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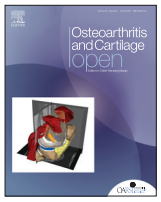

Stromal cell-based injection therapies for the treatment of knee osteoarthritis: A systematic review of level I randomized controlled trials

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ABSTRACT

Objective: To systematically review randomized controlled trials (RCTs) to compare clinical outcomes of stromal cell-based injection therapies versus other non-operative treatment modalities for the treatment of knee osteoarthritis (OA).
Method: A systematic review was performed by searching PubMed, Cochrane Library, and EMBASE to locate RCTs, published since 2019, comparing stromal cell-based injection therapies versus other non-operative modalities for the treatment of knee OA. The search terms used were: *knee AND osteoarthritis AND injection AND randomized.*
Results: Seventeen studies (all Level I evidence) were included in this review with 972 patients undergoing treatment with stromal cell-based therapy (Intervention Group) and 651 patients in the control group (Control Group). Among the 17 studies, 7 used autologous adipose-derived mesenchymal stromal cells (MSCs) (ADMSCs), 2 studies used allogeneic ADMSCs, 4 used autologous bone marrow-derived MSCs (BMMSCs), 1 used allogeneic BMMSCs, 1 used allogeneic placental MSCs, 1 used umbilical cord-derived MSCs (UCMSCs), and 1 study used autologous ADMSCs, BMMSCs, or allogeneic UCMSCs. All but 3 studies reported significantly better clinical or radiological outcomes in the Intervention Group at final follow-up. A total of 5 and 3 studies reported adverse events occurring in the Intervention and the Control groups, respectively, but they were all self-limiting.
Conclusions: Patients undergoing treatment of knee OA with MSCs might be expected to experience improvements in clinical and radiological outcomes in comparison to other non-operative modalities. Additional studies with mid-to long-term outcomes are needed to better determine the efficacy and safety of MSCs for the treatment of knee OA.

1. Introduction

Osteoarthritis (OA) is one of the most common articular cartilage pathologies in the United States and is a leading cause of chronic disability worldwide [1]. It has been estimated that 16.7 % of people older than 45 years have symptomatic knee OA, with 27.8 % showing radiographic signs of cartilage degeneration [2]. Various non-surgical treatment options, such as the use of non-steroidal anti-inflammatory drugs (NSAIDs), physical therapy, and intra-articular injections of corticosteroids, hyaluronic acid (HA), or platelet-rich plasma (PRP) have been employed to alleviate symptoms of knee OA [3–5]. However, none of these treatment options have been shown to reverse or slow the progression of cartilage degeneration.

Recently, cell-based therapies, such as those employing mesenchymal stromal cells (MSCs), have gained attention as a potential disease-modifying treatment. MSCs hold immense biological potential, possessing the ability to differentiate into various cell types, modulate immune responses, and secrete bioactive molecules that promote tissue repair and regeneration [6]. These multipotent cells are particularly intriguing for their anti-inflammatory and immunomodulatory properties, making them attractive candidates for therapeutic applications in conditions such as knee OA [7,8]. Furthermore, recent research has substantiated the improved healing mechanisms in the host facilitated by the paracrine effects of MSCs [9,10]. Given the success observed in preclinical investigations focusing on cartilage restoration with MSCs, there has been a growing trend in the clinical utilization of MSCs for cartilage repair [11,

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12]. Various human tissues, such as bone marrow, adipose tissue, umbilical cord blood, and synovium are recognized as reliable sources of MSCs [13]. Several studies have investigated the role of cell-based therapy in the treatment of knee OA and have been inconclusive or contradictory [14,15]. The purpose of this study was to systematically review randomized controlled trials (RCTs) to compare clinical outcomes of stromal cell-based injection therapies versus other non-operative treatment modalities for the treatment of knee OA. The authors hypothesized that stromal cell-based therapy would result in improved clinical outcomes.

