# Intra-articular Mesenchymal Stem Cell Therapy for the Human Joint

## A Systematic Review

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**Background:** Stem cell therapy is emerging as a potential treatment of osteoarthritis (OA) and chondral defects (CDs). However, there is a great deal of heterogeneity in the literature. The indications for stem cell use, the ideal tissue source, and the preferred outcome measures for stem cell–based treatments have yet to be determined.

**Purpose:** To provide clinicians with a comprehensive overview of the entire body of the current human literature investigating the safety and efficacy of intra-articular mesenchymal stem cell (MSC) therapy in all joints.

**Methods:** To provide a comprehensive overview of the current literature, all clinical studies investigating the safety and efficacy of intra-articular MSC therapy were included. PubMed, MEDLINE, and Cochrane Library databases were searched for published human clinical trials involving the use of MSCs for the treatment of OA and CDs in all joints. A total of 3867 publications were screened.

**Results:** Twenty-eight studies met the criteria to be included in this review. Fourteen studies treating osteoarthritis and 14 studies treating focal chondral defects were included. MSCs originating from bone marrow (13), adipose tissue (12), synovial tissue (2), or peripheral blood (2) were administered to 584 distinct individuals. MSCs were administered into the knee (523 knees), foot/ankle (61), and hip (5). The mean follow-up time was 24.4 months after MSC therapy. All studies reported improvement from baseline in at least 1 clinical outcome measure, and no study reported major adverse events attributable to MSC therapy.

**Discussion:** The studies included in this review suggest that intra-articular MSC therapy is safe. While clinical and, in some cases, radiological improvements were reported for both OA and CD trials, the overall quality of the literature was poor, and heterogeneity and lack of reproducibility limit firm conclusions regarding the efficacy of these treatments.

**Conclusion:** This review provides strong evidence that autologous intra-articular MSC therapy is safe, with generally positive clinical outcomes.

**Keywords:** mesenchymal stem cell; MSC; intra-articular; stem cell; human

Adult cartilage is characterized by a limited intrinsic repair capacity after injury, owing to the sparse distribution of highly differentiated chondrocytes, the low supply of progenitor cells, and the lack of vascular supply.[44] Traumatic or pathologic injury to articular hyaline cartilage commonly leads to progressive damage and irreversible joint degeneration. Osteoarthritis (OA) affects an estimated 15% of the world's population and is the most common joint disorder in the United States.[27]

To address the critical need for new therapies and the limited intrinsic repair capacity of cartilage, a number of groups have turned to stem cell–based treatments. Indeed, stem cell therapy is emerging as a potential strategy for tissue repair and regeneration within many fields of medicine.[1-4] In orthopaedics, mesenchymal stem cells (MSCs) have shown promising therapeutic potential for patients with OA,[1] chondral defects,[26,28,32] and soft tissue injuries.[44]

MSCs are cells of mesodermal origin and are precursors to bone, cartilage, fat, tendon, and ligament.[37] They can be grown in culture with relative ease, and large-scale manufacturing protocols and regulatory guidelines for

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MSCs have been established. MSCs secrete a broad range of bioactive molecules, including growth factors, cytokines, and chemokines, which is thought to constitute one of their most biologically significant roles under injury conditions.[3,30,49] Research has suggested that MSCs initiate regenerative repair by influencing local endogenous progenitor cells via paracrine communication,[4] although the in vivo therapeutic mechanisms of MSCs are still unclear.

Previous attempts to review intra-articular MSC-based therapy have been limited by a lack of quality literature on the topic. To provide clinicians with a comprehensive overview of the literature, the following review includes all clinical studies investigating the safety and efficacy of intra-articular MSC therapy in all joints.

## METHODS

A comprehensive search of the literature was carried out in October 2016 (Figure 1). Electronic databases (PubMed, MEDLINE, Cochrane Library) were utilized to identify relevant published studies. The search terms were "mesenchymal stem cells" followed by 1 of the following: "intra-articular injection," "implantation," "chondral defects," "osteoarthritis," or "joint treatment." This yielded 3867 results, which were further filtered in PubMed/MEDLINE with the "human" species (ie, MSCs AND intra-articular injection AND Human[Mesh]), leaving 2038 abstracts for review. Irrelevant, duplicate, and non-English articles, in addition to studies with nonhuman subjects, were excluded, yielding 55 full texts for review. These articles and bibliographies were analyzed for studies where MSCs were administered to human joints via intra-articular injection or implantation as a treatment for focal chondral defects or OA and the treatment's efficacy and safety were both measured. Case studies with $\leq$2 patients and studies published only in abstract form were excluded. Eight publications were added from bibliographies, leaving 28 articles for final inclusion.

The studies included in this review were sorted into 2 groups: intra-articular injection for OA and treatment for focal cartilage defects (CDs). Information collected on study design included pathologic findings, number of subjects receiving MSC therapy, joint type, cell source, cell identification method, mean cell number, cell passages, adjuvant, comparator, mean follow-up, and adverse events (Tables 1 and 2 for OA and CDs, respectively). Information collected on study results included mean follow-up, clinical outcome measures and their corresponding scores, whether scores improved significantly from baseline, whether one group was significantly different than its comparator (if applicable), imaging outcomes measured, and other outcomes measured (Tables 3 and 4 for OA and CD, respectively). Other outcome measures include outcomes with nonnumerical results and subscales of the clinical outcome measures if those subscales were not explicitly designated as an outcome of interest in the study. Additionally, we elected to use the format "tissue source–MSC" (eg, "A-MSC" for adipose-derived MSCs, "BM-MSC" for bone marrow–derived MSCs) when defining the source of the MSCs to standardize the nomenclature. Nomenclature is a topic of debate, but we believe that this is an easily interpreted format when comparing MSCs from multiple tissue sources.

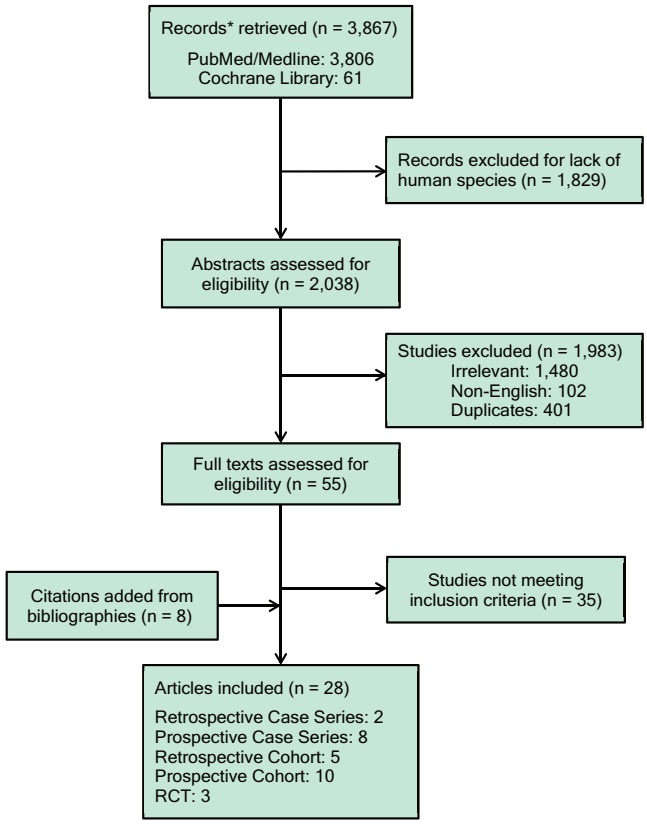


**Figure 1.** Flow chart describing literature evaluation methods. Asterisk (*) indicates records defined as search results recovered in PubMed/MEDLINE. RCT, randomized controlled trial.

