Journal of Stem Cell Research

Genesis-JSCR-7(3)-91
Volume 7 | Issue 3
Open Access
ISSN: 2582-8797

Chondrocyte and Mesenchymal Stem Cell–Based Regenerative Therapies for Osteoarthritis and Degenerative Bone Disorders

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Citation: Castrellon PD, Bluguermann C, Jenkins I, Casazza K, Robinson B, Mutto A, Lakey JRT. Chondrocyte and Mesenchymal Stem Cell–Based Regenerative Therapies for Osteoarthritis and Degenerative Bone Disorders. J Stem Cell Res. 7(3):1-16.

Received: August 05, 2026 | **Published**: August 16, 2026

Abstract

Background

Osteoarthritis (OA) and related degenerative osteochondral disorders are driven by chondrocyte dysfunction, extracellular-matrix degradation, synovitis and subchondral-bone remodelling. Regenerative cellular therapies — bone-marrow–derived mesenchymal stem cells (BM-MSC) and aspirate concentrate (BMAC), adipose-derived MSC (AD-MSC), stromal vascular fraction (SVF), microfragmented adipose tissue (MFAT) and umbilical-cord MSC (UC-MSC) — are proposed as disease-modifying interventions, but their comparative efficacy and safety remain contested.

Objectives

To evaluate the efficacy (pain, function, joint structure) and safety of chondrocyte/MSC-based regenerative therapies for knee OA using a Cochrane-aligned systematic review, a DerSimonian–Laird random-effects meta-analysis of extractable trial data, and an exploratory network meta-analysis (NMA); and to contextualise degenerative osteochondral and non-knee disease narratively.

DOI: https://doi.org/10.52793/JSCR.2026.7(3)-91

Methods

PubMed/MEDLINE and PubMed Central were searched from inception to August 2026, cross-referenced against nine recent systematic reviews/NMAs. Randomized/controlled trials of intra-articular cellular therapy in adults with knee OA were eligible. Two-domain screening, standardized extraction, and Cochrane Risk-of-Bias 2 (RoB 2) assessment were performed. Continuous outcomes were pooled as Hedges' g standardized mean differences (SMD; positive = favours cell therapy); adverse events as risk ratios (RR). Heterogeneity was quantified with I^2 and τ^2, with 95% prediction intervals. Certainty was rated with GRADE.

Results

Twenty-six controlled trials (23 primary RCTs) were included; twelve contributed extractable quantitative data. Cell therapy improved the WOMAC composite versus control at 6 months (SMD +0.39, 95% CI −0.00 to +0.77; I^2=0%; k=3) and 12 months (SMD +0.41, 95% CI +0.02 to +0.80; I^2=0%; k=3). Pain (VAS) at 12 months favoured cell therapy but was non-significant and extremely heterogeneous (SMD +0.48, 95% CI −0.65 to +1.61; I^2=90%; k=3; prediction interval −4.27 to +5.23). Two small trials with quantitative MRI suggested cartilage-volume preservation (SMD +1.18, 95% CI +0.64 to +1.71; k=2), contradicted by the null structural findings of the largest phase III trials. Safety was favourable: any adverse event RR 1.11 (0.59–2.08; k=5) and serious adverse events RR 0.63 (0.15–2.68; k=6), with no tumorigenesis or accelerated joint destruction. The pragmatic multicentre MILES trial found no cell product superior to corticosteroid at 12 months.

Conclusions

Regenerative cellular therapies produce small-to-moderate improvements in self-reported function and are safe over 6–12 months, but robust superiority over active intra-articular comparators and definitive structural disease modification are not established. Certainty ranges from low to very low, limited by small trials, heterogeneity, industry sponsorship and unreported dispersion in pivotal trials. Adequately powered, standardized head-to-head trials with compositional MRI beyond 12 months are required.

Keywords

Osteoarthritis; Chondrocytes; Mesenchymal stem cells; Stromal vascular fraction; Cartilage regeneration; meta-analysis; Network meta-analysis

Introduction

Do stem-cell injections help people with knee osteoarthritis, and are they safe? Osteoarthritis wears down the cushioning cartilage of the knee, causing pain and stiffness. Several cell-based injections — from bone marrow, fat tissue, or umbilical cord — are marketed as ways to repair the joint. We gathered the randomized trials that tested these injections against dummy injection, lubricant (hyaluronic acid), platelet injections, or steroid.

What we found: across the trials that reported usable numbers, cell injections gave a small improvement in day-to-day knee function over 6–12 months and appeared safe — side effects were mostly short-lived swelling or pain, and serious problems were rare and not clearly linked to the cells. However, the improvement in pain was inconsistent between trials, evidence that the cells rebuild cartilage was weak and conflicted by the two largest trials, and the single biggest, most rigorous trial found stem-cell

DOI: https://doi.org/10.52793/JSCR.2026.7(3)-91

injections were no better than a standard steroid injection after one year. Overall certainty is low. People considering these treatments should know the benefits are modest and unproven relative to cheaper standard injections.

Background

Osteoarthritis is a chronic, progressive, whole-joint disease and a leading global cause of pain and disability, affecting more than 500 million people worldwide. Once framed as mechanical "wear and tear," OA is now understood as an active biological process involving articular-cartilage degradation, synovial inflammation, subchondral-bone remodelling, meniscal pathology and periarticular soft-tissue change. Central to its pathogenesis is failure of the articular chondrocyte — the sole cell maintaining cartilage extracellular matrix (ECM) — which shifts from an anabolic phenotype (type II collagen, aggrecan) toward senescence, hypertrophy and catabolism (MMP-13, ADAMTS-4/5).

