

Umbilical Cord–Derived Stem Cells for the Treatment of Knee Osteoarthritis

A Systematic Review

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Background: The use of mesenchymal stem cells (MSCs) for the treatment of knee osteoarthritis (OA) has gained recent interest in the orthopaedics community.

Purpose: To review the literature to evaluate the efficacy of umbilical cord–derived MSCs in the treatment of OA of the knee joint.

Study Design: Systematic review; Level of evidence, 4.

Methods: We searched the PubMed, Cochrane Library, and Embase databases to identify studies with evidence levels from 1 to 4 that evaluated the clinical efficacy of human umbilical cord–derived MSC (hUC-MSC) injections for knee OA. The search phrase used was “umbilical cord knee osteoarthritis.” In the studies reviewed, patients were assessed based on the macroscopic International Cartilage Regeneration & Joint Preservation Society (ICRS) score, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), visual analog scale (VAS) for pain, and the subjective International Knee Documentation Committee (IKDC) score.

Results: A total of 7 studies met inclusion criteria, including 385 patients undergoing injection of hUC-MSCs (mean age, 59.7 years). The mean follow-up was 23.4 months. Weighted averages of the WOMAC, macroscopic ICRS, subjective IKDC, and VAS scores all showed improvement from before to after treatment. No severe adverse reactions were recorded.

Conclusion: Patients undergoing treatment of knee OA with hUC-MSCs might be expected to experience improvements in clinical outcomes. Additional high-quality randomized studies are needed to better determine the efficacy of hUC-MSC for the treatment of knee OA.

Keywords: knee osteoarthritis; mesenchymal stem cells; umbilical cord

As the use of biologic therapies has received increasing interest in recent years in the field of orthopaedics, clinicians are continuously finding new methods to treat symptoms in patients with early osteoarthritis (OA) or focal chondral defects. These biologic therapies may include platelet-rich plasma (PRP),² bone marrow aspirate concentrate,^{18,21,30} and mesenchymal stem cells (MSCs).³⁶ MSCs can be further differentiated as deriving from bone marrow,¹¹ adipose tissue,³⁸ synovial tissue,²⁰ and the umbilical cord,²⁴ among other harvest sites.

In clinical studies using MSCs, it is important to distinguish the harvest site, as these cells may exhibit differential characteristics regarding rates of proliferation and chondrogenic differentiation potential.^{1,28} Whereas bone

marrow– and adipose-derived MSCs have been studied extensively for the treatment of knee OA,^{12,17} human umbilical cord–derived MSCs (hUC-MSCs) are a relatively novel source of MSCs studied in the treatment of knee OA. Derived from the Wharton jelly of the umbilical cord, hUC-MSCs offer the advantages of greater proliferative capacity without being subjected to ethical controversy in the same way as human embryonic stem cells.¹³

The purpose of this study was to perform a systematic review of the literature to evaluate the efficacy of hUC-MSCs in the treatment of OA of the knee joint. It was hypothesized that hUC-MSC treatment would significantly improve pain relief.

METHODS

This systematic review was conducted according to PRISMA (Preferred Reporting Items for Systematic

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Reviews and Meta-Analyses) guidelines and followed a PRISMA checklist. Two independent reviewers (J.W.B., M.J.K.) searched PubMed, Embase, and the Cochrane Library up to January 20, 2021. The electronic search strategy used was *umbilical cord knee osteoarthritis*. A total of 128 studies were reviewed by title and/or abstract to determine study eligibility based on inclusion criteria. In cases of disagreement, a third reviewer (A.J.S.) made the final decision. The inclusion criteria were human studies that assessed the use of hUC-MSCs for knee OA, studies that were published in English, and studies with a minimum 6-month follow-up. Exclusion criteria included nonhuman studies and studies unrelated to the knee.

Data extraction from each study was performed independently and reviewed by a second author (J.W.B.). There was no need for funding or a third party to obtain any of the collected data. Risk of bias was assessed for 6 studies according to the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool,³⁴ which incorporates an assessment of bias based on confounding, selection of participants, deviations from intended interventions, completeness of outcome data, selection of outcomes reported, and other sources of bias.^{5,6,9,26,29,33} A Cohen kappa score was calculated to determine the level of intraobserver agreement between reviewers. A score of <0.20 indicated poor agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, good agreement; and 0.81-1.00, very good agreement.²⁵ Risk of bias for 1 randomized study²⁴ was assessed according to the Cochrane risk of bias tool,¹⁵ which incorporates an assessment of randomization, blinding, completeness of outcome data, selection of outcomes reported, and other sources of bias.