## RESULTS

Twenty-eight publications investigating the safety and efficacy of human intra-articular implantation and/or injection of MSCs for the treatment of OA (14) and focal chondral defects (14) were included in this study (Tables 1 and 2). Several study designs were utilized, including 8 prospective and 2 retrospective case series, 10 prospective and 5 retrospective cohort studies, and 3 randomized controlled trials. A mean of 23 individuals (range, 3-70) per study were treated with MSCs, and 7 studies treated $\leq$10 individuals with stem cells.[2,7,8,10,13,40,47]

MSCs originating from autologous iliac crest bone marrow (12 studies), autologous adipose tissue (12), autologous synovial tissue (2), autologous peripheral blood (2), or allogenic bone marrow (1) were injected or implanted into a total of 584 distinct individuals. Autologous adipose tissue was acquired from 3 sources: buttocks (8 studies),

TABLE 1
Study Design for Osteoarthritis Studies[a]

| Citation | Design | Patients Receiving MSC Therapy, No. | Joint Type (No.) | Cell Source | Cell Identification Method | Mean No. of Injected Cells × $10^6$ | Cell Passages | Adjuvant | Comparator | Mean Follow-up, mo |
|---|---|---|---|---|---|---|---|---|---|---|
| Davatchi (2011)[7] | Prospective case series | 4 | Knee (4) | Autologous iliac crest BM | FC | 8.50 | 1 | Saline and 2% albumin | None | 6 |
| Davatchi (2016)[8] | Prospective case series | 3[b] | Knee (3)[b] | Autologous iliac crest BM | FC | 8.50 | 1 | Saline and 2% albumin | None | 60 |
| Emadedin (2012)[10] | Prospective case series | 6 | Knee (6) | Autologous iliac crest BM | FC | 22.20 | 2 | Physiological serum | None | 12 |
| Emadedin (2015)[11] | Prospective case series | 17 | Ankle (6), hip (5), knee (6) | Autologous iliac crest BM | FC | N/A | N/A | Saline | None | 30 |
| Jo (2014)[14] | Prospective cohort study | 18 | Knee (18) | Autologous abdominal adipose | FC, DA | 10, 50, 100 | N/A | Saline | Dose escalation | 6 |
| Koh (2012)[19] | Retrospective cohort study | 25 | Knee (25) | Autologous infrapatella fat pad | FC | 1.89 | 0 | PRP | Arthroscopy followed by PRP only | 16.4 |
| Koh (2013)[22] | Retrospective case series | 18[c] | Knee (18)[c] | Autologous infrapatella fat pad | FC | 1.18 | 0 | PRP | None | 24.3 |
| Koh (2014)[23] | Prospective cohort study[d] | 21 | Knee (21) | Autologous buttocks adipose | FC, DA | 4.11 | 0 | PRP | PRP with medial HTO | 24.4 |
| Koh (2015)[21] | Prospective case series | 30 | Knee (30) | Autologous buttocks adipose | FC, DA | 4.04 | 0 | PRP | None | 25 |
| Orozco (2013)[33] | Prospective cohort study | 12 | Knee (12) | Autologous iliac crest BM | FC, DA | 40.00 | 3 | N/A | None | 12 |
| Orozco (2014)[34] | Prospective cohort study | 12[e] | Knee (12)[e] | Autologous iliac crest BM | FC, DA | 40.00 | 3 | N/A | None | 24 |
| Pers (2016)[36] | Prospective cohort study | 18 | Knee (18) | Autologous abdominal adipose | FC | 2, 10, 50 | 1 | None | Dose escalation | 6 |
| Vega (2015)[46] | Randomized controlled trial | 15 | Knee (15) | Allogenic (3 donors) iliac crest BM | FC, DA | 40.00 | 3 | None | HA | 12 |
| Wong (2013)[50] | Randomized controlled trial[d] | 28 | Knee (28) | Autologous iliac crest BM | FC | 14.60 | 1 | HA | HTO with microfracture without cell injection | 24 |

[a]The pathologic condition for each study was osteoarthritis, unless noted otherwise. BM, bone marrow; DA, differentiation assay; FC, flow cytometry; HA, hyaluronic acid; HTO, high tibial osteotomy; MSC, mesenchymal stem cell; N/A, not available; PRP, platelet-rich plasma.
[b]All from previous 2011 study.
[c]All from previous 2012 study.
[d]Pathologic condition: medial compartment osteoarthritis.
[e]All from previous 2013 study.

abdomen (2), and infrapatellar fat pad (2). Although there are publications on the safety and efficacy of other types of MSCs (ie, placenta derived), they were not included in this review, because they did not characterize the cells or define what exactly was in their mixture, other than saying that they used "tissue containing MSCs" and the like.

The mean cell count was $6.45 \times 10^6$ for the 23 studies that reported it. Four studies[2,11,32,47] failed to report the number of cells administered, and 1 study[41] offered only a range. MSC preparation procedures ranged from no cell expansion to 3 passages. All studies characterized the MSCs injected by flow cytometry and/or differentiation assay. All but 1 study[41] administered a single injection of MSCs or involved a single MSC implantation procedure. MSCs were administered into the knee (523 knees), foot/ankle (61), and hip (5). The mean follow-up time was 24.4 months. Two studies[14,36] assessed participant outcomes for <6 months after MSC therapy. All studies employed ≥1 imaging techniques as part of their outcome assessment and commonly used plain film radiography, magnetic resonance imaging (MRI), and/or second-look arthroscopy.

Procedure-related pain and swelling at the procedural site (ie, bone marrow aspiration, surgery, and injection sites) were commonly reported. However, only 3 serious adverse events were reported in the reviewed publications.[14,36,39] One was a urinary stone that occurred in a patient with a history of urinary stones and was resolved with extracorporeal shockwave lithotripsy and medication.[14] Another serious adverse event was a case of unstable angina without increased cardiac markers that occurred 3 months after treatment. The authors did not attribute the event to the treatment or injection but did not provide information on the ultimate clinical outcome of this patient.[36] The last serious adverse event reported was a postoperative deep vein thrombosis that occurred

TABLE 2
Study Design for Chondral Defect Studies[a]

| Citation | Design | Patients Receiving MSC Therapy, No. | Joint Type (No.) | Cell Source | Cell Identification Method | Mean No. of Injected Cells × $10^6$ | Cell Passages | Adjuvant | Comparator | Mean Follow-up, mo |
|---|---|---|---|---|---|---|---|---|---|---|
| Akgun (2015)[2] | Prospective cohort study | 7 | Knee (7) | Autologous femoral synovial tissue (m-AMI) | FC, DA | N/A | 3 | Matrix-induced autologous MSC implantation | m-ACI | 24.0 |
| Haleem (2010)[13] | Prospective case series | 5 | Knee (5) | Autologous iliac crest BM | FC | 15 | N/A | PR-FG and periosteal flap | None | 14.2 |
| Kim (2013)[18] | Retrospective cohort study | 30 | Ankle/ foot (31) | Autologous buttocks adipose | FC, DA | 3.9 | 0 | SVF and arthroscopic marrow stimulation | Microfracture | 21.8 |
| Kim (2014)[17] | Retrospective cohort study | 24 new (26 from Kim[18]) | Ankle/ foot (24) | Autologous buttocks adipose | FC, DA | 3.94 | 0 | SVF and arthroscopic marrow stimulation | Microfracture | 27.1 |
| Koh (2014)[20] | Retrospective case series | 35 | Knee (37) | Autologous buttocks adipose | FC, DA | 3.8 | 0 | None | None | 26.5 |
| Kim (2015)[15] | Retrospective cohort study | 19 new (35 from Koh[20]) | Knee (19) | Autologous buttocks adipose | FC, DA | 3.9 | 0 | Fibrin glue | MSCs without vs with scaffold | 28.6 |
| Kim (2015)[16] | Retrospective cohort study | 40 | Knee (40) | Autologous buttocks adipose | FC, DA | 4.01 | N/A | PRP, fibrin glue | Implantation vs injection | 28.5 |
| Koh (2016)[24] | Prospective cohort study | 40 | Knee (40) | Autologous buttocks adipose | FC, DA | 4.97 | N/A | Fibrin glue, microfracture | Microfracture | 27.4 |
| Lee (2012)[28] | Prospective cohort study | 70 | Knee (70) | Autologous iliac crest BM | FC | 10 | 1 | Autologous serum, HA, and periosteal patch | Open surgical technique vs arthroscopic microfracture and injections | 24.5 |
| Nejadnik (2010)[32] | Prospective cohort study | 36 | Knee (36) | Autologous iliac crest BM | FC | N/A | 1 | Fibrin glue and periosteal patch | ACI | 24.0 |
| Saw (2013)[39] | Randomized controlled trial | 25 | Knee (25) | Autologous peripheral blood MSCs | FC | 20 | 0 | HA | HA | 24.0 |
| Sekiya (2015)[40] | Prospective case series | 10 | Knee (10) | Autologous femoral synovial tissue | FC, DA | 47 | 0 | Acetate Ringer solution | None | 52.0 |
| Skowroński (2013)[41] | Prospective cohort study | 46 | Knee (46) | Autologous iliac crest BM concentrate vs peripheral blood MSCs | FC | 0.45-2.65, 1.25-5.2 | 0 | Chondro-Gide, bone graft, fibrin glue | Autologous iliac crest BM vs peripheral blood MSCs | 60.0 |
| Wakitani (2007)[47] | Prospective case series | 3 | Knee (5) | Autologous iliac crest BM | FC | N/A | 1 | 0.25% type I acid soluble type I collagen from porcine tendon on collagen sheet and 15% autologous serum and periosteum | None | 18.3 |

[a]The pathologic condition for each study was chondral defect. ACI, autologous chondrocyte implantation; BM, bone marrow; DA, differentiation assay; FC, flow cytometry; HA, hyaluronic acid; m-AMI, matrix-induced autologous bone marrow mesenchymal stem cell implantation; MSC, mesenchymal stem cell; N/A, not available; PR-FG, platelet-rich fibrin glue; PRP, platelet-rich plasma; SVF, stromal vascular fraction.

in a control group patient (did not receive MSC therapy) and resolved with anticoagulation therapy.[41]

## OA Studies

Data on design and results for the 14 OA studies are presented in Tables 1 and 3, respectively. No procedure-related adverse events were reported in the reviewed literature unless specifically designated in the study summary.