Mitochondrial dysfunction is increasingly recognised as an upstream driver: impaired oxidative phosphorylation, reduced mitochondrial biogenesis, excess reactive oxygen species and mitochondrial-DNA damage generate oxidative stress that activates NF-κB, MAPK and AP-1 signalling and amplifies catabolism. Damaged mitochondria release damage-associated molecular patterns that engage Toll-like and NLRP3 receptors, driving sterile low-grade synovitis and a self-reinforcing degenerative cycle that destabilises the whole osteochondral unit.

Current care remains largely palliative. NSAIDs, intra-articular corticosteroids and viscosupplementation give transient relief without halting structural progression; no disease-modifying OA drug is approved, and arthroplasty — though definitive — carries cost, perioperative risk and finite implant longevity. This gap motivates regenerative strategies. MSCs from bone marrow, adipose tissue, synovium and umbilical cord, together with SVF, MFAT and chondroprogenitors, act less through durable engraftment than through paracrine, immunomodulatory and metabolic effects — secreting growth factors, cytokines, extracellular vesicles and microRNAs, repolarising macrophages, dampening IL-1/TNF/NF-κB catabolism, and, in preclinical models, transferring functional mitochondria to stressed chondrocytes. These mechanisms provide a biologically plausible basis for symptomatic benefit and, potentially, structural stabilisation.

Prior syntheses have often focused narrowly on symptom scores or single comparators, reached discordant conclusions, and rarely integrated comparative (network) evidence across cell platforms. This review provides an integrated, quantitative, mechanism-aware synthesis of the controlled clinical evidence.

Objectives

Primary objective: to determine the efficacy (pain, physical function, joint structure) and safety of intra-articular chondrocyte/MSC-based regenerative therapies versus placebo/saline, hyaluronic acid (HA), platelet-rich plasma (PRP) or corticosteroid in adults with knee OA. Secondary objectives: to compare cell sources (BM-MSC/BMAC, AD-MSC, SVF, MFAT, UC-MSC) through an exploratory NMA and published network syntheses; and to summarise evidence for hip, ankle and other degenerative osteochondral/bone disorders narratively.

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Methods

This review was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported per PRISMA 2020 and, for the network component, PRISMA-NMA. Because it was executed as a rapid, reproducible synthesis, the protocol was defined a priori (PICOS below) and cross-checked against nine recent peer-reviewed systematic reviews/NMAs to ensure the study pool was complete.

Eligibility criteria (PICOS)

Element	Criterion
Population	Adults with symptomatic knee OA (primary quantitative focus). Hip/ankle/osteochondral and degenerative-bone disease considered narratively.
Intervention	Intra-articular cellular/regenerative therapy: BM-MSC, BMAC, AD-MSC (autologous or allogeneic, culture-expanded), SVF, MFAT, UC-MSC / perinatal MSC.
Comparators	Placebo/saline, hyaluronic acid (HA), platelet-rich plasma (PRP), corticosteroid, or usual care.
Outcomes	Primary: validated pain (VAS, WOMAC-pain, KOOS-pain) and function (WOMAC, KOOS-ADL, IKDC). Secondary: MRI/structural (cartilage volume, WORMS, MOCART, defect size); adverse events (AE) and serious adverse events (SAE).
Study design	Randomized controlled trials and controlled clinical trials. Single-arm, uncontrolled, in-vitro and animal studies excluded from synthesis (uncontrolled trials noted narratively).

Information sources and search

PubMed/MEDLINE and PubMed Central were systematically searched from database inception to 10 August 2026 using combinations of controlled vocabulary and free-text terms for regenerative cell therapies (“mesenchymal stem cells”, “stromal vascular fraction”, “microfragmented adipose tissue”, “bone marrow aspirate concentrate”, “umbilical cord mesenchymal stem cells”) with disease terms (“knee osteoarthritis”, “degenerative cartilage/bone disease”) and design filters (“randomized controlled trial”). Reference lists of eligible trials and of nine recent systematic reviews/NMAs (2020–2025) were hand-screened to capture all candidate trials.

Selection, extraction and risk of bias

Records were screened by title/abstract then full text (or PubMed Central full text/abstract where paywalled). For each trial we extracted design, blinding, sample size per arm, population (age, Kellgren–Lawrence grade), cell source/dose, comparator, and per-arm outcome data (mean, standard deviation, n) at the timepoints nearest 6 and 12 months, plus AE/SAE counts. Risk of bias was assessed with the Cochrane RoB 2 tool across five domains (randomization; deviations from intended interventions/blinding; missing outcome data; measurement of the outcome; selective reporting) with an overall judgement.

Effect measures and synthesis

Continuous outcomes measured on different instruments (e.g., VAS 0–10 vs 0–100; WOMAC vs KOOS) were combined as standardized mean differences (Hedges’ g, with small-sample correction), oriented so that a positive value favours the cell therapy. Adverse events were pooled as risk ratios (log-RR, 0.5

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continuity correction for zero cells). Pooling used the DerSimonian–Laird random-effects model. Heterogeneity was quantified by the Q-test, I^2 and between-study variance τ^2, and by 95% prediction intervals where k≥3. Analyses were performed in Python (NumPy/SciPy); forest plots were generated in-house. Subgroups (cell source; comparator type) and the effect of excluding high-risk and active-comparator trials were examined. An exploratory frequentist NMA was planned; its feasibility is reported honestly in Section 9. Certainty of evidence was rated with GRADE.