Reporting Outcomes

Outcomes assessed included patient-reported outcomes such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score,³ the visual analog scale (VAS) for pain, the subjective International Knee Documentation Committee (IKDC) score,¹⁴ and the macroscopic International Cartilage Regeneration & Joint Preservation Society (ICRS) score.³¹ A total of 5 studies used the WOMAC score,^{5,6,9,24,33} 4 studies used the VAS,^{9,24,29,33} 4 studies used the subjective IKDC score,^{6,9,29,33} and 3 studies used the macroscopic ICRS score.^{6,29,33} The macroscopic ICRS score evaluates the macroscopic outcome of cartilage repair, in which grade 1 indicates normal cartilage and grade 4 indicates severely

abnormal cartilage. For the VAS, all scores were standardized to a 100-point scale.

Study Methodology Assessment

The Modified Coleman Methodology Score (MCMS)⁷ was used to evaluate studies' quality of methodology. The MCMS has a scaled potential score ranging from 0 to 100. Scores ranging from 85 to 100 are excellent, 70 to 84 are good, 55 to 69 are fair, and less than 55 are poor. The primary outcomes assessed by the MCMS are study size and type, follow-up time, attrition rates, number of interventions per group, and proper description of study methodology.

Statistical Analysis

A weighted average was calculated for numerical demographics (ie, age, duration of follow-up, body mass index, and sex percentages).

RESULTS

Seven studies met inclusion and exclusion criteria (Figure 1),^{5,6,9,24,26,29,33} including a total of 385 knees undergoing treatment with hUC-MSCs. Patient age ranged from 29.0 to 94.0 years and the mean follow-up time was 23.4 months (range, 6.0-84.0 months). The overall percentage of male patients was 43.2% (Table 1). Of the 2 studies that included an overlapping cohort of patients,^{32,33} 1 limited the cohort to patients 60 years and older³²; therefore, only the study that did not limit its cohort based on age was included in the analyses.³³

Modified Coleman Methodology Score

Table 2 lists the MCMS scores from the 7 included studies. Four studies received good scores,^{6,9,24,33} and 3 studies received fair scores.^{5,26,29}

Methodological Quality Assessment

The results of the methodological quality assessment (using the ROBINS-I tool) of the 6 nonrandomized studies are presented in Figure 2. The 6 studies showed a low risk of bias due to confounding,^{5,6,9,26,29,33} as there were adequate prognostic variables that predicted baseline intervention. No studies excluded eligible patients or used variable

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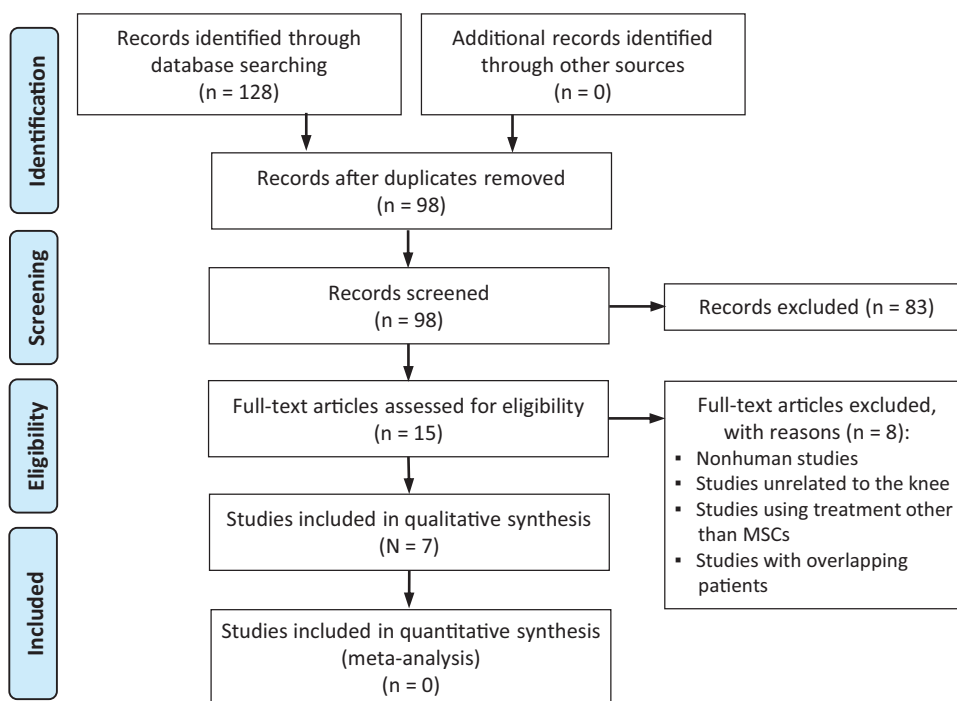


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. MSC, mesenchymal stem cell.

