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-related structural outcomes.

Methods: Ovid Medline and EMBASE were searched from their inception 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 in interventions and outcome measures.

Results: Thirteen randomised controlled trials (phase I or II) were identified, 10 in osteoarthritis populations and three in populations at risk of osteoarthritis, with low (n=9), moderate (n=3) or high (n=1) risk of bias. Seven studies used allogeneic MSCs (bone marrow 4; umbilical cord 1; placenta 1; adipose tissue 1), six studies used autologous MSCs (adipose tissue 3; bone marrow 2; peripheral blood 1). Among the 11 studies examining cartilage

outcomes, 10 studies showed 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 with all three studies in populations at risk of osteoarthritis showing beneficial effects. Sixteen unpublished, eligible trials were identified by searching trial registries, eight with actual or estimated completion date before 2016.

Conclusion: This systematic review of early phase clinical trials showed consistent evidence for a beneficial effect of intra-articular 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 osteoarthritis.

Introduction

Osteoarthritis (OA) causes disability, impaired quality of life, and significant financial burden(1, 2). Current treatment modalities, including analgesics, non-steroidal anti-inflammatory drugs, opiates, intra-articular injections of steroids and hyaluronans, and physical therapies(3-5), only alleviate symptoms with short-term, small to moderate effects(6). No drugs have shown effects on slowing structural progression of OA to be approved as disease-modifying OA drugs(7).

Adult mesenchymal stem cells (MSCs) are multipotent, undifferentiated cells which 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 anti-inflammatory and immunomodulatory activities(8-11). Whilst the use of MSCs has gained momentum in the recent decades, their potential as a treatment for OA remains unclear as studies have shown that few stem cells survive after injection(12-14) and there is a lack of data on the long-term safety and efficacy from larger clinical trials(15-17).

Several systematic reviews that focus on patient-reported outcomes have shown the safety and effectiveness of intra-articular injections of MSCs in improving pain and function in OA(17-24). 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 including six 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). There is a continuum from the normal joint through to established OA and end-stage OA, and pre-clinical diseases, such as focal chondral defect, partial meniscectomy, and anterior cruciate ligament injury, identify those at risk of OA in whom therapies such as MSCs 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

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines(38).

Search strategy

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

Study selection

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

Data extraction and synthesis

Two authors (JG and JF) extracted data on target population, number, sex and age 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's tool for assessing risk of bias in randomized trials(39). This tool covers six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Studies were assessed as "high" or "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). The agreement between the two authors was 86%. Different 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 to the current systematic review but not published: US National Institutes of Health Trial Register (http://www.clinicaltrials.gov), WHO International Clinical Trials Registry Platform (http://apps.who.int), European Clinical Trial Register (http://www.clinicaltrialsregister.eu), Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au), and International Standard Randomised Controlled Trial Number registry (http://www.isrctn.com).

Results

Study selection

Figure 1 shows 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, one on spine). No additional articles were found after searching the references of published research or review articles. The study on degenerative disc disease(40) was further excluded as 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), two from Spain(28, 30), and single studies from Malaysia(25), Singapore(26), Iran(34), USA(27), Chile(33), South Korea(36), China(37) and India(29). The mean age of participants ranged 26-66 years and percentage of men ranged 10%-71%. Ten studies included patients with knee OA, defined using Kellgren and Lawrence (K-L) grade(28-30, 32-37) or criteria not clearly specified(26). Other studies examined patients with International Cartilage Repair Society (ICRS) grade 3-4 cartilage lesions(25), partial meniscectomy(27), or unilateral anterior cruciate ligament injury(31). The follow-up was 6(34, 36), 12(26, 28-30, 32, 33, 35, 37), 18(25), or 24(27, 31) months. Six studies were funded by companies(27, 29, 31, 32, 35, 36), four studies by government(25, 28, 30, 34), one study by company and government(37), two 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(27-29, 31), umbilical cord(33), placenta(34), or adipose tissue(32). Six studies used autologous MSCs, derived from adipose tissue(35-37), bone marrow(26, 30), or peripheral blood(25). Twelve trials performed immunophenotypic characterization of MSCs(25-31, 33-37), reporting positive CD105, CD90, or CD73(26-30, 33-35, 37), and negative CD34, CD35, CD14, CD19, or Human Leukocyte Antigen - antigen D Relate (HLA-DR)(26-30, 33-35, 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 intra-articular injection of varying doses. Eleven studies involved a single injection(26-36) with two studies also involving two injections at baseline and 6-month(33, 35). One study applied 8 injections(25). One study involved two injections at weeks 0 and 3(37). Seven studies used a single dose(25, 26, 28, 31, 34, 36, 37), five studies had two dose groups(27, 30, 32, 33, 35), and one 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(34-36), HA, human serum albumin and Plasma-Lyte A(27), Ringer's 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 intra-articular injection of HA(25-28, 30, 31, 33, 37), normal saline(34, 36), Plasma-Lyte A(29), or cell culture media and cryopreservative(32). One study used standard care as the control(35).