Results Study Selection

The search and cross-referencing identified 267 primary-search records and nine systematic-review/NMA sources. After duplicate removal and title/abstract screening, 63 reports were assessed in full. Twenty-six controlled trials (23 primary RCTs) met inclusion for the systematic review; twelve trials provided real, extractable numerical data for quantitative synthesis. Uncontrolled dose-finding and single-arm studies (e.g., Jo 2014/2017, Song 2018, Dilogo 2020) were catalogued but excluded from pooling. The flow of studies is shown in **(Figure 1).**

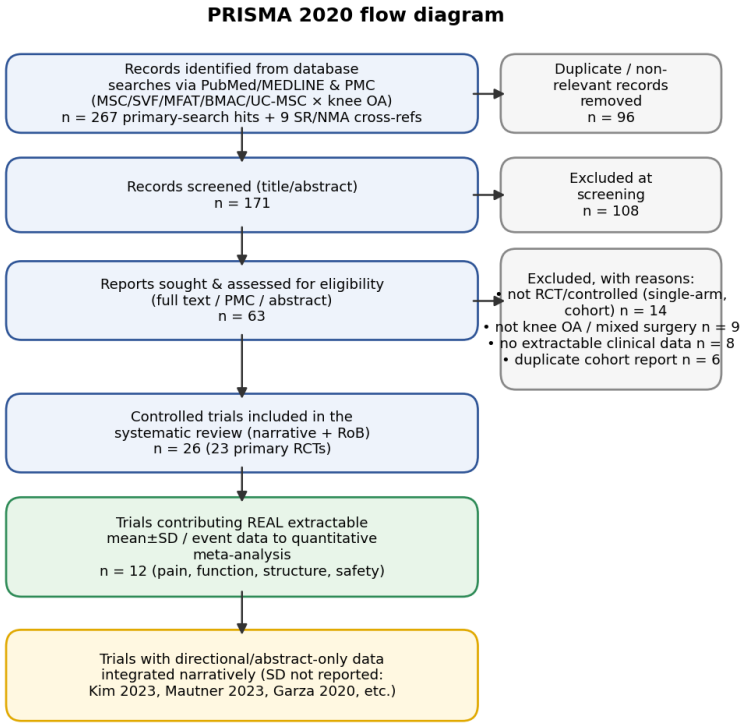

Figure 1: PRISMA 2020 study-selection flow.

Characteristics of included trials

Included trials clustered into three mechanistic families: (i) bone-marrow strategies (autologous BM-MSC, allogeneic pooled BM-MSC, BMAC); (ii) adipose-derived approaches (culture-expanded AD-MSC, point-of-care SVF and MFAT); and (iii) perinatal/allogeneic UC-MSC and placental MSC. The dominant phenotype was mild-to-moderate tibiofemoral OA (Kellgren–Lawrence II–III); follow-up ranged from 6 weeks to 4 years. Table 1 summarises the controlled trials.

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Trial (year)	Cell product	Comparator	N (arms)	KL	F/U mo	Main outcomes
Vega 2015	Allo BM-MSC 40M	HA	30 (2)	–	12	Algofunction; T2 MRI
Lamo-Espinosa 2016/18	Auto BM-MSC 10/100M +HA	HA	30–32 (3)	≥II	12–48	VAS, WOMAC, WORMS
Emadedin 2018	Auto BM-MSC 40M	Saline (placebo)	43 (2)	II–IV	6	WOMAC, VAS
Gupta 2016 (Stempeucel)	Allo BM-MSC 25–150M	Placebo	60 (dose)	II–III	12	VAS, WOMAC, WORMS
Bastos 2018/2020	Auto BM-MSC ±PRP	Corticosteroid	18 / 47	–	12	KOOS; cytokines
Lu 2019 (Re-Join)	Auto AD-MSC 50M	HA	53 (2)	1–3	12	WOMAC, VAS, MRI vol
Lee 2019 (JointStem)	Auto AD-MSC 100M	Saline (placebo)	24 (2)	II–IV	6	WOMAC, VAS, MRI defect
Kim 2023 (phase III)	Auto AD-MSC	Placebo	252 (2)	III	6	VAS, WOMAC, MRI
Kuah 2018 (Progenza)	Allo AD-MSC+supern.	Placebo	20 (dose)	1–3	12	VAS, WOMAC, MRI vol
Freitag 2019	Auto AD-MSC 100M	Usual care	30 (3)	–	12	KOOS, WOMAC, MOAKS
Freitag 2024 (MAG200)	Allo AD-MSC 10–100M	Placebo	40 (dose)	2–3	12	NPRS, KOOS-ADL, MRI vol
Pers 2025 (ADIPOA2)	Auto AD-MSC 2/10M	Placebo	135 (3)	–	12	OARSI resp., MRI thickness
Matas 2019	Allo UC-MSC 20M (×1/×2)	HA	29 (3)	1–3	12	VAS, WOMAC, WORMS
Tong 2025	Allo UC-MSC 2M	Placebo & HA	55 (3)	1–3	6	WOMAC, VAS, MOAKS
Pico 2024 (CellistemOA)	Allo UC-MSC 50M	Triamcinolone	30 (2)	II–III	12	WOMAC, NRS, WORMS
Khalifeh Soltani 2019	Allo placental MSC	Placebo	20 (2)	–	6	KOOS, VAS, MR arthrography
Nguyen 2017	SVF+PRP (+microfx)	Saline (+microfx)	30 (2)	2–3	18	WOMAC, Lysholm, MRI
Garza 2020	Auto SVF (dose)	Placebo	39 (3)	–	12	WOMAC %change, MRI
Hong 2019	Auto SVF	HA (self-control)	16 (2)	II–III	12	VAS, WOMAC, WORMS, MOCART
Zhang 2022 (Yin)	Auto SVF	HA	95 (2)	2–3	12	WOMAC, VAS, WORMS, MOCART

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Trial (year)	Cell product	Comparator	N (arms)	KL	F/U mo	Main outcomes
Zhang 2022 (Shengyang)	Auto SVF	HA	126 (2)	2–3	12–60	VAS, WOMAC, survival
Baria 2022/2024	MFAT (Lipogems)	Leukocyte-rich PRP	71 (2)	1–4	12	KOOS, VAS-ADL
Gobbi/D'Ambrosi 2022	MFAT (AMAT)	LP-PRP + HA	50 (2)	0–2	12–24	VAS, KOOS, IKDC
Richter 2024	MFAT	Corticosteroid & saline	75 (3)	–	12	KOOS-pain
Mautner 2023 (MILES)	BMAC / SVF / UCT-MSC	Corticosteroid	480 (4)	II–IV	12	VAS, KOOS, MRI (composite)

Table 1: Characteristics of included controlled trials. M = $\times 10^6$ cells; F/U = follow-up; KL = Kellgren–Lawrence grade; – = not reported/mixed.