TABLE 1
Studies Included^a

Lead Author (Year)	LOE	Knees, n ^b	Patient age, y	Follow-up, months	BMI	Sex, % Male
Castellanos (2019) ⁵	2	20	71.0 ± 6.4	6.0	29.7 ± 4.3	25.0
Chung (2021) ⁶	2	93	56.6 (43.0-65.0)	20.4 (12.0-42.0)	25.8 (20.9-33.2)	NR
Dilogo (2020) ⁹	2	57	58.3 ± 9.6	12.0	27.1 ± 4.4	58.6
Matas (2019) ²⁴	1	18	56.4 (40.0-65.0)	12.0	27.8 ± 2.6	61.1
Mead (2020) ²⁶	3	42	74.1 ± 9.0 (52.0-94.0)	12.0	27.7 ± 4.1 (20.3-35.3)	57.1
Park (2017) ²⁹	2	7	58.7 ± 15.4 (29.0-77.0)	72.9 (12.0-84.0)	26.4	28.6
Song (2020) ³³	4	128	56.5 ± 7.9 (40.0-78.0)	36.1 ± 6.4 (25.0-47.0)	24.6 ± 3.6 (17.0-45.8)	32.8
Total	—	385	59.7 (29.0-94.0)	23.4 (12.0-84.0)	26.1 (17.0-45.8)	43.2

^aPatient age, follow-up, and BMI are reported as mean ± SD (range) (if reported), with the “Total” row reported as a weighted average. BMI, body mass index; LOE, level of evidence; NR, not reported. Dashes indicate not applicable.

^bNumber of knees injected with human umbilical cord mesenchymal stem cells in each study.

TABLE 2
Results of MCMS Evaluation^a

Study	MCMS
Castellanos (2019) ⁵	68
Chung (2021) ⁶	73
Dilogo (2020) ⁹	70
Matas (2019) ²⁴	78
Mead (2020) ²⁶	64
Park (2017) ²⁹	66
Song (2020) ³³	72
Total, mean ± SD	70.1 ± 4.7

^aMCMS, Modified Coleman Methodology Score.

follow-up times based on intervention (ie, low risk of bias), no studies deviated from the intended intervention (ie, low risk of bias), and all studies clearly classified treatment type (ie, low risk of bias). Three studies used physicians and outcome assessors that were not blinded to the treatment group (ie, serious risk of bias) as well as nonblinded post-treatment protocols (ie, moderate risk of bias).^{9,26,33} None of the 6 studies showed bias due to missing data (ie, low risk of bias). Finally, no studies showed bias due to selective reporting (ie, low risk of bias). A Cohen kappa of 0.83 reflected a very good agreement between reviewers.

The remaining randomized study²⁴ was assessed for methodological quality using the Cochrane Collaboration