Assessment of structural outcomes

Structural outcomes were the primary outcome in four studies(25, 27, 30, 34) and the secondary outcome in nine studies(26, 28, 29, 31-33, 35-37) (Supplementary Table 2). Knee structure was assessed in eight studies by magnetic resonance imaging (MRI) only(26-28, 32-35, 37), four studies by both MRI and x-ray(29-31, 36), and one 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 using validated arthroscopy grading systems(25). Subchondral bone outcomes were tibial bone area(31, 32), bone marrow lesions(25, 32, 35), subchondral bone sclerosis and osteophyte formation(27, 34, 35) from MRI. Composite MRI scores of multiple features were assessed using 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). X-ray outcome was joint space width(30, 31, 36) or not specified(29).

Risk of bias assessment

The overall risk of bias was low in nine trials(25, 27, 29, 30, 32-35, 37), moderate in three trials(26, 31, 36), and high in one trial(28) (Table 3). 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 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, 32-37) (Table 4). Wong et al showed significantly better Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score and more prevalent cartilage coverage (complete and >50%) and 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 two groups at 12-month(28). Kuah'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 over 12-month(32). Khalifeh Soltani et al showed increased cartilage thickness in the intervention group while no significant change in the control group over 24-week; no significant change in meniscus lesions was seen in either group(34). Freitag et al showed significantly reduced progression of cartilage loss in those treated with two MSC injections (11%), compared with those treated with one MSC injection (30%) or the controls (67%) at 12-month(35). Lee et al demonstrated a significant increase in cartilage defect size in the control group but not in the MSC group at 6-month(36). Lu et al showed a significant increase in knee cartilage volume at 12-month in the MSC group, whereas the control group had a significant reduction in cartilage volume(37). In contrast, Matas et al showed no significant difference in articular cartilage or meniscal integrity scores between the intervention and control groups over 6- or 12-month(33).

Three studies examined articular cartilage in populations at risk of OA(25, 27, 31) (Table 4). In Saw'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-month(25). In Vangsness's 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-month(27). At 2-year follow-up, 18% of patients treated with 50 million MSCs had significant increase in meniscal volume which was not observed in the 150 million MSC group or control group, with no significant differences between either MSC group and control group(27). Wang et al found no significant difference in tibial cartilage volume loss over 6-, 12-, and 24-month between the intervention group treated with mesenchymal precursor cells (MPC) and the control group(31). There was a trend for MPC group having a reduced rate of medial tibial cartilage volume loss over the first 6-month(31).

Effect of MSCs on subchondral bone outcomes

Three studies examined subchondral bone in OA populations(32, 34, 35) (Table 4). Freitag et al showed a non-significant trend of less extension of osteophyte formation over 12-month in patients receiving two MSC injections (11%), compared with those receiving one 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, and control groups over 12-month(32). Khalifeh Soltani's study found no significant change in spur or erosion in either group over 24-week(34).

Three studies examined subchondral bone in populations at risk of OA(25, 27, 31) (Table 4). Wang et al found significantly reduced rate of tibial bone expansion in the MPC group compared with the control group over 6-month, with the trend maintained over 12- and 24-month(31). Saw et al showed moderate to severe edema was 2% in the intervention group vs. 10% in the control group at 18-month(25). In Vangsness's study, subchondral bone sclerosis and osteophyte formation were found in 6% of the MSC group and 21% of the control group

at one-year(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 4). Saw et al found morphological MRI grading was significantly higher in the intervention group than the control group at 18-month(25). Lamo-Espinosa et al showed a median improvement of 4 points in WORMS score in 100M MSC group at 12-month, with 25% of patients having an improvement of 22 points, while no improvement in either 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-month(29, 33).