Risk of bias

Risk of bias was low in only two trials (Gupta 2016; and, for blinding, several placebo-controlled trials), some concerns in roughly one third, and high in the remainder — chiefly because of open-label or single-blind designs where the harvest procedure precludes participant blinding (Freitag 2019, Baria, Gobbi, Lamo-Espinosa), substantial or differential attrition (Baria, Pers/ADIPOA2), or selective/figure-only outcome reporting (MAG200, Kim 2023). Industry sponsorship or manufacturer authorship was frequent among the trials reporting the largest structural or symptomatic effects (Kuah, MAG200, CellistemOA), an important source of potential bias. The domain-level assessment is shown in **(Figure 2)**.

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Figure 2: Cochrane RoB 2 traffic-light plot across five domains and overall judgement.

Effects of interventions (meta-analysis)

Pain

At 12 months, cell therapy was associated with a moderate but statistically non-significant reduction in pain versus control (SMD +0.48, 95% CI −0.65 to +1.61; k=3; I^2=90%; τ^2=0.89). The estimate was dominated by extreme heterogeneity: repeated-dose UC-MSC (Matas 2019) produced a very large effect versus HA, whereas MFAT versus platelet-rich plasma + HA (Gobbi 2022, an active comparator with baseline imbalance) favoured the comparator. The 95% prediction interval (−4.27 to +5.23) crosses the null, so the direction of effect in a new setting is uncertain. Within-group pain reductions were consistently large across trials, but between-group effects against active comparators were not.

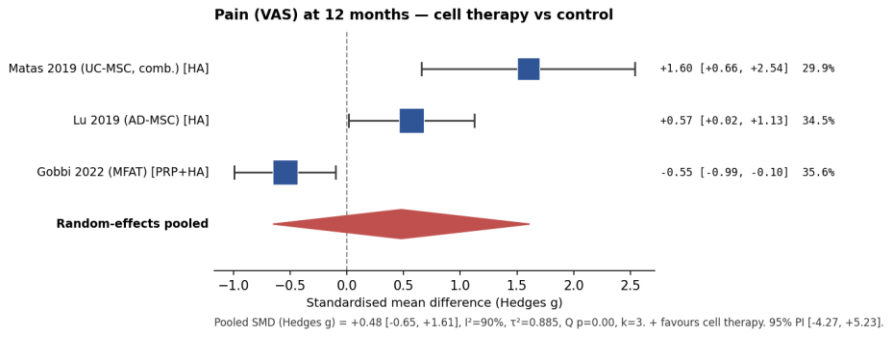

Figure 3: Pain (VAS) at 12 months — cell therapy vs control (positive favours cell therapy).

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Function

The WOMAC composite favoured cell therapy at both 6 months (SMD +0.39, 95% CI −0.00 to +0.77; k=3; I^2=0%) and 12 months (SMD +0.41, 95% CI +0.02 to +0.80; k=3; I^2=0%). Heterogeneity was absent, but all contributing trials were small (Lu 2019, Matas 2019, Nguyen 2017) and the 95% prediction intervals crossed the null (12-month: −0.44 to +1.26), indicating fragile precision rather than robust replicated benefit. The phase III trials that reported functional means without dispersion (Kim 2023: WOMAC improvement 21.7 vs 14.3, p=0.002; MILES: no arm superior to corticosteroid) are consistent in direction with a small functional benefit over inactive comparators but not over active ones.

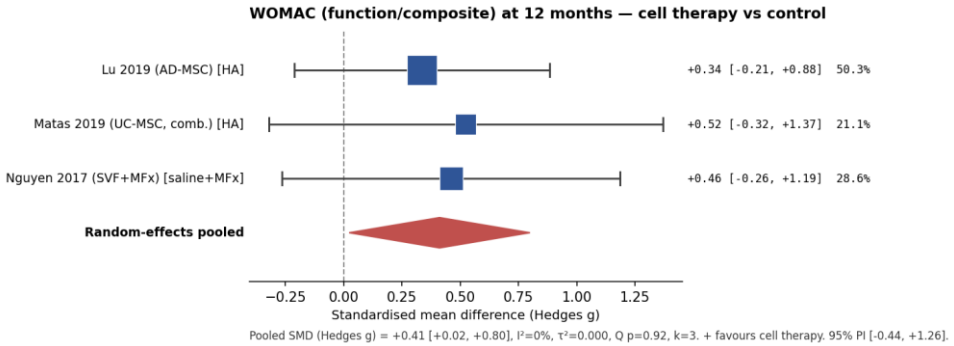

Figure 4: WOMAC (function/composite) at 12 months — cell therapy vs control.