Davatchi et al[7] performed a pilot study among 4 patients with radiographic evidence of knee OA. Patients received autologous BM-MSC injections with saline and were followed for 6 months. Walking time until onset of pain, stairs climbed until onset of pain, patellar crepitus, and other activities of daily living-specific assessments improved. All 4 patients had pre- and postimplantation radiographs, but no postimplantation radiographic changes were noted. This group recently reported 5-year follow-up data on 3 of the original 4 patients.[8] The 6-month after-injection improvements reported in the initial study had receded slightly but were still better than baseline clinical measurements.

Emadedin et al[10,11] published 2 studies investigating the use of autologous MSCs for the treatment of OA. In the first study,[10] 6 patients were injected with autologous

TABLE 3
Study Results for OA Studies[a]

| Citation | Mean Follow-up, mo | Clinical Outcome Measure | Scores: Baseline vs Final Follow-up | Significant Improvement From Baseline | Significant Difference Between Groups | Imaging Evaluation | Other Outcome Measures[b] |
|---|---|---|---|---|---|---|---|
| Davatchi (2011)[7] | 12 | VAS (pain) | 86.25 vs 52.5 | N/A | N/A | X-ray | Walking time, stairs climbed, resting time to induce the gelling pain, ROM, patellar crepitus |
| Davatchi (2016)[8] | 60 | VAS (pain) | 85 vs 31 | N/A | N/A | X-ray | Walking time, stairs climbed, resting time to induce the gelling pain, ROM, patellar crepitus |
| Emadedin (2012)[10] | 12 | VAS | 57 ± 33 vs 11.6 ± 24 | N/A | N/A | MRI | Walking distance, knee flexion, MRI |
| | | WOMAC | 1.89 ± 0.3 vs 2.91 ± 0.37 | N/A | N/A | | |
| Emadedin (2015)[11] | 30 | HHS | 57 ± 3.2 vs 79.8 ± 16.8 | Yes, $P < .05$ | N/A | MRI | WOMAC pain and stiffness subscores, walking distance |
| | | WOMAC (hip OA group) | 45.2 ± 10.0 vs 29.1 ± 18.9 | No, $P < .05$ | N/A | | |
| | | FAOS | 48.9 ± 10.1 vs 78.7 | Yes, $P < .05$ | N/A | | |
| | | WOMAC (ankle OA group) | Graphic only | Yes, $P < .05$ | N/A | | |
| | | WOMAC (knee OA group) | 72.7 vs 43.4 | Yes, $P < .05$ | N/A | | |
| Jo (2014)[14] | 6 | WOMAC | Low dose A-MSC: 43 ± 22.0 vs N/A.<br>Middose A-MSC: 69 ± 10.2 vs N/A.<br>High dose A-MSC: 54.2 ± 5.2 vs 32.8 ± 6.3 | No, $P > .05$.<br>No, $P > .05$.<br>Yes, $P = .003$ | N/A | MRI evaluation; second-look arthroscopy | KSS subscores, second-look histologic outcomes |
| | | VAS | Low dose A-MSC: 70 ± 17.3 vs N/A.<br>Middose A-MSC: 78 ± 2.9 vs N/A.<br>High dose A-MSC: 79.6 ± 2.2 vs 44.2 ± 6.3 | No, $P > .05$.<br>No, $P > .05$.<br>Yes, $P < .001$ | N/A | | |
| Koh (2012)[19] | 16.4 | Lysholm score | A-MSC + PRP: 41.2 ± 12.4 vs 68.1 ± 18.5.<br>PRP: 50.0 ± 11.1 vs 69.4 ± 20.4 | Yes, $P < .001$ | No, $P = .812$ | No | No |
| | | Tegner Activity Scale | A-MSC + PRP: 1.5 ± 0.5 vs 2.8 ± 1.2.<br>PRP: 2.1 ± 0.8 vs 2.9 ± 1.0 | Yes, $P < .001$ | No, $P = .706$ | | |
| | | VAS (pain) | A-MSC + PRP: 4.9 ± 1.2 vs 2.7 ± 1.8.<br>PRP: 3.9 ± 1.0 vs 2.2 ± 1.7 | Yes, $P < .001$ | No, $P = .338$ | | |
| Koh (2013)[22] | 24.3 | Lysholm score | 40.1 ± 12.1 vs 73.4 ± 13.5 | Yes, $P < .001$ | N/A | Whole-organ MRI score | No |
| | | WOMAC | 49.9 ± 12.6 vs 30.3 ± 9.2 | Yes, $P < .001$ | N/A | | |
| | | VAS (pain) | 4.8 ± 1.6 vs 2.0 ± 1.1 | Yes, $P < .001$ | N/A | | |
| Koh (2014)[23] | 24.4 | Lysholm score | A-MSC + PRP: 55.7 ± 11.5 vs 84.7 ± 16.2.<br>PRP: 56.7 ± 12.2 vs 80.6 ± 13.5 | Yes, $P < .001$ | No, $P = .357$ | Second-look arthroscopy | KOOS subscores |
| | | KOOS | N/A | N/A | N/A | | |
| | | VAS | A-MSC + PRP: 44.3 ± 5.7 vs 10.2 ± 5.7.<br>PRP: 45.4 ± 7.1 vs 16.2 ± 4.6 | Yes, $P < .001$ | Yes, $P < .001$ | | |
| Koh (2015)[21] | 24.4 | Lysholm score | A-MSC: 54.3 ± 15.4 vs 74.2 ± 13.4 | Yes, $P = .05$ | Yes, $P < .05$ | Second-look arthroscopy | No |
| | | VAS | A-MSC: 4.7 ± 1.6 vs 1.7 ± 1.4 | Yes, $P = .05$ | Yes, $P < .05$ | | |
| Orozco (2013)[33] | 12 | VAS-DA | 46.9 ± 7.5 vs 15.4 ± 3.8 | Yes, $P < .001$ | N/A | MRI with T2 mapping | Poor Cartilage Index/T2 mapping, SF-36, VAS-SP |
| | | WOMAC | 19.4 ± 3.6 vs 8.3 ± 2.7 | Yes, $P < .001$ | N/A | | |
| | | Lequesne | 45.1 ± 5.6 vs 14.9 ± 4.1 | Yes, $P < .01$ | N/A | | |
| Orozco (2014)[34] | 24 | VAS-DA | Graphic only | N/A | N/A | MRI with T2 mapping | Poor Cartilage Index/T2 mapping |
| | | WOMAC | Graphic only | N/A | N/A | | |
| | | Lequesne | Graphic only | N/A | N/A | | |