2. Methods and materials

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines using a PRISMA checklist. Two independent reviewers (J.D.,J.A.M.) searched PubMed, EMBASE, and the Cochrane Library up to March 10, 2024. The electronic search strategy used was: *knee AND osteoarthritis AND injection AND randomized*. A total of 3953 studies were reviewed by title and/or abstract to determine study eligibility based on inclusion criteria. In cases of disagreement, a third reviewer (M.J.K.) made the final decision. Inclusion criteria were randomized controlled trials of Level I evidence, published since 2019, comparing stromal cell-based injection therapies versus non-operative treatment modalities for the treatment of knee OA. Studies were limited to those published since 2019 in order to limit this review to the most recent and highest quality of evidence on this topic. Studies were excluded if they were nonclinical, nonrandomized, studies unrelated to the knee joint, studies that did not isolate MSCs from bone marrow aspirate or adipose tissue, and studies involving patients undergoing MSC therapy with a concomitant surgical procedure. Data extraction from each study was performed independently and then reviewed by a third author (M.J.K.). There was no need for funding or a third party to obtain any of the collected data. Risk of bias was assessed according to the Cochrane Collaboration's risk of bias tool [16], which incorporates an assessment of randomization, blinding, completeness of outcomes data, selection of outcomes reported, and other sources of bias. A Cohen kappa score was calculated to determine the level of intraobserver agreement between reviewers. A score of <0.20 indicates poor agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, good agreement; and 0.81 to 1.00, very good agreement [17].

2.1. Reporting outcomes

Outcomes assessed included patient-reported outcomes (PROs), radiological outcomes, range of motion (ROM), and adverse events. PROs included knee pain with a visual analog scale (VAS) and the numerical pain rating scale (NPRS), the Knee Injury and Osteoarthritis Outcome Score (KOOS) [18], the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [19], the SF-36 questionnaire [20], the Knee Society Clinical Rating System (KSCRS) [21], the Osteoarthritis Research Society International Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire [22], and the Modified Knee Society Score-Short Form (KSSSF) [23].

Radiological outcomes were assessed using the Magnetic Resonance Imaging (MRI) Osteoarthritis Knee Score (MOAKS) [24], cartilage degeneration with the modified Outerbridge Classification [25], the modified whole-organ MRI score (WORMS) [26], MRI T2 mapping, and the magnetic resonance observation of cartilage repair tissue (MOCART) score [27].

2.2. Study methodology assessment

The Modified Coleman Methodology Score (MCMS) [28] was used to evaluate study methodology quality. 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.

3. Results

Seventeen studies [29–45] met inclusion criteria (Fig. 1). A total of 1622 patients were included with 972 patients undergoing treatment with stromal cell-based therapy (Intervention Group) and 651 patients undergoing treatment with a control (Control Group). Patient age ranged from 52.0 to 67.2 years and 51.5–70.5 years in the Intervention and Control Groups, respectively. The mean follow-up time ranged from 6.0 to 36.0 months. The average body mass index ranged from 24.3 to 30.8 kg/m^2, and the overall percentage of males ranged from 10 % to 66.7 % (Table 1).

In the Intervention Groups, 9 studies [31,33,35,36,41–45] utilized autologous adipose-derived MSCs (ADMSCs), 2 studies [29,39] utilized allogeneic ADMSCs, 4 studies [34,38,40,45] utilized autologous bone marrow-derived MSCs (BMMSCs), 1 study [30] used allogeneic BMMSCs, 2 studies [37,45] utilized allogeneic umbilical cord-derived MSCS (UCMSCs), and 1 study [32] used allogeneic placenta as their source (Table 2). In the Control Groups, 7 studies [32,33,35,39–41,43] used normal saline, 6 studies [29–31,36,37,44] used HA, 1 study [34] used PRP, 1 study [45] used corticosteroids, and 2 studies [38,42] used a combination of analgesia and physical therapy.

In 5 studies [34,40,42–44], all injections were administered under ultrasound guidance through a superolateral approach. In 1 study [31], injections were administered intra-articularly under direct visualization during arthroscopy. In 3 studies [30,33,35], injections were administered under ultrasound guidance without further details regarding approach. In 8 studies [29,32,36–39,41,45] details of injection administration were not reported.

3.1. Outcomes reported

In terms of PROs, 13 studies [29–41] assessed knee pain with a visual analog scale (VAS) and 1 study [42] with the numerical pain rating scale (NPRS); 5 studies [32,35,39,41,42] used the Knee Injury and Osteoarthritis Outcome Score (KOOS); 11 studies [29–31,33–37,39,43,44] used the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); 2 studies [36,39] used the SF-36 questionnaire; 1 study [29] used the Knee Society Clinical Rating System (KSCRS); 1 study [40] used the Osteoarthritis Research Society International Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire; and 1 study [38] used the Modified Knee Society Score-Short Form (KSSSF).