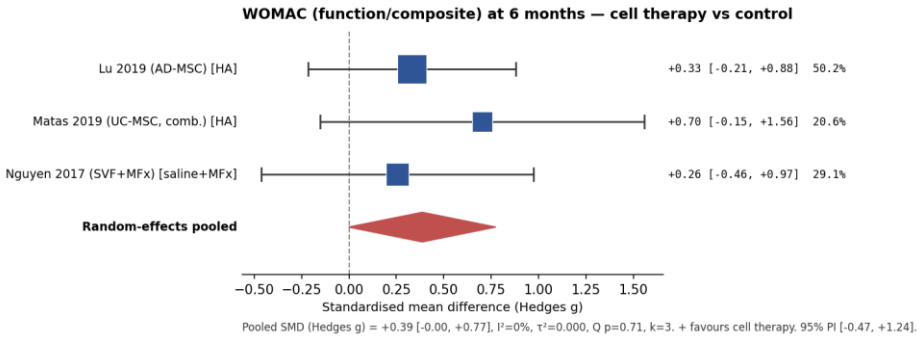

Figure 5: WOMAC (function/composite) at 6 months — cell therapy vs control.

Structure (MRI)

Two small controlled trials with quantitative MRI cartilage-volume endpoints (Lu 2019 vs HA; Kuah/Progenza 2018 vs placebo) produced a large pooled effect favouring cartilage-volume preservation (SMD +1.18, 95% CI +0.64 to +1.71; k=2; I^2=0%). This finding must be read with strong caution: both trials were small and industry-associated, one reported change scores as confidence intervals (converted to SDs), and it directly conflicts with the null structural findings of the two largest and most rigorous trials — Kim 2023 (no between-group difference in cartilage-defect change) and MILES (no significant MRI change in any arm). Semiquantitative WORMS/MOCART results were mixed (favouring SVF in Zhang 2022 but not UC-MSC in Matas 2019). Evidence for true short-horizon structural regeneration therefore remains unproven.

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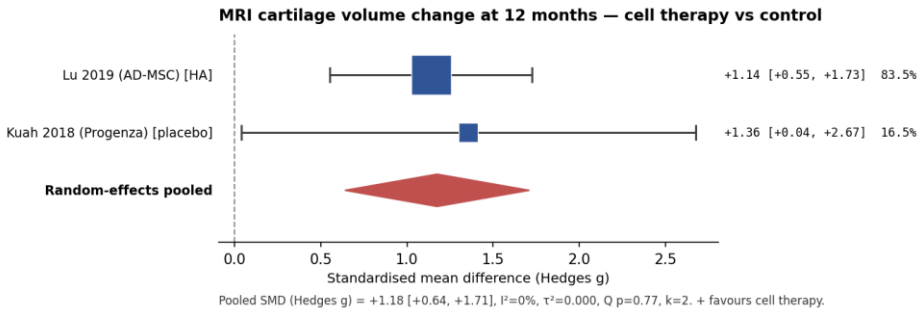

Figure 6: MRI cartilage-volume change — cell therapy vs control (positive favours cartilage preservation).

Safety

Cell therapy did not significantly increase the risk of any adverse event (RR 1.11, 95% CI 0.59–2.08; k=5; I^2=58%); events were predominantly transient injection-site pain and swelling, occasionally more frequent with cell products than with placebo (Tong 2025, Lee 2019) but less frequent than with multi-injection PRP+HA (Gobbi 2022). Serious adverse events were rare in both arms with no signal of harm (RR 0.63, 95% CI 0.15–2.68; k=6); no trial reported treatment-related tumorigenesis or accelerated joint destruction within available follow-up. The two published network meta-analyses nonetheless rank cell therapies slightly worse than placebo/HA for adverse events, consistent with a modest excess of benign local reactions.

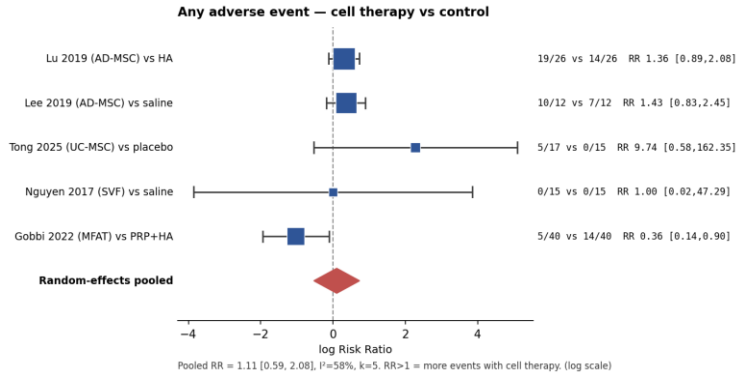

Figure 7: Any adverse event — cell therapy vs control (RR>1 favours control).

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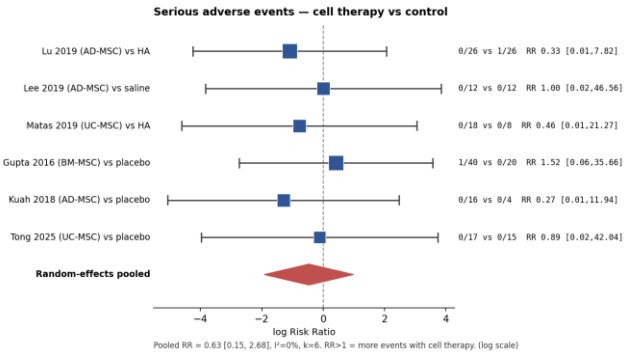

Figure 8: Serious adverse events — cell therapy vs control.

Triangulation with published systematic reviews

Because several pivotal trials could not enter our pooled analysis (dispersion not reported), we triangulated our estimates against nine recent peer-reviewed syntheses (Table 2). The direction is concordant — cell therapy tends to improve pain and function versus inactive comparators — but the magnitude and significance vary widely, and the most methodologically rigorous synthesis (Sadeghirad 2024, GRADE-based) concluded that MSCs probably provide little-to-no clinically important benefit, echoing the pragmatic MILES result.