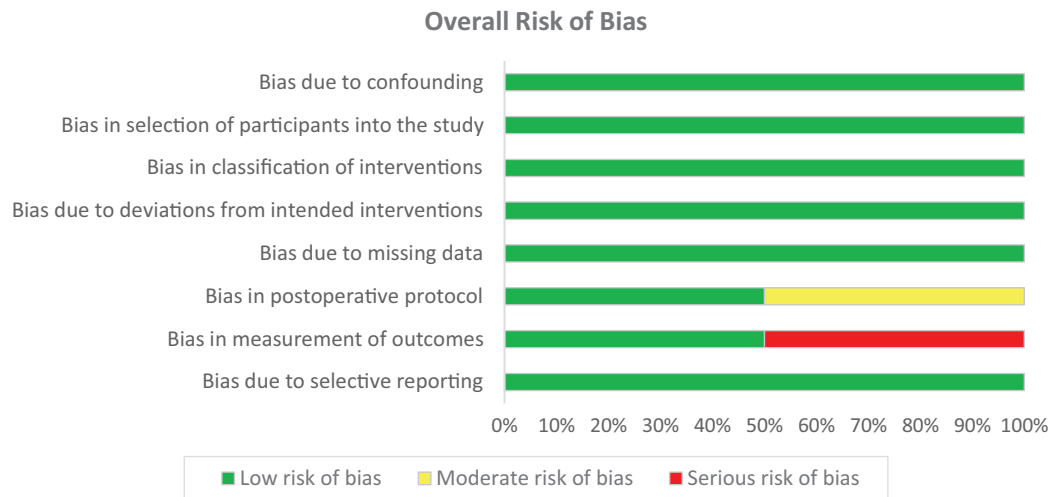


Figure 2. Results of ROBINS-I (Risk of Bias in Nonrandomized Studies of Interventions) assessment. Risk of bias is presented as a percentage across all included studies.

risk-of-bias tool. Sequence generation and allocation were adequately reported (ie, low risk of bias). Blinding of patients and clinicians was not possible owing to the nature of the study (ie, high risk of bias), although outcome assessors to the intervention were blinded (ie, low risk of bias). No significant loss to follow-up was reported (ie, low risk of bias), and there was not selective reporting or incomplete outcome data (ie, low risk of bias).

Isolation of Stem Cells

In 2 studies,^{5,26} Clarix FLO (Amnio Medical) was used for stem cell isolation. hUC-MSCs were derived from human placental tissue in which the amniotic membrane and umbilical cord particulate were removed from the placenta and cleaned of blood under aseptic conditions. The process was followed by lyophilization, micronization, and terminal sterilization. The final product was a powder and stored at room temperature. Next, either 100 mg or 50 mg of the amniotic membrane/umbilical cord particulate was added to 2-mL saline.^{5,26}

In 3 studies,^{6,29,33} the product CARTISTEM (MEDIPOST) was used to isolate hUC-MSCs from umbilical cord blood. To isolate the hUC-MSCs, human umbilical cord blood was collected from maternal umbilical veins at the time of delivery. Mononuclear cells were then separated via centrifugation using a Ficoll-Hypaque solution (Sigma-Aldrich). The isolated mononuclear cells were washed, suspended in a culture medium (minimum essential medium [MEM]), supplemented with 10% fetal bovine serum (FBS), and seeded into culture flasks. Cultures were maintained at 37°C and 5% CO₂ for 2 weeks. Next, cells were trypsinized, washed, and resuspended in culture medium (MEM with 10% FBS).

In 1 study,⁹ cells were harvested from the umbilical artery and vein when they were discarded and minced at

birth. The cells were immersed in a small amount of medium and cultured in an incubator at 37°C and 5% CO₂. The cells were harvested at roughly 80% confluence. In another study,²⁴ Cellstem OA (Cells for Cells) was used for isolation. Umbilical cords were obtained from full-term placentas by cesarean delivery and stored in sterile phosphate-buffered saline, mixed with 100-U/mL penicillin and 100-μg/mL streptomycin. Wharton jelly was cut into small pieces, seeded into culture plates, and mixed with MEM Eagle Alpha Modifications (Gibco) high glucose, 10% heat-inactive FBS, 1% penicillin/streptomycin, and 2 mM L-glutamine (Gibco). At 80% confluence, cells were detached by treatment with TrypLE TM Express (Gibco) and then harvested and preserved in Profreeze (Lonza).

Injection Method

In 1 study,²⁶ injections were administered superolaterally into the intra-articular space under direct visualization, using an arthroscopic portal approach, whereas another study described using an anterolateral approach with the knee in 90° flexion.²⁴ In another study,⁵ all injections were ultrasound guided.

Surgical Technique

In 1 study,³³ to inject the solution, an arthrotomy was performed to expose the medial femoral condyle. After removal of sclerotic subchondral bone, holes with a depth and circumference of 4 mm were drilled 2 mm apart and filled with hUC-MSCs. Microfracture was performed if lesions were located on the tibial plateau and drilling was not possible. Two other studies described exposing the cartilage defect site at the medial femoral condyle,^{6,29} drilling holes 4 to 5 mm in depth and diameter, and filling them with hUC-MSCs.