Regarding radiological outcomes, 1 study [42] used the Magnetic Resonance Imaging (MRI) Osteoarthritis Knee Score (MOAKS); 1 study [43] assessed cartilage degeneration with the modified Outerbridge Classification; 5 studies [31,33,34,37,44] used the modified whole-organ MRI score (WORMS); 2 studies [30,40] used MRI T2 mapping, and 1 study [31] used the magnetic resonance observation of cartilage repair tissue (MOCART) score.

One study [39] reported on the presence of inflammatory cytokines in the peripheral blood.

3.2. Autologous adipose-derived MSCs

Nine studies [31,33,35,36,41–45] evaluated the efficacy of autologous ADMSCs. Frietag et al. [42] found no difference in knee pain, as measured by the NPRS, between groups, though the authors did find a significant difference in each KOOS subscale score favoring the Intervention Group at final follow-up ($p < 0.05$). Furthermore, there was a significant progression of articular cartilage pathology in the Control Group as measured by the MOAKS score, in comparison to the intervention group ($p = 0.04$). In 1 study, the high- and low-dose groups had statistically significant improvements in WOMAC scores when compared

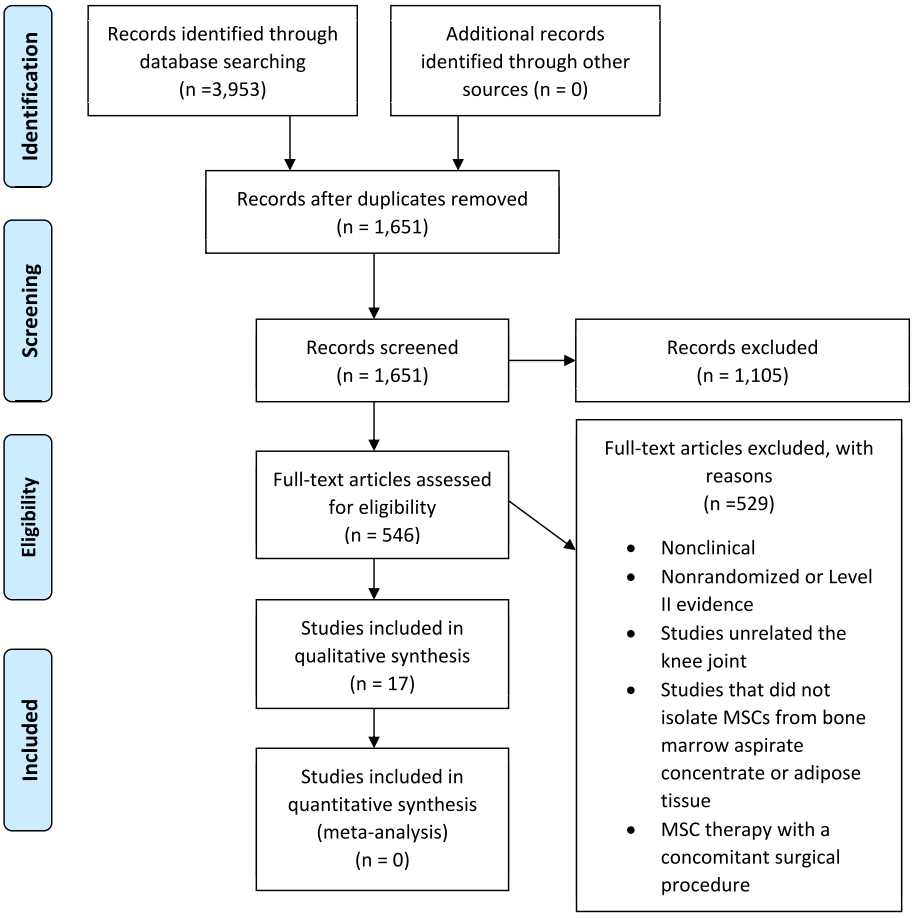

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

with the placebo group ($p = 0.04$, $p = 0.02$). Furthermore, MRI revealed no changes in cartilage thickness after treatment between groups ($p > 0.05$). One study [35] found a significant improvement in the WOMAC score, all subscales of the KOOS score, reduction in pain, and range of motion, favoring the Intervention Group at final follow-up ($p < 0.05$, $p < 0.05$, $p < 0.01$, $p = 0.03$, respectively). Furthermore, at the final follow-up, there was a significant difference in the change in cartilage defect size in the medial femoral condyle, as measured on MRI, favoring the MSC group ($p = 0.0051$); while the MSC group showed no significant change in cartilage defect size at 6 months, the defect in the control group increased in size. Another study [36] found a significant improvement in the SF-36 questionnaire favoring the Intervention Group ($p = 0.0097$) but no significant differences were found between groups with regards to the WOMAC score ($p = 0.655$) or the VAS for pain ($p > 0.05$) at final follow-up. There was a significant increase in femoral cartilage thickness, as measured on MRI between the patella-femoral condyles, favoring the Intervention Group at final follow-up ($p < 0.05$). One study [33] found a significant improvement in the WOMAC and VAS scores, favoring