Synthesis	RCTs (n)	Key pooled result	Interpretation
Cao 2025	8 (502)	WOMAC MD 7.44 (6 mo) & 10.31 (12 mo) favouring MSC; VAS & KOOS improved; AE ns	MSC alone improves pain/function; adipose & higher dose better
Sadeghirad 2024	16 (807)	VAS −0.74 cm (3–6 mo, <MID); SF-36 PF +2.2; AE RR 2.67	Probably little-to-no important benefit; MSC may increase AEs (moderate–low certainty)
Tabet 2024	25 (1048)	VAS −1.91 vs viscosupplementation; −0.99 vs placebo (12 mo)	Probable small pain benefit; very-low→moderate certainty
Chen 2024 (NMA)	15 (585)	Autologous BM-MSC best for pain/ROM; UC-MSC best WORMS; AD-MSC best WOMAC	Ranking varies by outcome; MSC>traditional therapy
Tang 2024 (NMA)	16 (1005)	AD-MSC best (VAS SMD 0.97 vs placebo); UC-MSC best WOMAC (SMD 1.65)	AD-MSC/UC-MSC rank highest; placebo safest
Gadelkarim 2022	15 (463)	AD-MSC: WOMAC-pain MD −1.85 (12 mo); SAE ns	Single-arm gains not confirmed in double-arm
Song 2020	19 (584)	VAS ↓ at 12 mo; WOMAC ↓ at 6 mo; AE ns	Effective & safe (mixed designs, lower certainty)
Yang 2025 (AD-MSC)	11 (510)	WOMAC MD −25.32; VAS −3.45; QoL +18.3	AD-MSC reduces pain, improves function/QoL
Xiao 2024 (UC-MSC)	3	WOMAC MD −25.85; Lysholm +18.33	UC-MSC improves function/pain (few trials)

Table 2: Recent peer-reviewed systematic reviews / network meta-analyses used for triangulation. MD = mean

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difference; MID = minimal important difference; ns = not significant.

Network meta-analysis

A network linking the cell products (BM-MSC/BMAC, AD-MSC, SVF, MFAT, UC-MSC) with placebo/saline, HA, PRP and corticosteroid was mapped (Figure 9). Most comparators connect to cell nodes through only one or two small trials, several loops are informed indirectly, and the single trial providing direct head-to-head cell-vs-cell-vs-corticosteroid data (MILES) reported change scores without usable dispersion. A de novo random-effects NMA restricted to trials with complete mean±SD data was therefore not robustly estimable without strong imputation, which we judged would create a false impression of precision. We instead report network geometry and synthesise the two published frequentist NMAs.

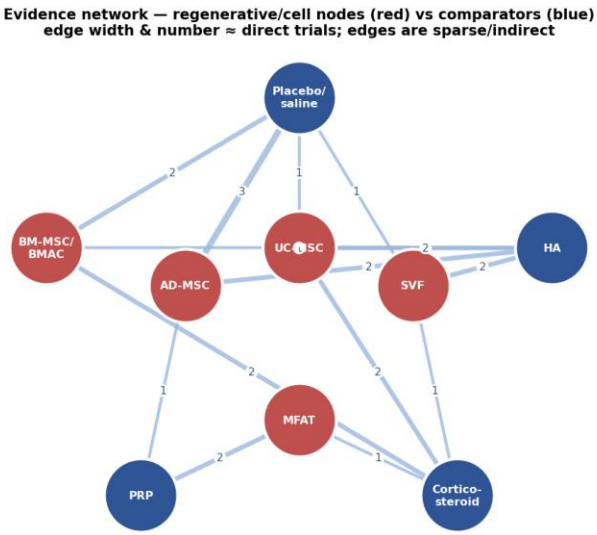

Figure 9: Evidence network. Node colour: red = regenerative/cell, blue = comparator; edge width/number ≈ direct trials.

Across the published NMAs, adipose- and umbilical-cord–derived products rank highest for symptomatic outcomes: Tang 2024 ranked AD-MSC first for pain (VAS SMD 0.97 vs placebo) and UC-MSC first for WOMAC (SMD 1.65), while Chen 2024 ranked autologous BM-MSC best for pain and range of motion, UC-MSC best for the structural WORMS score (SUCRA 94%), and AD-MSC best for WOMAC. Both NMAs agree that comparators (placebo/HA) are safer than cell products for (mostly benign) adverse events. These rankings are hypothesis-generating only: networks are sparse, dominated by small single-centre trials, and inconsistent with the pragmatic MILES finding that no cell product outperformed corticosteroid at one year.

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Certainty of evidence (GRADE) — Summary of findings

Outcome (timepoint)	Pooled effect	95% CI	Studies (n)	Certainty (GRADE)	What it means
Function — WOMAC (12 mo)	SMD +0.41	+0.02 to +0.80	3 (≈100)	⨁⨁◯◯ Low	Cell therapy probably yields a small improvement vs inactive comparators; unproven vs active
Function — WOMAC (6 mo)	SMD +0.39	−0.00 to +0.77	3 (≈100)	⨁⨁◯◯ Low	Small early functional gain; borderline precision
Pain — VAS (12 mo)	SMD +0.48	−0.65 to +1.61	3 (≈110)	⨁◯◯◯ Very low	Direction favours cells but inconsistent; effect could be null or large
Structure — MRI cartilage vol (12 mo)	SMD +1.18	+0.64 to +1.71	2 (≈64)	⨁◯◯◯ Very low	Signal of cartilage preservation in small industry trials; contradicted by large trials
Any adverse event	RR 1.11	0.59 to 2.08	5 (≈200)	⨁⨁◯◯ Low	Little-to-no increase; mostly transient local reactions
Serious adverse events	RR 0.63	0.15 to 2.68	6 (≈230)	⨁⨁◯◯ Low	No signal of serious harm; events rare in both arms

Table 3: GRADE Summary of Findings. Certainty downgraded for risk of bias, imprecision (small samples, wide/–crossing intervals), inconsistency (pain, I^2=90%), and suspected publication/sponsorship bias (structure).