Effect of MSCs on x-ray outcomes

Three studies assessed joint space width in populations with OA(30, 36) and at risk of OA(31) (Table 4). Wang et al showed a greater increase in joint space width at 12-, 18- and 24-month in the MPC+HA group than the HA alone group(31). Lamo-Espinosa et al showed no significant change in joint space width in the MSC groups at 12-month, but a borderline reduction in the control group(30). Lee's study showed no significant change in joint space width in either group over 6-month(36). Gupta's study found no clinically meaningful changes in x-ray parameters (details not reported) at 3- and 6-month in either group(29).

Unpublished studies

Search 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). Eight trials had the actual or estimated completion date prior to 2016 and one trial started in 2013 but lacked a

recorded completion date. Seven trials had the actual or estimated completion date 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 14 phase I or II randomized controlled trials comprised of 513 participants; nine of high quality(25, 27, 29, 30, 32-35, 37), three of moderate quality(26, 31, 36), and one of low quality(28). There was consistent evidence that MSC treatment improved cartilage outcomes assessed from MRI, arthroscopy, or histology, and consistent evidence for beneficial effects on subchondral bone in populations at risk of OA. However, there were 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(25-28, 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 from 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 difference 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 three studies showing an effect on bone expansion(31), edema(25), sclerosis and osteophyte formation(27). The evidence in OA

populations was conflicting, with one study showing a beneficial effect on osteophyte formation(35). Although the other two 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 to demonstrate an effect on subchondral bone. Bone manifestation 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 two studies reporting beneficial effect(25, 30) and two 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, it 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 one study showed an effect of MSCs on increasing joint space width over 24-month(31), two studies found no effect over 6- or 12-month(30, 36). Another study reported no clinically meaningful change in x-ray parameters over 6-month(29). A follow-up up to 12 months may not be enough to observe meaningful change in radiographic outcomes.

This systematic review has limitations. Due to the heterogeneity in study populations, sources and contents of MSCs, doses, frequencies and schedules of MSC administration, media in which MSCs were suspended before administration, treatment modalities in the control group, and structural outcome measures, performing a meta-analysis was not possible, so a qualitative evidence synthesis was performed. The media in which stem cells were suspended was used as the control intervention in six studies(25-27, 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 the 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, but all systematic reviews examining stem cells, including our one, have been based on early stage clinical trials, we conducted a review of clinical trials databases to examine the potential of publication bias, i.e. only those studies with positive findings being published. We identified a further eight possible eligible trials with actual or estimated completion date before 2016 and one trial starting 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. Seven studies were supported by industry funders(27, 29, 31, 32, 35-37), which might introduce reporting bias. There is a mixed use in nomenclature of MSCs and cell concentrates in the literature, although 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 its increasing popularity as an intervention in degenerative diseases(43-45). Inflammation plays an important role in cartilage damage and structural progression of OA(46-48). MSCs may have beneficial effects on articular cartilage and subchondral bone via their anti-inflammatory and immunomodulatory properties that intra-articular injection of MSCs may affect the local environment of the joint(8-11), with supportive 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(12-14). The optimal tissue source, type, dose and duration of MSC treatment is unknown, demonstrated by the variation in intervention in this review, and dose-response relationship has not been established.

This systematic review, based on 14 phase I or II clinical trials, showed consistent evidence for a beneficial effect of intra-articular injections of MSCs on articular cartilage and subchondral bone, irrespective of the sources or contents of MSCs. Due to the heterogeneity in source and composition of injected MSCs, 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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Figure Legends