Table 1
Studies included. n refers to the number of knees that underwent treatment with either MSCs (Intervention Group) or control (Control Group). Gender is reported as a percentage. Age, follow-up, and body mass index (BMI) are reported as mean ± SD (if available). KL, Kellgren-Lawrence; LOE, level of evidence; NR, not reported; USA, United States of America.

Study	n (Intervention, Control)	Patient Age (Intervention, Control), y	Follow-up, mo	BMI, kg/m^2	Male, %	Country	KL Grade
Frietag et al., 2019 [42]	20, 10	54.7 ± 8.3, 51.5 ± 6.1	12.0	29.1	66.7	Australia	2 to 3
Garza et al., 2020 [43]	26, 13	60.0 ± 9.8, 57.1 ± 9.1	12.0	27.8	43.6	USA	2 to 3
Hong et al., 2019 [31]	16, 16	52.0 ± 8.7, 52.0 ± 8.7	12.0	26.3	18.8	China	2 to 3
Khalifeh et al., 2019 [32]	10, 10	NR	6.0	NR	NR	Iran	2 to 4
Lee et al., 2019 [35]	12, 12	62.2 ± 6.5, 63.2 ± 4.2	6.0	25.4	25.0	South Korea	2 to 4
Lu et al., 2019 [36]	26, 27	55.0 ± 9.2, 59.6 ± 6.0	12.0	24.3	14.0	China	1 to 3
Matas et al., 2019 [37]	20, 9	56.4 ± 5.5, 54.8 ± 4.5	12.0	27.6	44.8	Chile	1 to 3
Shapiro et al., 2019 [40]	25, 25	60.0 ± 6.5, 60.0 ± 6.5	12.0	27.1	28.0	USA	1 to 3
Kim et al., 2023 [33]	125, 127	63.7 ± 7.1, 63.8 ± 7.2	6.0	26.1	25.4	South Korea	3
Sadri et al., 2023 [39]	20, 20	52.8 ± 7.5, 56.1 ± 7.2	12.0	28.7	10.0	Iran	2 to 3
Gupta et al., 2023 [30]	73,73	51.6 ± 6.8, 53.6 ± 6.8	12.0	26.4	32.9	India	2 to 3
Chen et al., 2021 [29]	49, 8	67.2, 70.5	6.0	26.5	19.3	Taiwan	2 to 3
Mautner et al., 2023 [45]	360, 80	58.2, 58.3	12.0	30.8	45.0	USA	2 to 4
Lamo-Espinosa et al., 2020 [34]	24, 26	56.0, 54.6	12.0	26.1	46.0	Spain	2 to 4
Sadat-Ali et al., 2021 [38]	30, 27	56.2 ± 6.6, 56.8 ± 5.8	24.0	NR	40.4	Saudi Arabia	2 to 3
Tantuway et al., 2023 [41]	115, 116	52.0, 52.0	36.0	NR	37.9	India	1 to 3
Zhang et al., 2024 [44]	35, 35	57.6 ± 12.3, 54.6 ± 11.3	12.0	24.2	18.5	China	1 to 3

Table 2
Preparation and administration protocols of MSCs. AT, adipose tissue; BM, bone marrow; HA, hyaluronic acid; MSC, mesenchymal stem cell; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; UC, umbilical cord.