Administration Strategy

Four studies administered 1 injection to each patient.^{6,26,29,33} In 1 study,⁹ patients were injected once with hUC-MSCs and then an additional 2 times with hyaluronic acid (HA) at 1-week intervals. Another study described administering 1 injection for all patients,⁵ and, for those who did not demonstrate a >30% reduction in pain based on the WOMAC pain subscore, a second injection was given 6 weeks later. In another study,²⁴ one group received hUC-MSCs at baseline and 6 months and another group received hUC-MSCs at baseline followed by a placebo at 6 months.

Number of hUC-MSCs

Three studies used hUC-MSC dosages of 500 mL/cm² of chondral defect with a cell concentration of 5×10⁶ cells/mL.^{6,29,33} Two studies used cell concentrations of 20×10⁶ and 10×10⁶ cells/mL, respectively.^{9,24}

Kellgren-Lawrence Grade

Two studies^{24,33} included patients with grade 1, 2, or 3 OA based on the Kellgren-Lawrence scale,¹⁹ while 2 studies^{6,29} included patients with only grade 3 lesions. One study included patients with grade 1 or 2 lesions,⁹ and 1 study included patients with grade 3 or 4 lesions.²⁶

Patient-Reported Outcomes

Of the 5 studies that reported overall WOMAC scores,^{5,6,9,24,33} 4 demonstrated significant improvement from pretreatment to latest follow-up (Table 3).^{5,6,24,33} Another study that reported WOMAC subscores found significant improvements only in the WOMAC pain, WOMAC physical function, and the WOMAC global subscores from pretreatment to latest follow-up ($P < .05$).⁵ Results of the subjective IKDC score were reported by 4 studies,^{6,9,29,33} 2 of which found patients to improve significantly from pretreatment to latest follow-up (Table 3).^{6,33} Of the 4 studies that reported results of the VAS score,^{9,24,29,33} 2 found patients to improve significantly from pretreatment to latest follow-up (Table 3).^{24,33} Three studies reported results of the macroscopic ICRS score (Table 3).^{6,29,33} The macroscopic changes reported by the studies were appearance of cartilage, degree of defect repair, and integration to the border zone. None of these studies reported P values for this outcome.

In 1 study,²⁶ swelling in the knee was seen in 1 patient within 36 hours, although progressive improvement was reported to the point of a pain-free knee at 6 weeks. In another study,²⁹ arthralgia, back pain, bladder distension, and elevated antithyroglobulin antibody levels were reported in 5 patients. Chung et al⁶ described moderate knee swelling in multiple patients for up to 1 month after surgery. However, there was no persistent effusion, synovitis, localized eruption, or localized erythema that was considered an allergic reaction. In another study,²⁴ 6 patients had acute synovitis after the first injection plus an additional 4 after the second injection. Three patients

TABLE 3
Outcome Scores^a

Study	Preinjection	Postinjection	P
WOMAC score ^b			
Chung (2021) ⁶	44.5 ± 15.1	11.0 ± 3.7	<.001
Dilogo (2020) ⁹	24.66	14.7	.06
Song (2020) ³³	57.3 ± 11.4	10.2 ± 7.9	.000
Matas (2019) ²⁴	35.6 ± 10.1	4.2 ± 3.9	.04
Total	39.3	11.0	—
IKDC score			
Chung (2021) ⁶	39.0 ± 10.4	71.3 ± 5.9	<.001
Dilogo (2020) ⁹	51.4	60.7	.14
Song (2020) ³³	24.3 ± 11.1	68.5 ± 12.7	.000
Park (2017) ²⁹	39.1	63.2	.18
Total	40.9	67.3	—
VAS pain score			
Dilogo (2020) ⁹	45.3	27.5	.16
Song (2020) ³³	76.4 ± 16.6	12.8 ± 11.7	.000
Matas (2019) ²⁴	39.4 ± 21.4	2.4 ± 2.1	.02
Park (2017) ²⁹	49.1	19.3	.18
Total	50.7	17.7	—
Macroscopic ICRS score			
Chung (2021) ⁶	4.0	2.14 ± 0.54	NR
Song (2020) ³³	NR	1.57 ± 0.51	NR
Park (2017) ²⁹	4.0	2 ± 0	NR
Total	4.0	1.8	—

^aScores are reported as a mean ± SD (when reported, or just the mean) at latest follow-up, with the Total row reported as a weighted mean. Boldface P values indicate statistically significant difference between pre- and postinjection ($P < .05$). Dashes indicate not applicable. ICRS, International Cartilage Regeneration & Joint Preservation Society; IKDC, International Knee Documentation Committee; NR, not reported; VAS, visual analog scale for pain; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

^bOne study did not report exact numerical data for this score and was excluded from this table.⁵

exhibited pain after the first injection with an additional patient exhibiting pain after the second injection. In 3 studies,^{5,9,33} no adverse reactions were reported.