Figure 1: PRISMA flow diagram of included articles

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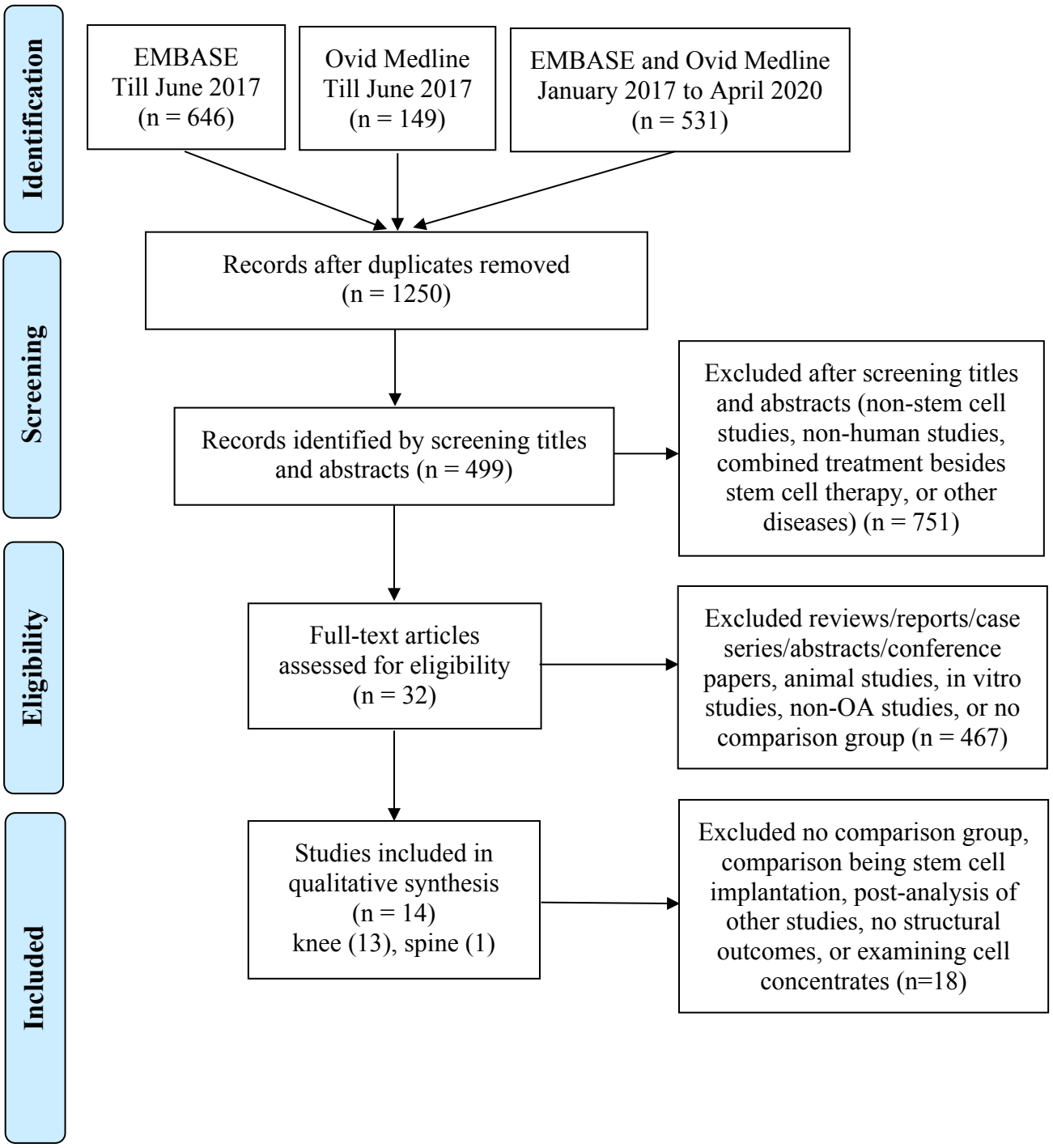

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Table 1. Search terms and inclusion and exclusion criteria

Search terms		
Injection	Stem cell	Joint structure or osetoarthritis
injections or intramuscular injections or spinal injections or intra-articular 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
Searches were limited to human studies and English language.		
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.		

Table 2: General characteristics of included studies

Author Country Year Trial phase	Study population (% men)	Age of study participants, years (mean±SD)	Source of stem cells	Immunophenotypic characterisation	Route of administration & number of injections	Outcome measures	Duration of follow-up	Source of funding
Saw et al. Malaysia 2013(25) Phase II	49 patients with International Cartilage Repair Society (ICRS) grade 3 and 4 lesions of the knee who underwent arthroscopic subchondral drilling and abrasion chondroplasty (Men 35%)	Stem cell group: 38±7.33 HA group: 42±5.91	Autologous peripheral blood stem cells	Positive CD34 and CD105	Intra-articular injection of the knee 8 (First 5 injections began at 1 week on a weekly basis. Three additional injections administered at 6 months at weekly intervals)	MRI: Repaired cartilage signal, repaired lesion morphologic features, repaired cartilage fill, peripheral repaired cartilage integration, subchondral oedema, and osseous overgrowth (maximum score of 12) Second-look arthroscopy with chondral core biopsy, histologic evaluation and	18 months	The Ministry of Science, Technology and Innovation Technofund, Malaysia