Study	MSC source	Autologous or Allogeneic	Culturing	Injections	MSC volume per injection (mL)	MSC count per injection	Control
Frietag et al., 2019 [42]	AT	Autologous	Yes	1 versus 2	3	1.0×10^8	Combination of analgesia, exercise, weight management
Garza et al., 2020 [43]	AT	Autologous	No	1	3 to 4	High dose, 3.0×10^7; low dose, 1.5×10^7	Normal saline
Hong et al., 2019 [31]	AT	Autologous	No	1	4	7.5×10^6	HA
Khalifeh et al., 2019 [32]	Placenta	Allogeneic	Yes	1	10	6×10^7	Normal saline
Lee et al., 2019 [35]	AT	Autologous	No	1	3	1.0×10^8	Normal saline
Lu et al., 2019 [36]	AT	Autologous	Yes	2	2.5	5.0×10^7	HA
Matas et al., 2019 [37]	UC	Allogeneic	Yes	1 versus 2	3	2.0×10^7	HA
Shapiro et al., 2019 [40]	BM (iliac crest)	Autologous	No	1	15	3.4×10^7	Normal saline
Kim et al., 2023 [33]	AT	Autologous	Yes	1	3	1.0×10^8	Normal saline
Sadri et al., 2023 [39]	AT	Allogeneic	Yes	1	5	1.0×10^6	Normal saline
Gupta et al., 2023 [30]	BM	Allogeneic	Yes	1	2	2.5×10^6	HA
Chen et al., 2021 [29]	AT	Allogeneic	Yes	1	NR	8.0×10^6	HA
Lamo-Espinosa et al., 2020 [34]	BM (iliac crest)	Autologous	Yes	3	8	1.0×10^7	PRP
Mautner et al., 2021 [45]	BM (iliac crest), AT, UC	Autologous, Allogeneic	NR	NR	NR	NR	Corticosteroid
Sadat-Ali et al., 2021 [38]	BM (iliac crest)	Autologous	Yes	NR	NR	1.0×10^6	NSAIDs and physical therapy
Tantuway et al., 2023 [41]	AT	Autologous	No	NR	5	5.0×10^7	Normal saline
Zhang et al., 2024 [44]	AT	Autologous	No	1	15	4.7×10^6	HA

ADMSCs at final follow-up ($p = 0.02$ and $p = 0.004$, respectively). However, the modified WORMS on MRI evaluation did not significantly differ between the two groups ($p > 0.05$). Hong et al. [31] found that ADMSCs resulted in significant improvement in the mean VAS, WOMAC scores, and ROM at 12-month follow-up compared to baseline ($p < 0.001$, $p < 0.01$, and $p < 0.05$, respectively). In contrast, the mean VAS, WOMAC scores, and ROM of the Control Group did not demonstrate a statistically significant change from baseline to the last follow-up visit. WORMS and MOCART measurements revealed a significant improvement in knees injected with ADMSCs compared to HA ($p < 0.05$ and $p < 0.01$, respectively). Mautner et al. [45] found no significant differences in clinical or radiological outcomes between groups at final follow-up ($p > 0.05$). In another study [41], patients in the Intervention Group had a significant improvement in the VAS score and KOOS score compared to the Control Group at final follow-up (both $p < 0.001$). One study [44] found a significant improvement in VAS, WOMAC, and MRI findings favoring the Intervention Group at final follow-up (all $p < 0.05$).

3.3. Allogeneic adipose-derived MSCs

Two studies [29,39] evaluated allogeneic ADMSCs. One study [39] found a significant improvement in the WOMAC score, VAS for pain, all KOOS subscales, and the SF-36 questionnaire favoring the Intervention Group at final follow-up (all $p < 0.001$). There were also significant increases in cartilage thickness in the medial posterior and medial anterior regions of the tibial plateau in the ADMSC group, compared to the Control Group ($p < 0.01$ and $p < 0.05$, respectively). Furthermore, cartilage oligomeric matrix protein (COMP) concentration was significantly decreased, indicating lower inflammatory biomarkers in the peripheral blood, in patients who underwent ADMSC injection compared with the Control Group ($p < 0.05$). Another study [29] found no significant differences in the WOMAC total score between groups ($p > 0.05$), though there were significant improvements in the VAS score for knee pain and KSCRS functional activities score at final follow-up, favoring the ADMSC group (both $p < 0.05$).

