et* al showed no significant change in joint space width in either group over 6 months[36]. Gupta, *et al*'s study found no clinically meaningful changes in radiograph parameters (details not reported) at 3 and 6 months in either group[29].

Unpublished studies. Searches of trial registers and registries yielded a further 16 possible eligible trials for which no additional full-text reports could be obtained (Supplementary Table 3, available from the authors on request). Eight trials had an actual or estimated completion date prior to 2016, and 1 trial started in 2013 but lacked a recorded completion date. Seven trials had the actual or estimated completion dates between May 2017 and June 2019.

DISCUSSION

We systematically reviewed the evidence for the efficacy of MSC injections in improving OA-related structural outcomes. The evidence syntheses were derived from 13 phase I or II randomized controlled trials comprising 513 participants: 9 of high quality[25,27,29,30,32–35,37], 3 of moderate quality[26,31,36], and 1 of low quality[28]. There was consistent evidence that MSC treatment improved cartilage outcomes assessed by MRI, arthroscopy, or histology, and that it has beneficial effects on subchondral bone in populations at risk of OA. However, there was significant heterogeneity in injected MSCs, modest sample sizes, methodological limitations, and potential for publication bias.

We found consistent evidence for a beneficial effect of MSC therapy on articular cartilage. Among the 11 studies examining cartilage using MRI or arthroscopy, 10 studies showed a beneficial effect of MSC injections[25,26,27,28,31,32,34–37], evidenced by improved cartilage volume/thickness[27,31,32,34,37], morphology[35,36], quality[28], and regeneration and repair[25,26], assessed by MRI, arthroscopy, or histology. Results tended to be similar, regardless of the type (allogeneic or autologous) and origin (bone marrow, adipose tissue, peripheral blood, or placenta) of MSCs, and the differences in study population (stage of OA).

Six studies examined subchondral bone from MRI[25,27,31,32,34,35]. There was consistent evidence for a beneficial effect of MSC therapy on subchondral bone in populations at risk of knee OA, with all 3 studies showing an effect on bone expansion[31], edema[25], sclerosis, and osteophyte formation[27]. The evidence in OA populations was conflicting, with 1 study showing a beneficial effect on osteophyte formation[35]. Although the other 2 OA studies found no effect of MSC injections on tibial bone area, bone marrow lesions[32], spur, or erosion[34], the follow-up of the latter study was only 24 weeks, which may not be enough time to demonstrate an effect on subchondral bone. Bone manifestations are varied and may not be influenced by the same factors.

Four studies examining the effect of MSCs on composite MRI scores of the knee reported inconsistent results, with 2 studies reporting beneficial effect[25,30] and 2 studies reporting no effect[29,33]. Although the overall effect of MSCs on knee structures can be assessed using the composite scores of the whole knee, this method cannot differentiate the effect of MSCs on different joint structures.

Three studies reported inconsistent results for the effect of MSCs on joint space width. While 1 study showed an effect of MSCs on increasing joint space width over 24 months[31], 2 studies found no effect over 6 or 12 months[30,36]. Another study reported no clinically meaningful change in radiograph parameters after 6 months[29]. A follow-up period of up to 12 months might not be enough time to observe meaningful change in radiographic outcomes.

Our systematic review has limitations. Due to the heterogeneity in study populations; sources and contents of MSCs; dose, frequency, and schedule of MSC injections; media in which MSCs were suspended before administration; treatment modalities in the control group; and structural outcome measures, performing a metaanalysis was not possible, so a qualitative evidence synthesis was performed instead. The media in which stem cells were suspended was used as the control intervention in 6 studies[25,26,27,29,31,36]. Although these heterogeneities may limit the ability of our study to draw reliable conclusions, we found consistent evidence that MSC treatment improved cartilage outcomes. However, there was a lack of high-level evidence to support this due to the methodological issues in some studies. Future studies will need to reduce the bias commonly identified in previous studies. It is important to consider that all the studies included in our systematic review were phase I or II trials with modest sample sizes. Given that efficacy is generally not the main aim of phase I or II trials, and that all systematic reviews examining stem cells, including ours, have been based on early-stage clinical trials, we conducted a review of clinical trials databases to examine the potential of publication bias (e.g., only those studies with positive findings being published). We identified a further 8 possible eligible trials with an actual or estimated completion date before 2016 and 1 trial beginning in 2013 that have not been published. The reason these studies have not been published is unknown. However, this needs to be considered, as it may have inflated the effect of stem cell therapy. A further 7 studies were supported by industry funders[27,29,31,32,35,36,37], which might introduce reporting bias. MSC and cell concentrate nomenclature tends to be used interchangeably in the literature, despite the fact that they are different products. It has been suggested that commonly used cell concentrates should be distinguished from laboratory-purified stem cells[41,42]. In our study, we only included studies of laboratory-purified/expanded stem cells.

The ability of MSCs to produce trophic factors for neuronal development and stimulate local tissue repair are key hallmarks for their increasing popularity as an intervention in degenerative diseases[43,44,45]. Inflammation plays an important role in cartilage damage and structural progression in OA[46,47,48]. MSCs may have beneficial effects on articular cartilage and subchondral bone through their antiinflammatory and immunomodulatory properties, since intraarticular injections of MSCs may affect the local environment of the joint[8,9,10,11], as supported by data from animal studies[49]. However, the MSC metabolism and related therapeutic effects are complex, and the composition of injected MSCs is unclear and likely to be highly variable, with few stem cells surviving after injection[12,13,14]. The optimal tissue source, type, dose, and duration of MSC treatment is unknown, as demonstrated by the variation in intervention in this review, and a dose-response relationship has not been established.

Our systematic review, based on 13 phase I or II clinical trials, found consistent evidence for a beneficial effect of intraarticular injections of MSCs on articular cartilage and subchondral bone, irrespective of the source or contents of the MSCs. Due to the heterogeneity in the source and composition of injected MSCs, the early stage of the trials, modest sample sizes, methodological limitations, and potential for publication bias, more work is needed before the therapy is recommended in the management of OA.

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