						grading using the ICRS II (maximum score of 1400)		
Wong et al. Singapore 2013(26) Phase not specified	56 patients with medial-compartment OA and genu varum who underwent arthroscopic microfracture and medial opening-wedge high tibial osteotomy (Men 48%)	MSC group: 53 (36-54) HA group: 49 (24-54)	Autologous bone marrow-derived MSCs	Positive CD73, CD90, and CD105 Negative CD14, CD20, CD34, and CD45	Intra-articular injection of the knee 1	MRI: Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score	12 months	No funding reported
Vangsness et al. USA 2014(27) Phase I/II	55 patients with a partial medial meniscectomy (Men 63%)	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 MSCs	Positive CD105, CD 73, CD29, CD44, CD71, CD90, CD106, CD120a, CD124, CD166 Negative markers of hematopoietic lineages, CD14, CD34, and CD45	Intra-articular injection of the knee 1	MRI: meniscus regeneration: >15% increase in meniscal volume WORMS: cartilage degeneration, thickening, sclerosis of subchondral bone, osteophyte	24 months	Osiris Therapeutics, Columbia, Maryland

						formation, and femoral or tibial edema		
Vega et al. Spain 2015(28) Phase I/II	30 patients with Kellgren-Lawrence grade 2-4 knee OA and chronic knee pain unresponsive to conservative treatments (Men 43%)	MSC group: 56.7±9.5 HA group: 57.3±9.4	Allogeneic bone marrow-derived MSCs	Strongly positive CD90 and CD166 Moderately positive CD105, CD106 and kinase insert domain receptor Negative CD34, CD45 and HLA-DR	Intra-articular injection of the knee 1	MRI: Articular cartilage quality assessed by quantitative T2 mapping	12 months	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
Gupta et al. India 2016(29)	60 patients with symptomatic radiographic knee OA	Cohort 1 MSC dose level 1: 58.1±8.2	Allogeneic bone marrow-derived MSCs	Positive CD73, CD105, CD90 and CD166	Intra-articular injection of the knee	X-ray no details provided MRI:	12 months	Stempeutics Research Pvt. Ltd., Bangalore

Phase II	(Kellgren-Lawrence grade 2 to 3) (Men 25%)	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±6.7 Placebo 2: 56.7±5.2		Negative CD34, CD45, CD133, CD14, CD19 and HLA-DR	1	WORMS: cartilage signal and morphology, marginal osteophytes, subarticular bone marrow abnormality, subarticular cysts, subarticular bone attrition, menisci, cruciate ligaments		
Lamo-Espinosa et al. Spain 2016(30) Phase I/II	30 patients with diagnosed knee OA and Kellgren-Lawrence grade ≥2 (Men 63%)	Low dose MSC group: 65.9 (59.5-70.6) High dose MSC group:	Autologous bone marrow-derived MSCs	Positive CD90, CD73 and CD44 Negative CD34 and CD45	Intra-articular injection of the knee 1	X-ray: joint space width MRI: WORMS: number and location of the lesions,	12 months	Instituto de Salud Carlos III

		57.8 (55.0-60.8) HA group: 60.3 (55.1-61.1)				cartilage thickness, signal intensity, subchondral bone alternation and volume		
Wang et al. Australia 2017(31) Phase Ib/IIa	17 patients with unilateral anterior cruciate ligament injury and subject to a reconstruction within 6 months but with no visual evidence of articular cartilage lesions (Men 71%)	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 HLAs measured by flow cytometry	Intra-articular injection of the knee 1	X-ray: joint space width MRI: tibial cartilage volume and bone area	24 months	Mesoblast Ltd.
Kuah et al. Australia 2018(32) Phase I	20 patients with Kellgren-Lawrence grade 1-3 knee OA with moderate to severe pain	MSC 3.9M group: 50.8±7.29	Allogeneic adipose-derived MSCs	Not reported	Intra-articular injection of the knee 1	MRI: tibial cartilage volume, tibial bone area, semi-quantitative assessment of	12 months	Regeneus Ltd.

	(Men 60%)	MSC 6.7M group: 55.0±5.15 Placebo group: 55.0±10.42				cartilage defects and bone marrow lesions		
Matas et al. Chile 2019(33) Phase I/II	29 patients with symptomatic knee OA (Kellgren-Lawrence grade 1-3), without meniscal rapture (Men 45%)	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 MSCs	Positive CD73, CD90 and CD105 Negative CD45, CD34, and HLA-DR	Intra-articular injection of the knee 1 (baseline) 2 (baseline and 6 month)	MRI: WORMS score (14 items, 0-332 points), articular cartilage score, meniscal integrity score	12 months	No funding reported.
Khalifeh Soltani et al. Iran 2019(34) Phase I/II	20 patients with symptomatic knee OA (Kellgren-Lawrence grade 2-4) (Men 10%)	MSC group: 57.5 years Control group: 55.8 years	Allogeneic placenta-derived MSCs	Positive CD73, CD90, and CD105 Negative CD34, CD45, and CD31	Intra-articular injection of the knee 1	MRI: Magnetic resonance arthrography: Cartilage thickness measured at 14 sites, synovial hypertrophy,	24 weeks	The National Institute For Medical Research Development