3.4. Autologous bone marrow-derived MSCs

Four studies [34,38,40,45] evaluated the efficacy of autologous BMMSCs. In 1 study [40], no significant differences were found between groups in terms of knee pain, ICOAP score, and T2 quantitative MRI mapping at final follow-up ($p > 0.05$). Lamo-Espinosa et al. [34] found no significant differences in VAS, WOMAC, or changes in knee joint space width or joint damage, based on X-ray and MRI (WORMS protocol), between patients undergoing treatment with BMMSCs + PRP or PRP alone at final follow-up (all $p > 0.05$). Another study [38] found a significant improvement in knee pain with VAS, KSSSF, and quality of life in the Intervention Group compared to the Control Group at final follow-up (all $p = 0.0001$). Mautner et al. [45] found no significant differences in clinical or radiological outcomes between groups at final follow-up ($p > 0.05$).

3.5. Allogeneic bone marrow-derived MSCs

One study [30] evaluated allogeneic BMMSCs. The Intervention Group showed significant improvements in the WOMAC total score and the VAS for pain compared with the placebo group at final follow-up (both $p < 0.01$). T2 mapping showed that there was no worsening of deep cartilage in the medial compartment of the knee joint in the BMMSC group at 12-month follow-up, whereas in the placebo group there was significant and gradual worsening of cartilage quality ($p < 0.001$).

3.6. Allogeneic placental MSCs

One study [32] evaluated allogeneic placental MSCs. Significant improvements were seen in the KOOS subscores of quality of life, activities

of daily living, sport/recreational activity and decreased OA symptoms in the MSC-injected group ($p < 0.05$) until 8 weeks, after which there were no differences between groups.

3.7. Allogeneic umbilical cord-derived MSCs

Two studies [37,45] evaluated allogeneic UCMSCs. At 12 months, patients in the double-dose MSC group demonstrated significantly lower pain levels based on the WOMAC pain subscale ($p = 0.04$) and the VAS ($p = 0.03$) compared with the HA group. For total WOMAC, MSC-2 had better scores than HA at 12 months ($p = 0.05$). No differences in MRI scores were detected between groups ($p > 0.05$). Mautner et al. [45] found no significant differences in clinical or radiological outcomes between groups at final follow-up ($p > 0.05$).

3.8. Adverse events

Sixteen studies [29–39,41–45] reported the incidence of adverse events. Nine studies [29,31,34,35,37,41,43–45] found no related serious adverse effects. In 1 study [42], 2 patients reported self-limiting pain and swelling for 4 weeks following autologous ADMSC therapy, requiring a period of unloading, analgesia, and/or oral anti-inflammatory use. In one study [36], 1 patient experienced a septic knee joint 2 months after injection of HA, which required irrigation and debridement. Another study [33] reported procedure-related joint pain in 3 ADMSC patients and 1 Control Group patient. Sadri et al. [39] reported 2 ADMSC patients developed swelling around the injection site which was self-limited. In 1 study [30], 4 patients in the BMMSC group and 1 patient in the placebo group had an adverse event which included joint swelling and pain as well as injection-site pain. All events of joint pain and swelling recovered completely within a few days of symptomatic treatment. Khalifeh et al. [32] reported on 4 patients in the MSC group who experienced a mild effusion and increased local pain, which resolved within 48–72 h. In another study [38], 1 patient in the Control Group experienced local cellulitis which was treated by oral antibiotics.

3.9. Modified coleman methodology score

Table 3 shows the MCMS scores from the 17 included studies. Four studies [30,33,41,44] received excellent scores and 13 studies [29,31,32,34–40,42,43,45] received a good score.

3.10. Methodological quality assessment

The results of the methodological quality assessment of included studies using the Cochrane Collaboration's risk of bias tool are presented in Fig. 2. Sequence generation and allocation were adequately reported by all studies (low risk of bias) [29–45]. Fourteen studies [30–37,39–45] were deemed to be at low risk for detection bias because of blinding of the outcome assessor and 3 studies [29,38,40] in which the outcome assessor was not blinded were deemed to be at a high risk of bias. Patients were unblinded to the intervention group (high risk of bias) in 5 studies [34,38,42,44,45] and blinded to their intervention group in 12 other studies [29–33,35–37,39–41,43] (low risk of bias). Seventeen studies [29–45] reported no significant loss of follow-up (low risk of bias). A Cohen kappa score of 0.84 reflected a very good agreement between reviewers.