Discussion

Across contemporary controlled trials, cellular regenerative injections for knee OA produced consistent within-group improvements in pain and function and a small, low-certainty between-group functional advantage over inactive comparators, with a favourable short-to-mid-term safety profile. However, the incremental benefit over rigorous active comparators is heterogeneous and, in the single largest

DOI: https://doi.org/10.52793/JSCR.2026.7(3)-91

pragmatic trial (MILES), absent: no orthobiologic — BMAC, SVF, or UC-tissue MSC — was superior to corticosteroid at 12 months on pain or structure. This disconnect between small "efficacy" signals and large pragmatic null findings is the central tension of the field.

The apparent contradiction is mechanistically coherent if OA is a whole-joint, multicompartment disease in which cartilage loss is downstream of interacting inflammatory, metabolic, mechanotransductive and subchondral-bone programmes. MSC-family products are unlikely to act through durable engraftment and chondrogenic replacement in established OA; convergent translational data favour paracrine and immunoregulatory mechanisms — macrophage repolarisation, dampening of IL-1/TNF/NF-κB catabolism, and trophic support for stressed chondrocytes — whose clinical expression depends on baseline inflammatory tone, alignment and disease stage. A specific bridge to "chondrocyte failure" is mitochondrial rescue: MSCs can transfer functional mitochondria or mitochondrial cargo to metabolically compromised chondrocytes, restoring redox balance and ATP generation and potentially explaining symptomatic improvement even when macroscopic cartilage morphology does not change quickly. Persistent senescence and the senescence-associated secretory phenotype may explain why benefits can plateau, motivating senescence-targeted and cell-free (exosome, mitochondrial, defined-peptide) next-generation strategies with clearer manufacturability and regulatory paths.

Our quantitative structural signal (SMD +1.18 favouring cartilage-volume preservation) illustrates the field's risk of over-interpretation: it derives from two small, industry-associated trials and is squarely contradicted by the larger phase III and pragmatic trials. Read against the GRADE-anchored synthesis of Sadeghirad and colleagues — which found little-to-no clinically important benefit and a possible excess of adverse events — the honest conclusion is that disease modification is not established and symptomatic superiority over standard active injections is unproven.

Degenerative bone and non-knee osteochondral disease

Controlled evidence outside the knee is sparse. For focal osteochondral/meniscal injury, allogeneic BM-MSC after partial meniscectomy increased meniscal volume in a minority of patients (Vangsness 2014); hip, ankle and generalized degenerative-bone applications rest largely on uncontrolled series and cannot be pooled. Extrapolation from knee OA to degenerative bone disorders is therefore not currently evidence-based and should be framed as a research priority rather than a supported indication.

Strengths and limitations

Strengths include a Cochrane-aligned protocol, RoB 2 and GRADE appraisal, de-novo random-effects synthesis computed transparently from primary data, prediction intervals, and triangulation against nine published syntheses and two NMAs. Limitations are substantial: the pooled analyses are small because several pivotal trials reported means without dispersion or figure-only data; comparators were heterogeneous (placebo, HA, PRP, corticosteroid); instruments and timepoints varied; many trials were small, single-centre and industry-associated; the search prioritised PubMed/PMC with cross-referencing rather than multi-database de-duplicated retrieval with dual independent screening; and non-English and grey literature were incompletely captured. The NMA is exploratory. These factors, not merely statistical, drive the low-to-very-low certainty.

DOI: https://doi.org/10.52793/JSCR.2026.7(3)-91

Conclusions and implications

Chondrocyte/MSC-based regenerative therapies can provide small, low-certainty improvements in self-reported knee function and appear safe over 6–12 months, with predominantly transient local adverse events and no signal of serious harm. Robust, generalisable superiority over established active intra-articular treatments — particularly corticosteroid — is not established, and claims of structural disease modification remain premature. For practice, patients should be counselled that benefits are modest and unproven relative to cheaper standard injections. For research, priorities are mechanism-aligned patient stratification (inflammation-high, bone-driven, senescence-dominant phenotypes), standardized manufacturing and reporting (cell identity, potency, dose, viability), harmonized compositional MRI endpoints, adequately powered head-to-head trials with follow-up beyond 12 months, and complete reporting of dispersion to enable valid meta-analysis and network meta-analysis.

Declarations

Funding: Not specified for this synthesis.

Contributions: all authors contributed to conception, interpretation and revision.

Competing interests: all authors declare any conflic tof interests

Data availability: the extraction dataset and analysis code accompany this report as supplementary files (dataset.py, run_analysis.py, results.json).