						spur, erosion, meniscus, and anterior cruciate ligament injury		
Freitag et al. Australia 2019(35) Phase II	30 patients with unilateral symptomatic knee OA (Kellgren-Lawrence grade 2-3) (Men 53%)	MSC one injection group: 54.6±6.3 MSC two injection group: 54.7±10.2 Control group: 51.5±6.1	Autologous adipose-derived MSCs	Positive CD90, CD73 and CD105 Negative CD14, CD19, CD34, and CD45	Intra-articular injection of the knee 1 (baseline) 2 (baseline and 6 month)	MRI: MRI Osteoarthritis Knee Score – bone marrow lesions and cysts, articular cartilage, osteophytes, synovitis, meniscus, peri-articular features	12 months	Magellan Stem Cells and Melbourne Stem Cell Centre
Lee et al. South Korea 2019(36) Phase IIb	24 patients with knee OA (Kellgren-Lawrence grade 2-4), pain intensity on visual analogue scale ≥4/10 for at least 12 weeks (Men 25%)	MSC group: 62.2±6.5 Control group: 63.2±4.2	Autologous adipose-derived MSCs	Tested for CD31, CD34, CD45, CD 73, CD 90	Intra-articular injection of the knee 1	X-ray: Kellgren-Lawrence grade, joint space width MRI: size and depth of cartilage defects	6 months	R-Bio Co., Ltd.

Lu et al. China 2019(37) Phase IIb	53 patients with knee OA (American College of Rheumatology criteria; Kellgren Lawrence grade 1-3) and pain (Male 11.5%)	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	Intra-articular injection of the knee 2 (weeks 0 and 3)	MRI: Knee cartilage volume (femur, tibia, and patella)	12 months	The Cellular Biomedicine Group and the National Key Research and Development Program of China

HA, hyaluronic acid or hyaluronan; OA, osteoarthritis; MSC, mesenchymal stem cell; HLA-DR, human leukocyte antigen-antigen D related; WORMS, whole-organ magnetic resonance imaging score

Table 3. Assessment of risk of bias

Clinical trials	Random Sequence Generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall bias assessment
Saw et al. Malaysia 2013(25)	low	low	low	low	high	low	low
Wong et al. Singapore 2013(26)	low	unclear	low	low	low	unclear	moderate
Vangsness et al. USA 2014(27)	low	low	low	low	unclear	low	low
Vega et al. Spain 2015(28)	unclear	unclear	low	low	unclear	low	high
Gupta et al. India 2016(29)	low	low	low	unclear	low	low	low
Lamo-Espinosa et al. Spain 2016(30)	low	low	low	low	low	low	low
Wang et al.	unclear	low	low	low	unclear	low	moderate

Australia 2017(31)							
Kuah et al. Australia 2018(32)	low	low	low	low	low	low	low
Matas et al. Chile 2019(33)	low	unclear	low	low	low	low	low
Khalifeh Soltani et al. Iran 2019(34)	low	low	low	low	low	low	low
Freitag et al. Australia 2019(35)	low	low	low	low	low	low	low
Lee et al. South Korea 2019(36)	unclear	unclear	low	low	low	low	moderate
Lu et al. China 2019(37)	low	low	low	low	low	low	low

Table 4: Effect of stem cell injections on joint structural outcomes

Author Country Year	Stem cells	Control	Structural outcomes	Results			
				Outcome measures	Intervention	Control	P value
Populations with OA							
Wong et al. Singapore 2013(26)	MSC 14.6 million + hyaluronic acid 2 mL (n=28)	hyaluronic acid 2 mL (n=28)	Articular cartilage	MOCART Score (evaluation of cartilage repair) Cartilage coverage Complete integration of regenerated cartilage	62.32±17.56 9 (32%) complete coverage; 10 (36%) >50% coverage 17 (61%)	43.21±13.55 0 complete coverage; 4 (14%) >50% coverage 4 (14%)	p<0.001 p<0.001 p<0.001
Vega et al. Spain 2015(28)	MSC 40 million (n=15) suspended in Ringer lactate solution containing 0.5% human albumin and 5 mM glucose	hyaluronic acid 60 mg (n=15)	Articular cartilage	Cartilage quality (T2 mapping): poor cartilage index (PCI) PCI improvement plotted against baseline score, slope of line (efficiency of treatment)	Significant decrease (p<0.05) 0.69	Non-significant decrease (p>0.05) 0.28	Not reported p>0.05