Table 3
Modified coleman methodology score (MCMS).

Study	MCMS
Tantuway et al., 2023 [41]	88
Kim et al., 2023 [33]	88
Gupta et al., 2023 [30]	88
Zhang et al., 2020 [44]	85
Chen et al., 2021 [29]	82
Garza et al., 2020 [43]	82
Hong et al., 2019 [31]	82
Shapiro et al., 2019 [40]	82
Lamo-Espinosa et al., 2020 [34]	81
Sadat-Ali et al., 2021 [38]	80
Sadri et al., 2023 [39]	80
Lu et al., 2019 [36]	80
Matas et al., 2019 [37]	78
Mautner et al., 2023 [45]	78
Frietag et al., 2019 [42]	77
Khalifeh et al., 2019 [32]	77
Lee et al., 2019 [35]	77
Total	**81.5 ± 3.8**

4. Discussion

Based on the results of this systematic review, many of the studies showed significant improvements following injection of 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 in comparison to other non-operative treatment options including HA and placebo. Furthermore, there is some evidence that MSCs may be able to prevent disease progression on imaging as well as reduce inflammatory cytokines. Mid- and long-term outcome studies are needed to confirm the positive outcomes found in this systematic review.

A systematic review published in 2017 [46] reviewed the published literature on the efficacy of stem cell injections for knee OA. A total of 6 studies, 5 RCTs and 1 non-RCT, were evaluated and the authors concluded that the studies demonstrated a high risk of bias and that contradictory trial results; heterogeneity in outcome measures and cointerventions such as surgery, HA or PRP injections; stem cell origin; culturing modes; and injection frequency/timing made a general statement for the efficacy of MSC undesirable. A more recent systematic review published in 2021 [47] included 13 RCTs, published from 2015 to 2020, with a total of 438 knees treated. The authors concluded that intra-articular MSC injections were not found to be superior to placebo in terms of pain relief and functional improvement for patients with symptomatic knee OA. This study builds upon the previous systematic reviews by limiting inclusion to the most up-to-date and highest quality (Level I evidence) studies, with a total of 17 studies and 1622 knees included, for a more recent and robust set of clinical findings.

The choice of harvest site for MSCs depends on various factors including accessibility, yield, quality, and intended therapeutic application, each with their own advantages and disadvantages. Bone marrow, particularly from the iliac crest, provides a rich source of MSCs, well-established harvesting techniques, and effectiveness in treating various diseases such as OA and focal chondral defects [48]. However, it is an invasive procedure causing discomfort and potential complications such as pain, bleeding, and infection, decreased cell yield and quality with age, and limited availability due to donor-site morbidity. Advantages of adipose tissue include its availability from multiple body sites, with higher cell yield compared to bone marrow, and less invasive harvesting techniques compared to bone marrow aspiration [48]. Disadvantages include increased technical expertise required for harvesting and processing, higher risk of contamination with other cell types, and ADMSCs may have lower differentiation potential compared to bone marrow-derived MSCs [49]. Umbilical cord tissue has benefits which include high accessibility and non-invasiveness, as umbilical cords are typically discarded after birth, and it is an abundant source of MSCs with higher proliferative capacity and lower immunogenicity compared to adult tissue-derived MSCs [50]. Disadvantages include limited availability and ethical concerns related to the collection process, potential risk of transmitting infections from the donor to the recipient, and overall less evidence compared to adult tissue-derived MSCs [51]. Furthermore, autologous MSCs offer the advantage of reduced risk of immune rejection as they are harvested from the patient's own tissues, ensuring compatibility. However, their availability may be limited, while allogeneic MSCs provide a broader accessibility but carry the risk of immune response and require careful matching to minimize rejection [52].