*(continued)*

TABLE 3
(continued)

| Citation | Mean Follow-up, mo | Clinical Outcome Measure | Scores: Baseline vs Final Follow-up | Significant Improvement From Baseline | Significant Difference Between Groups | Imaging Evaluation | Other Outcome Measures[b] |
|---|---|---|---|---|---|---|---|
| Pers (2016)[36] | 6 | VAS | Low dose: 77 ± 15.7 vs 35.8 ± 13.3.<br>Medium dose: 63.7 ± 20.5 vs 36.7 ± 11.9.<br>High dose: 43.7 ± 25.4 vs 24 ± 17.1 | Yes, $P < .05$.<br>No, $P > .05$.<br>No, $P > .05$ | N/A | MRI | SF-36, Short Arthritis Assessment Scale, Patient Global Assessment, histologic analysis |
| | | KOOS | Low dose: 34 ± 15 vs 65.8 ± 9.1.<br>Medium dose: 42 ± 9 vs 59.2 ± 6.5.<br>High dose: 45.2 ± 13.6 vs 65.2 ± 13.1 | Yes, $P < .01$.<br>No, $P > .05$.<br>No, $P > .05$ | N/A | | |
| | | WOMAC | Low, medium, high doses: Graphic/subscores only. | Yes, $P < .001$.<br>No, $P > .05$.<br>No, $P > .05$ | N/A | | |
| Vega (2015)[46] | 12 | VAS | BM-MSC: 54 ± 7 vs 33 ± 6.<br>HA: 64 ± 7 vs 51 ± 8 | Yes, $P < .001$.<br>No, $P > .05$ | Yes, $P < .001$.<br>Yes, $P < .01$ | MRI with T2 mapping | SF-12, WOMAC pain |
| | | WOMAC | BM-MSC: 41 ± 3 vs 28 ± 5.<br>HA: 45 ± 3 vs 41 ± 6 | Yes, $P < .001$.<br>No, $P > .05$ | Yes, $P < .001$.<br>No, $P > .05$ | | |
| | | Lequesne | BM-MSC: 39 ± 4 vs 30 ± 3.<br>HA: 45 ± 4 vs 42 ± 5 | Yes, $P < .01$.<br>No, $P > .05$ | Yes, $P < .01$.<br>No, $P > .05$ | | |
| Wong (2013)[50] | 12 | Tegner score | BM-MSC + HA: N/A.<br>HA: N/A.<br>Mixed effects model: 0.64 more improvement in BM-MSC group than HA group | N/A | Yes, $P = .021$ | MRI (MOCART) | No |
| | | Lysholm score | BM-MSC + HA: 41.9 ± 19.2 vs N/A.<br>HA: 50.4 ± 23.0 vs N/A.<br>Mixed effects model: 7.61 more improvement in BM-MSC group than HA group | N/A | Yes, $P = .016$ | | |
| | | IKDC | BM-MSC + HA: 33.9 ± 11.4 vs N/A.<br>HA: 36.0 ± 13.7 vs N/A.<br>Mixed effects model: 7.65 more improvement in BM-MSC group than HA group | N/A | Yes, $P = .001$ | | |

[a]A-MSC, adipose-derived mesenchymal stem cell; BM-MSC, bone marrow–derived mesenchymal stem cell; FAOS, Foot and Ankle Outcome Score; HA, hyaluronic acid; HHS, Harris Hip Score; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; KSS, Knee Society Score; MOCART, magnetic resonance observation of cartilage repair tissue; MRI, magnetic resonance imaging; N/A, not available; OA, osteoarthritis; PRP, platelet-rich plasma; ROM, range of motion; SF-36, 36-item Short Form Health Survey; VAS, visual analog scale; VAS-DA, visual analog scale–daily activities; VAS-SP, visual analog scale–sports activities; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[b]There were no serious adverse events in any study except Pers (2016)[36] (unstable angina pectoris) and Jo (2014)[14] (urinary stone).

BM-MSCs under fluoroscopic guidance. Patients were evaluated clinically with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and visual analog scale (VAS). Clinical outcomes were measured preoperatively and at 2 weeks and 1, 2, 6, and 12 months postoperatively. MRI was performed preoperatively and at the 6-month follow-up. Mean VAS and WOMAC scores were improved from baseline at 12 months, but the VAS scores reported at 12 months were worse than the scores reported at 6 months. The authors stated that there were improvements in knee cartilage thickness in 3 of the 6 patients, but they did not report their scoring methodology. The second study published by this group[11] used the same procedure to treat 17 patients with knee (n = 6), ankle (6), or hip (5) OA. All patients exhibited therapeutic benefits at 30 months. The mean WOMAC score was significantly better than the baseline score at the 6-, 12-, and 30-month follow-ups. VAS scores improved but did not reach statistical significance. Only mild adverse events (rash and erythema) were reported.

Orozco et al[33] conducted a pilot study to assess the feasibility and safety of mesenchymal stromal cells for patients with OA. Twelve patients who had chronic knee pain and radiologic evidence of OA and who were unresponsive to nonoperative treatments were treated with autologous expanded BM-MSCs. Patients were followed for 12 months. Efficacy was measured with the VAS, WOMAC, Lequesne, and 36-item Short Form Health

TABLE 4
Study Results for Chondral Defect Studies[a]

| Citation | Mean Follow-up, mo | Clinical Outcome Measures | Scores (Pre- vs Postoperative) | Significant Improvement From Baseline | Significant Difference Between Groups | Imaging Evaluation | Other Outcome Measures[b] |
|---|---|---|---|---|---|---|---|
| Akgun (2015)[2] | 24 | KOOS Pain subscale | m-AMI (S-MSC): 63.49 ± 2.50 vs 88.10 ± 2.64. m-ACI: 67.46 ± 2.64 vs 82.54 ± 3.48 | Yes, $P < .05$ | Yes, $P = .009$. m-AMI better than m-ACI | MRI: MOCART, bone edema, and joint effusion | All KOOS subscales, VAS-frequency, knee flexion deficit, knee extension deficit, straight-leg raise strength |
| | | VAS-Severity | m-AMI (S-MSC): 4.86 ± 0.69 vs 0.57 ± 0.53. m-ACI: 4.71 ± 1.11 vs 1.14 ± 0.69 | Yes, $P < .05$ | No, $P < .05$ | | |
| | | Tegner Activity Scale | m-AMI (S-MSC): 3.43 ± 0.98 vs 6.86 ± 0.38. m-ACI: 3.57 ± 0.79 vs 6.29 ± 0.49 | Yes, $P < .05$ | No, $P < .05$ | | |
| Haleem (2010)[13] | 12 | Lysholm | 41.2 ± 13.14 vs 86.0 ± 9.25 | Yes, $P < .05$ | N/A | X-ray. MRI. ICRS grading in 2 pts with second-look arthroscopy at 12 mo | N/A |
| | | RHSSK | 53.8 ± 15.39 vs 83.8 ± 9.78 | Yes, $P < .05$ | | | |
| Kim (2013)[18] | 21.8 ± 4.3 | VAS | MFX: 7.2 ± 1.1 vs 4.0 ± 0.7. MFX + A-MSC: 7.1 ± 1.0 vs 3.2 ± 0.9 | Yes, $P < .05$ | Yes, $P < .001$. MFX + A-MSC significantly better than MFX | X-ray. MRI and second-look arthroscopy in 5 and 1 pts | Roles and Maudsley Patient Satisfaction Score (greater improvement in group B than A, $P = .040$). Time until return to sport |
| | | AOFAS | MFX: 68.0 ± 5.5 vs 77.2 ± 4.8. MFX + A-MSC: 68.1 ± 5.6 vs 82.6 ± 6.4 | Yes, $P < .05$ | Yes, $P < .001$. MFX + A-MSC significantly better than MFX | | |
| | | Tegner Activity Scale | MFX: 3.5 ± 0.8 vs 3.6 ± 0.6. MFX + A-MSC: 3.5 ± 0.7 vs 3.8 ± 0.7 | Yes in MFX + MSC, $P = .041$. No in MFX | Yes, $P = .004$. MFX + A-MSC significantly better than MFX | | |
| Kim (2014)[17] | 27.1 ± 5.0 | VAS | MFX: 7.1 ± 1.2 vs 3.9 ± 0.8. MFX + A-MSC: 7.1 ± 0.8 vs 3.2 ± 0.8 | Yes, $P < .05$ | Yes, $P = .003$ | MOCART at a mean of 21.9 months PO: 49.4 ± 16.6 (conventional) vs 62.1 ± 21.8 (MSC) | N/A |
| | | AOFAS | MFX: 68.5 ± 5.6 vs 78.3 ± 4.9. MFX + A-MSC: 67.7 ± 4.7 vs 83.3 ± 7.0 | Yes, $P < .05$ | Yes, $P = .009$ | | |
| | | Tegner Activity Scale | MFX: 3.4 ± 0.6 vs 3.5 ± 0.8. MFX + A-MSC: 3.4 ± 0.5 vs 3.9 ± 0.7 | Yes in MFX + MSC, $P = .005$. No in MFX | Yes, $P = .041$ | | |
| Koh (2014)[20] | 26.5 ± 2.5 | IKDC | Without second-look arthroscopy: 36.8 ± 6.1 vs 61.1 ± 10.9. With second-look arthroscopy: 38.0 ± 7.8 vs 61.0 ± 11.0 | Yes, $P < .01$ | No, $P < .05$ | ICRS grading on second-look arthroscopy at mean 12.7 mo PO | N/A |
| | | Tegner Activity Scale | Without second-look arthroscopy: 2.4 ± 0.5 vs 3.5 ± 0.7. With second-look arthroscopy: 2.5 ± 0.5 vs 3.6 ± 0.7 | Yes, $P < .01$ | | | |
| Kim (2015)[15] | 28.6 ± 3.9 | IKDC | A-MSC implant with scaffold: 38.1 ± 7.7 vs 62.0 ± 11.7. A-MSC implant without scaffold: 36.1 ± 6.2 vs 64.4 ± 11.5 | Yes, $P < .01$ | No, $P < .05$ | ICRS grading on second-look arthroscopy at mean 12.3 mo PO | N/A |
| | | Tegner Activity Scale | A-MSC implant with scaffold: 2.5 ± 0.9 vs 3.5 ± 0.8. A-MSC implant without scaffold: 2.2 ± 0.8 vs 3.8 ± 0.8 | Yes, $P < .01$ | | | |
| Kim (2015)[16] | 28.6 | IKDC | A-MSC injection with PRP: 38.5 ± 9.2 vs 55.8 ± 14.7. A-MSC implant with fibrin glue scaffold: 36.6 ± 4.9 vs 64.8 ± 13.4 | Yes, $P < .01$ | Yes, $P = .049$. A-MSC implant with fibrin glue scaffold better than A-MSC injection with PRP | ICRS grading on second-look arthroscopy at mean 12.6 mo PO | N/A |
| | | Tegner Activity Scale | A-MSC injection with PRP: 2.5 ± 1.2 vs 3.5 ± 1.0. A-MSC implant with fibrin glue scaffold: 2.3 ± 0.9 vs 3.9 ± 1.0 | Yes, $P < .01$ | No, $P < .05$ | | |