Gupta et al. India 2016(29)	25 million (n=10) 50 million (n=10) 75 million (n=10) 150 million (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	p=0.55 p=0.74 p=0.53 p=0.06
			X-ray	Parameters not presented	No clinically meaningful change (data not presented)	No clinically meaningful change (data not presented)	Not reported
Lamo-Espinosa et al. Spain 2016(30)	10 million (n=10) 100 million (n=10) suspended in Ringer's lactate buffer containing 1% human	hyaluronic acid 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)	Not reported

	albumin		X-ray	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	Not reported
Kuah et al. Australia 2018(32)	Progenza (PRG) 3.9 million (n=8) 6.7 million (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)	p=0.964 p=0.022 p=0.685 p=0.475
				Cartilage defects	Very few change	Very few change	Not reported
			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)	Medial 1.4% (95% CI -1.6 to 4.3) Lateral -0.2% (95% CI -4.0 to 3.6)	p=0.712 p=0.993

					6.7M: Medial -1.0% (95% CI -3.1 to 1.1) Lateral -2.0% (95% CI -4.9 to -0.9)		p=0.205 p=0.436
				Bone marrow lesions	Very few change	Very few change	Not reported
Matas et al. Chile 2019(33)	20 million 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	3 mL of hyaluronic acid at baseline and 6 months (n=8)	Articular cartilage	Articular cartilage score	<u>6 months</u> Repeated dose: 21.3±14.1 Single dose: 22.4±10.8 <u>12 months</u> Repeated dose: 21.3±13.8 Single dose: 23.1±10.2	16.7±14.5 16.8±14.5	p=0.28 p=0.30
				Meniscal integrity score	<u>6 months</u> Repeated dose: 2.7±2.1 Single dose: 0.9±1.2 <u>12 months</u> Repeated dose: 2.7±2.1 Single dose: 0.9±1.2	1.7±1.6 1.7±1.6	p=0.13 p=0.13

	group: MSCs at baseline and 6 months (n=9)		Composite MRI score	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	p=0.30 p=0.15
Khalifeh Soltani et al. Iran 2019(34)	10 mL of MSCs, 50-60 million (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	Not reported
				Meniscus lesions	Stable 100%	Stable 100%	Not reported
			Subchondral bone	Spur	Stable 90%	Stable 100%	Not reported
				Erosion	Stable 40%	Stable 60%	Not reported

Freitag et al. Australia 2019(35)	100 million MSCs suspended in injectable sterile isotonic (0.9%) normal saline to a total of 3 mL One-injection group (n=10, baseline) Two-injection group (n=10, baseline and 6 month)	Ongoing conventional conservative management (n=10)	Articular cartilage	Progression of cartilage loss Progression of meniscus pathology	One-injection: 3 (30%) Two-injection: 1 (11%) One-injection: 1 (10%) Two-injection: 0	6 (67%) 1 (11%)	p=0.043 p=0.598
			Subchondral bone	Extension of osteophyte formation Progression of bone marrow lesions	One-injection: 5 (50%) Two-injection: 1 (11%) One injection: 3 (30%) Two-injection: 5 (56%)	5 (56%) 3 (33%)	p=0.107 p=0.474
Lee et al. South Korea 2019(36)	100 million 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)	p=0.0051
			X-ray	Kellgren-Lawrence grade Joint space width	No significant change No significant change	No significant change No significant change	Not reported Not reported
Lu et al. China 2019(37)	50 million mesenchymal progenitor cells	2.5 mL sodium hyaluronic acid injected at week	Articular cartilage	Change in total articular cartilage volume	6 months		