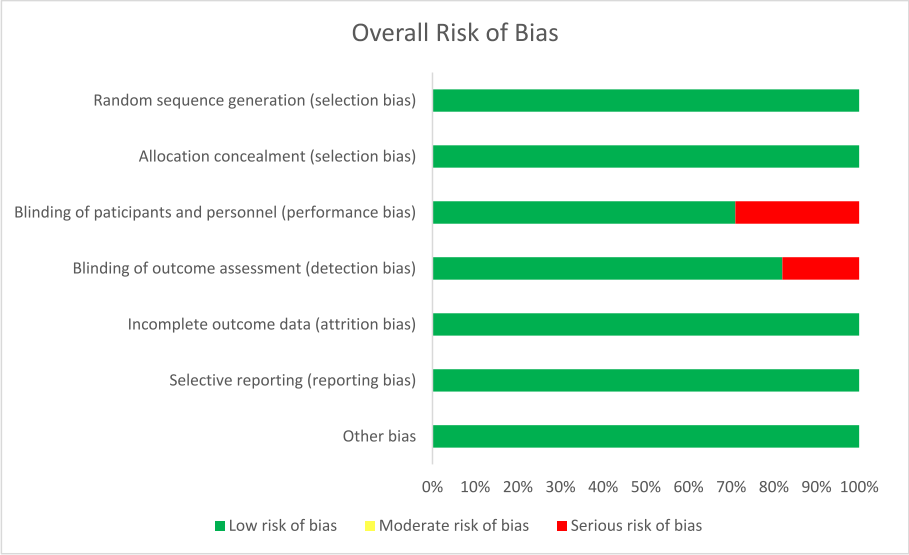

Fig. 2. Risk of bias graph. Risk of bias is presented as a percentage across all included studies (green, low risk; yellow, unclear; red, high risk).

Although existing treatments for OA aim to alleviate the symptoms of the disease, none have demonstrated efficacy in addressing the root cause or aiding in the reversal of associated cartilage damage [53]. MSC therapy is a potential emerging treatment option for patients with a higher demand. The precise mechanism through which MSCs exert their therapeutic effects is not completely understood. MSCs have the potential to differentiate into osteocytes, adipocytes, and chondrocytes, synthesizing proteins like aggrecan and type II collagen, and promoting chondrocyte proliferation [54]. Studies have demonstrated some evidence that, following MSC implantation, there is an observed enhancement in cartilage thickness and the extension of repaired tissue over the subchondral bone [14,47,55]. However, further studies are necessary to determine the true effects of MSC treatment on cartilage regeneration.

While this study demonstrates positive outcomes of MSCs in the treatment of knee OA, further long-term follow-up studies are needed to fully assess clinical outcomes and long-term safety. Furthermore, the cost of this treatment is needed to assess its relevance for the broader population dealing with knee OA, considering the cost-benefit ratio. Since this treatment currently lacks approval from the US Food and Drug Administration (FDA), patients often resort to seeking this treatment overseas and bear the out-of-pocket expenses, ranging from $10,000 to $30,000 per individual [56]. Long-term safety of these injections continues to be a concern as the majority of the studies included in this review followed patients for 6–12 months. This systematic review revealed no substantial disparity in adverse events between MSCs and the control group. The majority of reported adverse events consisted of pain or swelling at the injection site, and these incidents were self-limiting, typically necessitating a period of unloading, analgesics, or oral anti-inflammatory medications. However, a meta-analysis of 62 RCTs assessed the safety of MSC therapy, revealing a significant association between MSC administration and temporary occurrences of fever, adverse events at the administration site, constipation, fatigue, and sleeplessness [57]. In spite of these challenges, there is evidence indicating that the injection of MSCs can be beneficial for treating knee OA.

The limitations of this study should be noted. There was variability in the preparation and administration techniques across studies. In one study [34] the Intervention Group consisted of MSCs in combination with PRP. There was also heterogeneity in the source of cell-based therapy, the control groups, as well as the PROs reported, which precluded a meta-analysis and therefore the data was synthesized descriptively. Patients with all grades of knee OA were included and therefore it was not possible to determine the efficacy of MSC therapy in early and advanced stages of OA. In addition, follow-up times were short-term and highly variable, ranging from 6 to 36 months.

5. Conclusion

Patients undergoing treatment of knee OA with MSCs might be expected to experience improvements in clinical and radiological outcomes in comparison to other non-operative modalities. Additional studies with mid-to long-term outcomes are needed to better determine the efficacy and safety of MSCs for the treatment of knee OA.

Author contributions

Jaydeep Dhillon: Investigation, Data curation, Writing – Original draft.

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Matthew Kraeutler: Conceptualization, Methodology, Supervision, Writing – review and editing.

Conflict of interest

None.

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