*(continued)*

TABLE 4
(continued)

| Citation | Mean Follow-up, mo | Clinical Outcome Measures | Scores (Pre- vs Postoperative) | Significant Improvement From Baseline | Significant Difference Between Groups | Imaging Evaluation | Other Outcome Measures[b] |
|---|---|---|---|---|---|---|---|
| Koh (2016)[24] | 27.4 | VAS | MFX with A-MSC/fibrin glue: N/A.<br>MFX: N/A | Yes, $P < .001$ | Yes, $P = .032$. MFX with MSC/fibrin glue better than MFX | MOCART at 24 months PO | Histologic evaluation of biopsy with ICRS grading system in 34 pts. All KOOS subscales |
| | | Lysholm | MFX with A-MSC/fibrin glue: N/A.<br>MFX: N/A | Yes, $P < .001$ | No, $P = .431$ | | |
| | | KOOS Pain subscale | MFX with A-MSC/fibrin glue: score improved by 36.6 ± 11.9.<br>MFX: score improved by 30.1 ± 14.7 | Yes, $P < .001$ | Yes, $P = .034$. MFX with MSC/fibrin glue better than MFX alone | | |
| Lee (2012)[28] | 24.5 | VAS | MFX with BM-MSC and HA injection: N/A.<br>Open BM-MSC under periosteal patch: N/A | Yes, $P < .05$ | No, $P < .05$ | MRI at 12 months PO | N/A |
| | | IKDC | MFX with BM-MSC and HA injection: N/A.<br>Open BM-MSC under periosteal patch: N/A | Yes, $P < .05$ | Yes, $P < .001$. Injection group better than open patch group | | |
| | | Lysholm | MFX with BM-MSC and HA injection: N/A.<br>Open BM-MSC under periosteal patch: N/A | Yes, $P < .05$ | Yes, $P < .001$. Injection group better than open patch group | | |
| | | Tegner Activity Scale | MFX with BM-MSC and HA injection: N/A.<br>Open BM-MSC under periosteal patch: N/A | Yes, $P < .05$ | No, $P < .05$ | | |
| | | SF-36 | MFX with BM-MSC and HA injection: N/A.<br>Open BM-MSC under periosteal patch: N/A | Yes, $P < .05$ | No, $P < .05$ | | |
| Nejadnik (2010)[32] | 24 | VAS | BM-MSC: N/A.<br>ACI: N/A | Yes, $P < .05$ | No, $P < .05$ | ICRS grading on second-look arthroscopy in 7 pts at 9-12 mo PO | Histologic evaluation of biopsy specimen in 2 pts at 9-12 mo PO. Subscales of SF-36 |
| | | IKDC | BM-MSC: N/A.<br>ACI: N/A | Yes, $P < .05$ | No, $P < .05$ | | |
| | | Lysholm | BM-MSC: N/A.<br>ACI: N/A | Yes, $P < .05$ | No, $P < .05$ | | |
| | | Tegner Activity Scale | BM-MSC: N/A.<br>ACI: N/A | Yes, $P < .001$ | No, $P < .05$ | | |
| | | SF-36 | BM-MSC: N/A.<br>ACI: N/A | Yes, $P < .05$ | No, $P < .05$ | | |
| Saw (2013)[39] | 24 | IKDC | HA: 46.60 ± 15.79 vs 71.08 ± 16.49.<br>HA and PB-MSC: 48.68 ± 13.75 vs 74.82 ± 12.77 | Yes, $P < .05$ | No, $P < .05$ | MRI score 0-12 | Histologic evaluation of chondral core biopsy in 32 pts at 18 mo PO |
| Sekiya (2015)[40] | 52 | Lysholm<br>Tegner Activity Scale | S-MSC: 76 ± 7 vs 95 ± 3<br>S-MSC: No change | Yes, $P < .05$<br>No, $P < .05$ | N/A | MRI score 0-5 (1.0 ± 0.3 vs 5.0 ± 0.7). Second-look arthroscopy in 4 pts | Histologic evaluation of biopsy in 4 pts |
| Skowroński (2013)[41] | 60 | KOOS | BM concentrate: 58.3 vs 90.2.<br>PB-MSC: 61.3 vs 91.3 | Improved clinical scores at 6 and 12 mo vs baseline values noted in 86% | Yes, $P = .01$-$0.02$. PB-MSC better than BM concentrate in clinical scores | MRI | N/A |
| | | Lysholm | BM concentrate: 52.4 vs 88.9.<br>PB-MSC: 54.7 vs 89.2 | | | | |
| | | VAS | BM concentrate: 6.1 vs 1.2.<br>PB-MSC: 5.9 vs 1 | | | | |
| Wakitani (2007)[47] | 19 | IKDC | BM-MSC implantation:<br>Patient 1 knees: graph in publication.<br>Patient 2 Right knee: 30 vs 74.<br>Patient 2 Left knee: 11 vs 67.<br>Patient 3 Right knee: 64 vs 77 | N/A | N/A | Patient 1: Second-look arthroscopy and biopsy at 11 mo PO. Patient 2: MRI at 12 mo PO | N/A |

[a]ACI, autologous chondrocyte implantation; A-MSC, adipose-derived mesenchymal stem cell; AOFAS, American Orthopaedic Foot and Ankle Society; BM, bone marrow; BM-MSC, bone marrow–derived mesenchymal stem cell; HA, hyaluronic acid; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; m-ACI, matrix-induced autologous chondrocyte implantation; m-AMI, matrix-induced autologous bone marrow mesenchymal stem cell implantation; MFX, microfracture surgery; MOCART, magnetic resonance observation of cartilage repair tissue; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; N/A, not available; PB-MSC, peripheral blood–derived mesenchymal stem cell; PO, postoperative; PRP, platelet-rich plasma; pts, patients; RHSSK, Revised Hospital for Special Surgery Knee; SF-36, 36-item Short Form Health Survey; S-MSC, synovial mesenchymal stem cell; VAS, visual analog scale.

[b]There were no serious adverse events in any study except Saw (2013)[39] (deep venous thrombosis in control group).

Survey (SF-36). Articular cartilage quality was assessed with MRI with T2 mapping (Poor Cartilage Index). Significant improvements in all scores except SF-36 were observed at the 12-month follow-up. A number of minor adverse events were reported, including postimplantation pain in 50% of participants. In recent 2-year follow-up data published from this group,[34] no significant changes from the 1-year values were observed.