Registration: (To be registered at PROSPERO)

References

1. Vega A, et al. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. Transplantation. 2015;99(8):1681-90.
2. Lamo-Espinosa JM, et al. Intra-articular injection of two doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in knee OA. J Transl Med. 2016;14:246.
3. Lamo-Espinosa JM, et al. Long-term efficacy of autologous BM-MSC for knee OA. J Transl Med. 2018;16:213.
4. Emadedin M, et al. Intra-articular autologous BM-MSC in knee OA: a triple-blind placebo-controlled RCT. Cytotherapy. 2018;20(10):1238-46.
5. Gupta PK, et al. Efficacy and safety of allogeneic BM-MSC (Stempeucel) in knee OA: a phase 2 RCT. Arthritis Res Ther. 2016;18:301.
6. Bastos R, et al. Intra-articular BM-MSC ± PRP for knee OA. Knee Surg Sports Traumatol Arthrosc. 2018;26(11):3342-50.
7. Bastos R, et al. BM-MSC, BM-MSC+PRP vs corticosteroid for knee OA: an RCT. Knee Surg Sports Traumatol Arthrosc. 2020;28(6):1989-99.
8. Lu L, et al. Autologous adipose-derived MSC (Re-Join) vs HA for knee OA. Stem Cell Res Ther. 2019;10:143.
9. Lee WS, et al. Intra-articular AD-MSC vs saline for knee OA (JointStem). Stem Cells Transl Med. 2019;8(6):504-11.
10. Kim KI, et al. Autologous AD-MSC for knee OA: a phase III RCT. Am J Sports Med. 2023;51(9):2243-53.
11. Kuah D, et al. Progenza (allogeneic AD-MSC) in knee OA: RCT. J Transl Med. 2018;16:49.
12. Freitag J, et al. Autologous AD-MSC for knee OA: RCT. Regen Med. 2019;14(3):213-30.
13. Freitag J, et al. MAG200 allogeneic AD-MSC for knee OA: phase I/IIa RCT. Osteoarthr Cartil Open. 2024;6(3):100500.
14. Pers YM, et al. AD-MSC vs placebo for knee OA (ADIPOA2). Ann Rheum Dis. 2025;84(12):2103-14.
15. Matas J, et al. Umbilical cord MSC for knee OA: single vs repeated dose vs HA. Stem Cells Transl Med.

DOI: https://doi.org/10.52793/JSCR.2026.7(3)-91

2019;8(3):215-24.
16. Tong W, et al. UC-MSC vs placebo vs HA for knee OA. BMC Musculoskelet Disord. 2025;26:84.
17. Pico OA, et al. UC-MSC (CellistemOA) vs triamcinolone for knee OA. Cytotherapy. 2025;27(2):188-200.
18. Khalifeh Soltani S, et al. Allogeneic placental MSC for knee OA: RCT. Cytotherapy. 2019;21(1):54-63.
19. Nguyen PD, et al. SVF + PRP with microfracture for knee OA: RCT. Stem Cells Transl Med. 2017;6(1):187-95.
20. Garza JR, et al. Autologous SVF for knee OA: dose-ranging RCT. Am J Sports Med. 2020;48(3):588-98.
21. Hong Z, et al. SVF vs HA for knee OA (self-controlled). Int Orthop. 2019;43(5):1123-34.
22. Zhang Y, et al. SVF vs HA for knee OA: cartilage/MRI RCT. Biomed Res Int. 2022;2022:2777568.
23. Zhang S, et al. SVF vs HA for knee OA: mid-term RCT. Stem Cell Res Ther. 2022;13:105.
24. Baria M, et al. MFAT vs leukocyte-rich PRP for knee OA (6-mo). Orthop J Sports Med. 2022;10(9).
25. Baria M, et al. MFAT vs PRP for knee OA (12-mo). Orthop J Sports Med. 2024;12(3).
26. D'Ambrosi R/Gobbi A, et al. MFAT vs LP-PRP+HA for early knee OA. Eur J Orthop Surg Traumatol. 2022;33(5):1895-904.
27. Richter DL, et al. MFAT vs corticosteroid vs saline for knee OA. Arthroscopy. 2024;41(2):248-60.
28. Mautner K, et al. Cell-based vs corticosteroid injections for knee OA: phase 3 (MILES). Nat Med. 2023;29(12):3120-6.
29. Vangsness CT, et al. Allogeneic MSC after partial meniscectomy: RCT. J Bone Joint Surg Am. 2014;96(2):908.
30. Dilogo IH, et al. UC-MSC + secretome for knee OA (single-arm). Eur J Orthop Surg Traumatol. 2020;30(5):799-807.
31. Cao M, et al. Efficacy and safety of MSCs in knee OA: SR & meta-analysis. Stem Cell Res Ther. 2025;16:122.
32. Chen X, et al. Three MSC sources for knee OA: SR & network meta-analysis. J Orthop Surg Res. 2024;19:366.
33. Sadeghirad B, et al. MSCs for chronic knee pain from OA: SR & meta-analysis of RCTs. Osteoarthritis Cartilage. 2024;32(10):1207-19.
34. Tang X, et al. MSCs from varied sources in knee OA: SR & network meta-analysis. Exp Gerontol. 2024;192:112460.
35. Tabet CG, et al. Advanced MSC therapy for knee OA: SR & meta-analysis of RCTs. J Orthop Translat. 2024;48:176-89.
36. Gadelkarim M, et al. Safety and efficacy of AD-MSC for knee OA: SR & meta-analysis. Joint Bone Spine. 2022;89(5):105404.
37. Song Y, et al. MSCs in knee OA treatment: SR & meta-analysis. J Orthop Translat. 2020;24:121-30.
38. Yang Y, et al. AD-MSC for knee OA management: meta-analysis. Indian J Orthop. 2025;59(8):1078-89.
39. Xiao Z, et al. UC-MSC for knee OA: SR & meta-analysis. Medicine (Baltimore). 2024;103(46):e40490.
40. Page MJ, et al. The PRISMA 2020 statement. BMJ. 2021;372:n71.
41. Sterne JAC, et al. RoB 2: revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
42. Hutton B, et al. PRISMA extension for network meta-analyses (PRISMA-NMA). Ann Intern Med. 2015;162(11):777-84.
43. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.
44. Guyatt GH, et al. GRADE: an emerging consensus on rating quality of evidence. BMJ. 2008;336:924-6.