DISCUSSION

Based on the results of this systematic review, many of the studies showed significant improvements following injection of hUC-MSCs for the treatment of knee OA. Overall, the results illustrated positive clinical outcomes in the assessment of both pain and function at short-term follow-up. Furthermore, 3 studies included in this review evaluated the macroscopic ICRS score,^{6,29,33} with all 3 reporting improvement in scores, indicating that hUC-MSCs may actually repair cartilage damage from knee OA. Mid- and long-term outcome studies are needed to confirm the positive outcomes found in this systematic review and to compare these outcomes with other stem cell and non-stem cell treatment options for patients with knee OA.

Knee OA recently ranked as the 11th highest contributor to global disability and 38th in disability-adjusted life

years.⁸ While current treatments of OA act to improve the symptoms of the disease, none have been shown to treat the underlying cause or assist in reversing the resulting cartilage damage.¹⁶ Furthermore, treatments such as nonsteroidal anti-inflammatory drugs and analgesics are associated with adverse effects of the cardiovascular and gastrointestinal system when used for long durations.³⁹ In recent years, biological treatments such as PRP and bone marrow aspirate concentrate have gained traction owing to their safety and minimal invasiveness.^{2,4} Recently, hUC-MSCs have gained interest because of their potentially greater proliferative capacity without the ethical controversy of using human embryonic stem cells.¹³ The general premise is that perhaps hUC-MSCs could protect degradation of cartilage and bone in OA by increasing the expression of chondrocytes as well as inducing anti-inflammatory properties, which no other therapy has been shown to do.²⁷ hUC-MSCs have an extensive application clinically, as they have a higher proliferative potential as well as a lower immunogenicity than MSCs from other sources such as the bone marrow and adipose tissue.¹⁰ As umbilical cords are considered medical waste and discarded, there is an abundant supply of these types of cells, which minimizes the medical risks for the donor and diminishes the ethical concerns.³⁵

While this systematic review demonstrates positive outcomes of hUC-MSCs in the treatment of knee OA, further high-quality studies are needed to compare this with other treatments to determine its comparative efficacy. This may include non-stem cell treatments such as HA or PRP injections, as well as stem cells derived from other harvest sites. Furthermore, long-term follow-up studies are needed to fully assess clinical outcomes and long-term safety. The cost of this treatment must be further characterized to determine its applicability to the general population presenting with knee OA and the cost-benefit ratio. As it is currently not approved by the US Food and Drug Administration (FDA), many patients are forced to go overseas to seek such treatment. Patients are forced to pay out of pocket, which could cost an individual between \$8,000 and \$30,000.²³ Because the use of hUC-MSCs for the treatment of knee OA is not FDA approved, physicians in the United States cannot perform these treatments unless actively participating in an FDA clinical trial.

MSCs are not without systemic adverse effects. A meta-analysis evaluated the safety of MSC therapy over a 15-year period and found MSC administration to be associated significantly with transient fever, administration-site adverse events, constipation, fatigue, and sleeplessness.³⁷ Despite these obstacles, there is evidence showing that injection of hUC-MSCs can have beneficial use for the treatment of OA of the knee.

The limitations of this study should be noted. First, most of the studies included in this review were case series, and further studies are needed to compare the efficacy of hUC-MSCs with other forms of treatment for knee OA. Follow-up was limited to a mean of just under 2 years, and future studies should report on the mid- to long-term outcomes of this treatment. There was heterogeneity in the isolation, injection, and administration techniques

across studies. There was also heterogeneity across studies regarding the degree of OA of included patients. Three studies included HA as part of the injection solution.^{6,9,33} HA has been shown to improve knee function and pain in patients with knee OA,^{2,22} making it difficult to assess whether the positive outcomes in these studies were owing to the effect of HA or hUC-MSCs.

CONCLUSION

Patients undergoing treatment of knee OA with hUC-MSCs might be expected to experience improvements in clinical outcomes. Additional high-quality randomized studies are needed to better determine the efficacy of hUC-MSCs for the treatment of knee OA.

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