Jo et al[14] conducted a proof-of-concept study. Eighteen patients were treated with autologous adipose tissue–derived MSCs (A-MSCs). The study population was divided into 3 groups: low dose ($1 \times 10^7$ cells), middose ($5 \times 10^7$), and high dose ($1 \times 10^8$). Patients were followed for 6 months. The primary outcome measure was WOMAC score. Secondary outcomes were divided into 4 categories: clinical, radiological, arthroscopic, and histological. Clinical outcomes included VAS and the Knee Society Clinical Rating System score. Radiological outcomes were compared with Kellgren-Lawrence grade, joint space width of the medial compartment, and mechanical axis. Histological evaluations were performed on punch biopsy specimens taken during second-look arthroscopy 6 months after treatment. The VAS and WOMAC scores improved significantly but only in the high-dose group. Knee Society Clinical Rating System scores improved significantly but only in the low- and high-dose groups. Kellgren-Lawrence grade, joint space, mechanical axis, and anatomic axis had not changed significantly at 6-month follow-up in any of the dose cohorts. Second-look arthroscopy showed that the size of the CD had significantly decreased in the medial femoral and medial tibial condyles of the high-dose group. Histological evaluation of biopsy specimens demonstrated thick, hyaline-like cartilage regeneration. Adverse events were reported in 9 patients (pain, tenderness, nasopharyngitis). Only 1 serious adverse event (urinary stone) was reported, which was successfully treated.

Pers et al[36] conducted a dose escalation study aimed at evaluating the safety of adipose-derived stromal cells for the treatment of patients with knee OA. The study design consisted of 3 consecutive cohorts (n = 6 each): low dose ($2 \times 10^6$ cells), middose ($10 \times 10^6$), and high dose ($50 \times 10^6$). Patients were followed for 6 months and assessed with the following secondary clinical outcome measures: WOMAC, VAS, the Patient Global Assessment, the Short Arthritis Assessment Scale, and the Knee injury and Osteoarthritis Outcome Score (KOOS). Improvement for all clinical outcome parameters (pain, function, and mobility) regardless of the injected dose was observed, but improvements were statistically significant in only the low-dose group. A small number of patients underwent dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) or $T_{1rho}$, but no correlation between MRI and clinical changes was observed. Histologic analysis of cartilage and synovium at 3 months was available for 11 of 18 patients after arthroscopy. Four patients experienced transient knee joint pain and swelling after local injection.

Koh et al[19,21-23] published 4 articles investigating the use of autologous A-MSCs for the treatment of knee OA. The first article[19] presented preliminary results from a case-control study. Twenty-five patients received intra-articular A-MSC injections (mean, $1.89 \times 10^6$ cells) with platelet-rich plasma (PRP) after arthroscopic debridement. Patients were assessed with Lysholm, Tegner Activity Scale, and VAS scores preoperatively and at 6- and 12-month follow-up visits. A statistically significant improvement from the baseline was noted for all clinical scores at final follow-up, but the improvements were not significantly better than the case-matched controls, who had undergone arthroscopic debridement with PRP injection alone. The authors reported that some patients experienced slight pain during the first 2 to 3 days after the injection. One patient had marked pain and swelling at the injection site, but the pain resolved spontaneously after 2 weeks.

The second article published by Koh et al[22] was a subset analysis of 18 patients from their previous study. MRI was performed preoperatively and at final follow-up (mean, 24.3 months). All clinical outcomes (WOMAC, Lysholm score, and VAS) improved significantly by final follow-up (mean, 24.3 months after treatment). The whole-organ MRI score improved significantly.

The third article published by Koh et al[23] compared the clinical results and second-look arthroscopic findings of 44 patients (18 of whom were from their previous study[22]) who were undergoing open-wedge high tibial osteotomy for a varus deformity. Patients were given injections of A-MSCs and PRP (n = 21) or PRP only (n = 23). Prospective evaluations of both groups were performed with the Lysholm score, KOOS, and VAS. Second-look arthroscopy was carried out in all but 3 patients. At final follow-up (mean, 24.4 months), patients treated with MSCs showed significantly better improvements in KOOS subscales for pain and symptoms. Patients treated with MSCs also showed significantly better improvements in VAS score, but the Lysholm score, while significantly improved from baseline, was not significantly different from the control. Arthroscopic evaluation showed that partial or even fibrocartilage coverage was achieved in 50% of the patients treated with MSCs but in only 10% of controls.

In their most recent article, Koh et al[21] presented the clinical outcomes and second-look arthroscopic findings from 30 elderly patients (>65 years) with knee OA who were injected with A-MSCs after arthroscopic lavage. Patients were evaluated with KOOS, VAS, and Lysholm scores for a minimum of 24 months. Sixteen patients underwent second-look arthroscopy. Significant improvements in mean VAS, Lysholm, and KOOS scores were observed at final follow-up. The cartilage status was maintained or had improved for 87.5% of patients who underwent second-look arthroscopy. Three patients experienced knee pain during the first week after the stem cell injection, which resolved spontaneously within 1 week for 2 of these patients; the third patient's pain resolved within 2 weeks with anti-inflammatory medication.

In 1 of only 3 randomized clinical trials in this report, Vega and colleagues[46] compared allogenic BM-MSCs with hyaluronic acid (HA). Bone marrow mesenchymal stromal cells were obtained from 3 healthy donors (unknown age) and passaged 3 times. Cells underwent viability testing and immunophenotypic profiling in accordance with the International Society for Cellular Therapy criteria for MSCs.[9] Thirty patients were randomly assigned to receive BM-MSCs ($4 \times 10^6$ cells) or HA. Patients were evaluated

with VAS, WOMAC, Lequesne, and SF-12 forms. Clinical outcomes were measured 8 days and 3, 6, and 12 months after treatment. MRI examinations with T2 mapping were performed at baseline and at 6- and 12-month postinjection time points. VAS pain scores and all functional scores were significantly improved in the BM-MSC group at the 6- and 12-month postinjection follow-up. In the HA group, VAS score was significantly improved at only the 12-month time point, and there were no significant changes in functional scores. MRI was evaluated with a Poor Cartilage Index, where cartilage quality is quantitatively measured as a percentage of T2 relaxation values >50 milliseconds. Poor Cartilage Index values improved in both groups, but the improvement was significant in only the BM-MSC group.

Wong et al[50] conducted a prospective randomized controlled trial. Fifty-six patients <55 years old who had been diagnosed with both medial compartment knee OA and genu varum and had elected to have a medial opening-wedge high tibial osteotomy and microfracture procedure were recruited. Patients were randomized into 2 groups but were not blinded to their treatment. The study group (n = 28) was injected with autologous BM-MSCs suspended in HA 3 weeks after high tibial osteotomy. Two additional doses of HA (without stem cells) were given at weekly intervals after the initial MSC/HA injection. Patients in the control group (n = 28) were treated at the same time points as those in the treatment group, but they received only HA. Patients were followed clinically for up to 2 years. MRI evaluation was performed before and 1 year after treatment. The primary outcome measure was the International Knee Documentation Committee (IKDC). Secondary outcome measures were Tegner and Lysholm clinical scores and the MOCART score (magnetic resonance observation of cartilage repair tissue). At final follow-up, after adjusting for age, baseline score, and time of evaluation, patients treated with MSCs showed significantly better improvements in Tegner, Lysholm, and IKDC scores than controls. MOCART scores at the 1-year follow-up were significantly better in the treatment group.

## Focal CD Studies

Data on study design and results for the 14 included CD studies are presented in Tables 2 and 4, respectively. No procedure-related adverse events were reported in the reviewed literature unless designated in the study summary.

Akgun et al[2] published a prospective randomized cohort study on 14 patients being treated for focal CDs. Seven patients were treated with matrix-induced autologous chondrocyte implantation (m-ACI), while the other 7 patients were treated with matrix-induced autologous bone marrow MSC implantation (m-AMI). Clinical outcomes were measured before surgery and 3, 6, 12, and 24 months after surgery. Outcome measures included KOOS, VAS severity and frequency scores, and the Tegner Activity Scale. The primary outcome of interest was the KOOS Pain subscale. All subscales of the KOOS and Tegner Activity Scale were also analyzed between groups, although they were not initially stated as outcomes of interest. Both groups reported significant improvement from baseline in all outcome measures. However, the m-AMI group demonstrated significantly better outcomes than the m-ACI group at all time points in the following categories: motion deficit, straight-leg raise strength, and the KOOS subscales for pain, symptoms, activities of daily living, and sport/recreation. Graft status was assessed with MRI at 3, 12, and 24 months postoperatively. MOCART score, bone edema score, and joint effusion score were determined by blinded independent musculoskeletal radiologists. The degree of defect infill and surface contour in the m-AMI group was classified as "excellent" at 24 months, as opposed to "good" in m-ACI group. Bone marrow edema decreased to "normal" at 24 months in the m-AMI group, whereas that of the m-ACI group was classified as "less than small."