	combined with cell suspension solution (~2.5 mL) injected at weeks 0 and 3. Sham injection at weeks 1 and 2 (n=26)	0, 1, 2, and 3 (n=26)		Change in femoral cartilage volume over 12 months	Left: 17.25±394.23 mm^3 (p=0.8431 cf. baseline) Right: 77.81±155.37 mm^3 (p=0.0327 cf. baseline) 12 months Left: 193.36±282.80 mm^3 (p=0.0042 cf. baseline) Right: 108.70±220.13 mm^3 (p=0.0307 cf. baseline) Left: 134.63±189.16 mm^3 Right: 121.36±172.25 mm^3	Left: -54.00±227.21 mm^3 (p=0.2666 cf. baseline) Right: -10.15±201.59 mm^3 (p=0.8115 cf. baseline) Left: -101.88±224.30 mm^3 (p=0.0362 cf. baseline) Right: -23.47±291.37 mm^3 (p=0.6967 cf. baseline) Left: -63.50±222.71 mm^3 Right: -26.71±170.69 mm^3	p>0.05 p>0.05 p<0.001 p>0.05 p=0.0086 p=0.0038
Populations at risk of OA							
Saw et al. Malaysia	Stem cell 8 mL + hyaluronic acid 2	hyaluronic acid 2 mL (n=24)	Articular cartilage	Arthroscopy: histologic grading using ICRS II score	1066	957	p=0.022

2013(25)	mL (n=25)			Flush morphologic features Good repaired cartilage fill No gap cartilage integration	38 (68%) 46 (82%) 44 (79%)	32 (54%) 35 (59%) 35 (59%)	Not reported Not reported Not reported
			Subchondral bone	Moderate to severe subchondral edema	1 (2%)	6 (10%)	Not reported
			Composite MRI score	Morphological grading	9.9	8.5	p=0.013
Vangsness et al. USA 2014(27)	Group A (n=18): 50 million Group B (n=18): 150 million 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	<u>6 months</u> Group A: 1 (6%), p=0.472 (vs control) Group B: 1 (6%), p=0.486 (vs control) <u>12 months</u> Group A: 4 (24%), p=0.04 (vs control) Group B: 1 (6%), p=0.486 (vs control) <u>2 years</u> Group A: 3 (18%), p=0.103 (vs control)	0 0 0	Overall p=0.535 Overall p=0.022 Overall p=0.029

				Articular cartilage degeneration at 1 year	Group B: 0, p=1.00 (vs control) Group A: 2 (11%) Group B: 2 (11%)	1 (5%)	Not reported
			Subchondral bone	Subchondral sclerosis and osteophyte formation	Group A and B: 6%	21%	Not reported
Wang et al. Australia 2017(31)	75 million mesenchymal precursor cells (MPC) suspended in 2 mL sodium hyaluronate (n = 11)	sodium hyaluronate 2mL alone (n=6)	Articular cartilage	Annual tibial cartilage volume change	6 months Medial 0.7±5.9% Lateral -1.4±5.3% 12 months Medial 0.3±6.3% Lateral -4.7±3.4% 24 months Medial -1.4±4.2% Lateral -3.7±3.4%	Medial -4.0±3.9% Lateral -2.7±4.4% Medial -2.4±3.1% Lateral -2.6±2.5% Medial -3.3±5.3% Lateral -0.8±3.5%	p=0.10 p=0.65 p=0.36 p=0.25 p=0.54 p=0.22
			Subchondral bone	Rate of total tibial bone expansion	6 months 0.5±2.4% 12 months -1.2±2.8% 24 months	4.0±2.3% 1.7±2.0%	p=0.02 p=0.09

					-0.7±1.5%	1.0±1.1%	p=0.09
			X-ray	Change in joint space width	6 months Medial 0.06 (95% CI -0.25, 0.38) Lateral -0.41 (95% CI -0.81, -0.02) 12 months Medial 0.24 (95% CI -0.09, 0.56) Lateral 0.18 (95% CI -0.23, 0.58) 18 months Medial 0.76 (95% CI 0.44, 1.09) Lateral 0.43 (95% CI 0.04, 0.83) 24 months Medial 0.69 (95% CI 0.31, 1.07)	Medial -0.29 (95% CI -0.67, 0.10) Lateral -0.14 (95% CI -0.61, 0.33) Medial -0.07 (95% CI -0.45, 0.32) Lateral -0.64 (95% CI -1.11, -0.17) Medial 0.15 (95% CI -0.27, 0.58) Lateral -0.31 (95% CI -0.83, 0.22) Medial 0.15 (95% CI -0.27, 0.58)	p=0.17 p=0.37 p=0.25 p=0.01 p=0.03 p=0.03 p=0.07 p=0.04

					Lateral 0.25 (95% CI -0.22, 0.72)	Lateral -0.51 (95% CI -1.03, 0.02)	

MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; ICRS, International Cartilage Repair Society; MOCART, Magnetic Resonance Observation of Cartilage Repair Tissue; WORMS, whole-organ magnetic resonance imaging score; IQR, interquartile range; CI, confidence interval