In a pilot study by Haleem et al,[13] 5 individuals with full-thickness CDs (Outerbridge grade 3 or 4) of the femoral condyle were treated with autologous BM-MSCs implanted with platelet-rich fibrin glue. Lysholm scores, Revised Hospital for Special Surgery Knee scores, and MRI were used to clinically assess patients preoperatively and at 6 and 12 months postoperatively. Clinical scores at the 6- and 12-month follow-ups were significantly improved from preoperative scores. Postoperative MRI revealed partial incongruent defect filling of the repaired articular surface for 2 patients. For the other 3 patients, MRI showed complete congruent defect filling with native cartilage. Patients with coexisting degenerative disease showed less improvement after MSC implantation.

Kim and colleagues[17,18] published 2 similar retrospective cohort studies. In the first study, 30 patients with chondral lesions of the talus were treated with A-MSCs. The authors compared the clinical outcomes (VAS, AOFAS, and Tegner Activity Scale scores) between a group of patients who received arthroscopic bone marrow stimulation alone and a group that received both arthroscopic bone marrow stimulation and an injection of A-MSCs. In the second study, 24 new patients with chondral lesions of the talus were treated with A-MSCs, although the authors also included 26 of the 30 patients from their first study in their data analysis. The second study had the same study design. Significant improvements in all 3 clinical scores were observed in both treatment groups in both studies, with 1 exception: Tegner Activity Scale score did not improve significantly from baseline in the group that received arthroscopic bone marrow stimulation alone in both studies. The group that received A-MSCs scored significantly better in all clinical measures at final follow-up than the group that received marrow stimulation alone. The major difference between the studies is that the 2013 publication looked exclusively at clinical outcomes of patients >50 years old, while the 2014 publication evaluated clinical and radiological outcomes for patients of all ages. The 2014 publication compared MOCART scores between the treatment groups obtained at a mean 21.9 months after treatment and found that the A-MSC group had significantly higher scores than the group that received marrow stimulation alone.

Kim, Koh, and colleagues[15,20] also published 2 retrospective studies where A-MSCs were used to treat focal CDs in the knee. Thirty-five patients (37 knees) were included in both publications, although additional subjects

were added to the second study. The earlier of these 2 publications[20] reported clinical and second-look arthroscopic outcomes of a case series in which all 35 patients (37 knees) had A-MSCs implanted into their focal CDs without a scaffold. Patients were clinically assessed with IKDC and Tegner activity scores. Second-look arthroscopy was performed at a mean 12.9 months after the procedure. Cartilage quality was graded with the International Cartilage Repair Society (ICRS) form. Significant improvement in IKDC and Tegner activity scores were observed at final follow-up (mean, 26.5 months). This group's second study[15] included all the patients from their previous study as a control group and compared them with 17 patients (19 knees) who had A-MSCs implanted in a fibrin glue scaffold. The same outcome measures from their previous publication were used. The IKDC and Tegner activity scores of both groups had improved significantly from baseline at final follow-up (mean, 28.6 months). There was no significant difference the clinical outcomes between the groups; however, ICRS scores obtained on second-look arthroscopy in the fibrin glue scaffold group were significantly better than those in the scaffold-free group ($P = .028$).

In another study published by Kim et al,[16] 40 patients with focal knee CDs were either injected with a mixture of A-MSCs and PRP or given the previously mentioned A-MSC-seeded fibrin glue scaffold. IKDC and Tegner activity scores were again recorded as clinical measures. Subjects treated with the A-MSC-seeded fibrin glue scaffold had significantly better IKDC scores at final follow-up than subjects treated with the A-MSC and PRP injection, but Tegner activity scores were not significantly different between the groups. ICRS scores were recorded on second-look arthroscopy for all patients and were significantly better in the implantation group than the group that received the A-MSC/PRP injection ($P = .041$).

Most recently, Koh and colleagues[24] published a nonblinded prospective cohort study comparing microfracture surgery alone (MFX) with MFX with implantation of autologous A-MSCs in fibrin glue. Forty patients with isolated grade 3 or 4 chondral lesions were assigned to each group. Patients were evaluated with Lysholm, KOOS, and VAS scores at baseline and 3-, 12-, and 24-month follow-ups. At the 24-month follow-up, patients were also evaluated with MRI and MOCART scores. Improvements in the KOOS pain and symptom subscores were significantly better in the A-MSC/scaffold group at 24 months than they were in the MFX group, but the other 3 KOOS subscores were not significantly different. The MOCART scores at the 24-month point were also significantly better in the MSC group than the MFX group.

Lee et al[28] conducted a nonrandomized observational cohort study with matched controls among 70 individuals with symptomatic knee CDs. Individuals in the treatment group (n = 35) underwent standard MFX procedure and received a single intra-articular injection of BM-MSCs (mean, $10 \times 10^6$ cells) in HA 3 weeks after surgery, followed by 2 more HA injections at weekly intervals. MSC implantation ($8 \times 10^6$ cells/cm$^2$) in the comparator group (n = 35) was done with an open technique with a periosteal patch. Patients were assessed preoperatively and at 3, 6, 8, 12, and 24 months postoperatively with the ICRS Cartilage Injury Evaluation Package, which included the SF-36, IKDC, Lysholm, and Tegner Activity Scale questionnaires. Postoperative MRI was performed 1 year after surgery for all patients treated with the BM-MSCs and most of the matched (control) patients. SF-36, IKDC, and Lysholm scores improved significantly at the final follow-up (mean, 24.5 months) when compared with baseline. The IKDC and Lysholm scores were statistically better in the treatment group than the control group. MRI showed neocartilage with good fill/integration in the treatment group, although there was no explicit scoring described and no mention of the control group's MRI results.

Nejadnik and colleagues[32] compared clinical outcomes of patients treated with ACI with those treated with BM-MSCs. They prospectively evaluated 36 patients receiving BM-MSCs covered by a periosteal patch and sealed with fibrin glue, matching them by age and lesion size with 36 other patients who had been treated with ACI. Patients were evaluated clinically by completing SF-36, IKDC, Lysholm knee scale, and the Tegner activity level questionnaires before surgery and at 3, 6, 9, 12, 18, and 24 months after surgery. Additionally, 4 patients in the BM-MSC group and 3 patients in the ACI group underwent second-look arthroscopy between 9 and 12 months after implantation. A biopsy sample of the repaired tissue was obtained from 1 patient in each group. All clinical scores were significantly improved at all time points in both treatment groups. There were no differences in IKDC score, Lysholm knee scale score, or Tegner activity level between the groups; however, the Physical Role Functioning subscale scores of the SF-36 showed greater improvements among patients treated with BM-MSCs than those treated with ACI ($P = .044$).

Saw and colleagues[39] conducted 1 of the 3 randomized controlled trials and were the only group to administer multiple MSC injections. In their trial, 50 patients with ICRS grade 3 and 4 lesions in the knee underwent both arthroscopic subchondral drilling and abrasion chondroplasty and were randomly assigned to the control or treatment group postoperatively (1:1). Patients were unable to be blinded owing to the procedures involved. Each group received a total of 8 injections. The control group received 8 HA injections (2 mL each). The first 5 injections were given at weekly intervals beginning 1 week after surgery, and the last 3 were given at weekly intervals beginning 6 months postoperatively. The treatment group underwent apheresis to isolate peripheral blood MSCs (PB-MSCs) 1 week after surgery and received injections of PB-MSCs (8 mL) with HA (2 mL) at the same 8 time points as the control group. Cells were characterized by flow cytometry, and a mean of 20 million CD105+ cells were injected. Patients were evaluated clinically with IKDC scores preoperatively and at 6, 12, 18, and 24 months postoperatively. MRI was obtained preoperatively and at 1 day and 6, 12, and 18 months postoperatively. MRI was scored by a blinded musculoskeletal radiologist using the scoring system developed by Mithoefer et al.[31] Additionally, 32 patients (16 from each group) underwent second-look arthroscopy with chondral core biopsy 18 months after surgery. Biopsy

specimens were evaluated with ICRS II scoring by 2 independent blinded histopathologists. The treatment and control groups both showed significant improvements in IKDC scores from baseline at all time points, but no significant differences were found between the groups. MRI scores and ICRS II scores at 18 months were both significantly better in the treatment group. The only serious adverse event reported occurred in the control group.

Sekiya et al[40] reported on a prospective case series in which 10 patients with isolated chondral defects in the knee were treated with autologous synovial MSCs suspended in 0.5 mL of acetate Ringer solution. Patients were evaluated clinically with the Lysholm and Tegner activity scores preoperatively and at final follow-up (mean, 52 months postoperatively). Radiological outcomes were also reported with an author-developed MRI score before and after surgery (mean follow-up, 18 months; range, 3-72 months). MRI was scored from 0 to 5 (lowest to highest quality) with author-developed criteria before and after surgery. Second-look arthroscopy with needle biopsy was done in 4 patients between 11 and 18 months postoperatively. Biopsy specimens were evaluated histologically with qualitative measures. Lysholm scores significantly improved after treatment with autologous synovial MSCs, but Tegner activity scores were unchanged at final follow-up. MRI scores improved from 1.0 ± 0.3 before treatment to 5.0 ± 0.7 after treatment, which reached statistical significance ($P = .005$).

Skowroński and Rutka[41] published a prospective cohort study. Forty-six patients with isolated chondral lesions on the medial femoral condyle were recruited. Of the 46 total patients, 21 patients were treated with autologous bone marrow concentrate, and 25 were treated with PB-MSCs, which were identified by flow cytometry (according to the authors), although no specific markers were described. Patients were assessed with KOOS, Lysholm, and VAS scores before surgery and at 6 months, 1 year, and 5 years after treatment. The clinical outcome scores at the 5-year follow-up in both groups were slightly lower than those obtained at the 1-year follow-up but were still significantly better than the baseline scores. Patients treated with PB-MSCs showed significantly greater improvement in clinical outcomes than those treated with bone marrow concentrate.

Wakitani et al[47] published a prospective case series in which BM-MSCs were implanted into CDs in the patellae of 5 knees of 3 patients with collagen gel scaffolds that were embedded with BM-MSCs. Patients were evaluated clinically with IKDC scores before and after surgery at varying time points. Patient 1 had both knees operated on. The IKDC scores appear graphically in the text, although no distinct values are reported. Patient 1 also underwent second-look arthroscopy, which showed a patellar surface completely covered with cartilage-like tissue and a smooth surface with elastic properties. Histological evaluation of a biopsy specimen taken from the cartilage-like tissue confirmed that the tissue was cartilaginous in nature but not typical hyaline cartilage. Patient 2 also had both knees operated on. The IKDC scores for both of Patient 2's knees had improved at the 20-month follow-up, and MRI evaluation at 12 months revealed complete coverage of the defect. Patient 3's IKDC score at final follow-up (18 months) improved.

## DISCUSSION

The 14 OA studies reviewed reported positive clinical and, in some cases, radiographic outcomes. While encouraging, these efficacy results are difficult to extrapolate to a larger scale for a number of reasons, the most notable being the lack of controlled studies. Only 5 OA studies (36%) included a control group. Postinjection imaging studies were not always positive, and there was an occasional lack of congruity between imaging and clinical results, suggesting that other factors may have accounted for the clinical improvement. Moreover, follow-up procedures, including second-look arthroscopy and imaging, were often conducted on only a small subset of the subjects, increasing the potential influence of bias and limiting the validity of published results.

Based on the 14 studies investigating focal chondral defects, MSCs may be a useful treatment for chondral defects. Improvements were seen in all studies in at least 1 clinical outcome measure, and in some cases, MRI data suggest that MSCs may contribute to cartilage regeneration, albeit irregular. Despite positive findings, the use of different MSC adjuvants—including PRP,[16] HA,[28,39] fibrin glue,[13,15,32] scaffolds,[2,47] periosteum,[13,28,32,41,47] and additional surgical procedures,[17,18,32] as well as the combined use of >1 of these supplements[13,32,47]—limits the ability to determine the specific effect of MSC implementation.

The results reported by Vega et al[46] are particularly noteworthy because they were the only group to use allogenic stem cells. Allogenic treatments possess several advantages over autologous treatments, including more consistency in the cell product, more readily available treatment, and a less invasive procedure. The immunomodulatory effects and limited immunogenicity of stem cells suggests that the therapeutic efficacy of single-administration allogenic stem cell treatments for inflammation-associated disorders may be similar to the efficacy of autologous stem cell treatments and should be further investigated.

Seven unique stem cell sources were used in the studies included in this review. BM-MSCs are the most commonly used, likely because they were the first to be discovered. While there is insufficient comparison data to draw definitive clinical conclusions, other sources (ie, adipose, peripheral blood, synovial tissue, placenta) may be equally or more beneficial than BM-MSCs in the treatment of OA and CDs.[25,42,43,48] In this review, only 1 study[41] compared 2 MSC sources, although 1 group in this study was treated with bone marrow concentrate as opposed to isolated BM-MSCs. Their results demonstrated that PB-MSCs produced better clinical outcomes than bone marrow concentrate. Additionally, none of the studies reviewed used placenta-derived MSCs, despite encouraging preclinical results.[12,29,38]

Two of the largest studies that treated patients for intra-articular injuries with autologous MSCs were excluded because they did not provide clinical outcomes data for these treatments, which is the focus of this review. Pak et al[35] treated 91 patients (100 joints) with a mixture containing adipose tissue–derived stem cells (in the form of stromal vascular fraction), PRP, hyaluronic acid, and calcium chloride. The treatment was administered into the knees, hips, low backs, and ankles of patients with various

orthopaedic conditions. Swelling of the injected joints, tenosynovitis, and tendinitis were common, but no major adverse events were reported. Centeno and colleagues[5] treated 227 individuals. Patients with intra-articular knee (118), hip (78), spine (13), ankle/foot (10), shoulder (10), or hand/wrist (6) pathologic lesions were treated. Of the 227 individuals treated, only 7 cases of minor procedure-related complications were reported (pain, swelling, allergic reaction) and 1 case of cancer (possibly unrelated to the MSC therapy). While the ability of these studies to provide efficacy information is limited, their safety results are consistent with previous systemic reviews, which found adverse events associated with MSC and HA implantation in only 3.2% to 4.7% of cases.[37,45]

As mentioned, we chose to include all clinical studies investigating the safety and efficacy of intra-articular MSC therapy in this review. As a result, several low-powered studies without a control group were included, which weakens our ability to make conclusions pertaining to the clinical efficacy of these treatments. Other groups have published similar reviews with more constrained inclusion criteria. However, given the limited availability of level 1 studies, these reviews are not without problems of their own. For example, Chahla et al[6] recently published a well-done review where they concluded that intra-articular cellular therapy injections for OA and focal CDs are safe and may lead to modest clinical improvement. However, they were able to include only 6 studies (4 level 2 and 2 level 3) in their review—approximately one-fifth of the studies discussed in this article. If nothing else, we believe that our holistic review of the literature is at least equally valuable given the lack of double-blinded randomized controlled trials.

Our decision not to exclude low-powered studies also allows us to make a much stronger case that these treatments are safe. Of the almost 600 unique patients treated with autologous stem cell therapy, only 3 major adverse events were reported, none of which appeared to be related to MSCs. These conclusions are further strengthened by the safety results published by Pak et al[35] and Centeno and colleagues[5] discussed previously. Indeed, autologous MSCs appear to be safe when administered properly, with no apparent increased risk above the standard risks associated with an injection or surgery.

This review has several limitations. In addition to the lack of randomized controlled trials, roughly one-third (10) of the studies included in this review were produced by the same group[15-24] and account for 264 of the 584 (45%) distinct patients who received MSC therapy in this review. Thus, our data are skewed toward their procedures and findings. It is also possible that some studies were omitted because of the search criteria.

Several positives were noted during this review. The mean follow-up was approximately 2 years, and the majority of the studies (93%) followed patients clinically for >6 months. Most studies reported the number of cells injected (86%) and specified the number of passages (82%), which is critical to determine appropriate dosing and manufacturing going forward. Most studies (93%) also reported at least 1 disease-specific clinical outcome measure, which is more sensitive than generalized outcome measures. Most important, all studies identified the cell population with which they were treating patients and reported improvements in function, pain, or both.

In conclusion, the reviewed clinical studies suggest that intra-articular MSC therapies are safe when used to treat OA or focal chondral defects. However, the efficacy of these therapies cannot be determined until more standardized level 1 clinical evidence is available. Improving study methodology and standardizing cell harvesting, processing, characterization, and delivery techniques will be necessary before the efficacy of intra-articular MSC therapies can be determined. Future randomized blinded multiarm clinical studies aimed at determining the cells' mechanisms of action, the optimal cell source and count, the ideal target patient population, and the optimal method of intra-articular delivery are still required.

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