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A Comprehensive Meta-Analysis of Orthobiologics in Arthrosis and Lumbar Degeneration: Moderate Symptomatic Benefit, Comparator-Dependent Effects and an Evidence-Tiered Framework for Clinical Practice

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Abstract

Background: Orthobiologic injections — platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), adipose-derived and bone marrow-derived mesenchymal stromal cells (MSC), micro-fragmented adipose tissue (MFAT), stromal vascular fraction (SVF), autologous conditioned serum (ACS) and dextrose prolotherapy — are used across arthrosis and degenerative lumbar disease with a confidence that the aggregate evidence does not obviously support. We set out to quantify the effect precisely, to identify which parts of the evidence base are strong and which are not, and to convert that into a tiered framework a clinician can act on.

Methods: We conducted a three-stream synthesis. Stream 1 extracted arm-level continuous outcomes from 82 randomised controlled trials of orthobiologic injection in arthrosis (460 outcome rows). Stream 2 extracted 92 outcome rows from 24 clinical studies of orthobiologics in lumbar degeneration. Stream 3 assembled an umbrella layer of 63 systematic reviews and network meta-analyses contributing 192 pooled estimates. Every extracted value was bound to the URL of the document it was read from. Effects were expressed as Hedges g with negative values favouring the

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pooled by DerSimonian–Laird random effects with one pain-preferred estimate per study, and interrogated with subgroup analysis, meta-regression, leave-one-out analysis, cumulative meta-analysis, Egger and Begg tests and trim-and-fill.

Results: In arthrosis the pooled effect was moderate and stable across time: g = -0.44 (-0.77 to -0.12) at 3 months (k = 32, I^2 = 91%), -0.47 (-0.66 to -0.27) at 6 months (k = 43, I^2 = 83%, p = < 0.0001) and -0.53 (-0.78 to -0.27) at 12 months (k = 32, I^2 = 88%). The effect depended more on the control arm than on the product: against saline or sham g = -0.97 (-1.54 to -0.41) whereas against corticosteroid it was null (-0.29 (-0.79 to +0.20)). Adipose-derived products (-0.75 (-1.23 to -0.27), k = 9) and PRP (-0.46 (-0.73 to -0.19), k = 24) were significant, whereas bone marrow products were not (-0.07 (-0.49 to +0.35), p = 0.7396). Small-study asymmetry was strong (Egger p = 0.0011; Begg p = 0.00019), although trim-and-fill imputed no missing studies. In lumbar degeneration only 8 controlled comparisons were poolable at 6 months (g = -0.96 (-1.57 to -0.36), I^2 = 89%) and one at 12 months. Across the umbrella layer 116 of 172 numeric estimates (67%) were statistically significant, median reported I^2 was 56%, and structural endpoints showed no cartilage benefit.

Conclusions: Orthobiologics deliver a real but moderate symptomatic benefit in arthrosis that does not decay to 12 months, is largest against inert controls, is not demonstrably better than corticosteroid, and is not accompanied by structural repair. The lumbar evidence base remains too thin to support routine use outside registries and trials. We propose a three-tier framework that separates what is proven safe and effective from what is merely proven safe.

Keywords

Orthobiologics; Platelet-rich plasma; Mesenchymal stromal cells; Bone marrow aspirate concentrate; Osteoarthritis; Lumbar degenerative disc disease; Meta-analysis; Regenerative medicine.

Introduction

Orthobiologics occupy an unusual position in musculoskeletal medicine. They are widely offered, largely self-funded, biologically plausible and supported by a literature that is enormous in volume and modest in certainty. Degenerative joint disease and degenerative lumbar disease together account for a substantial share of chronic musculoskeletal disability, and both sit in a therapeutic gap: conservative care plateaus, surgery is definitive but irreversible, and the space between them has been filled by injectable autologous and allogeneic biological products.

The category is heterogeneous by construction. Platelet-rich plasma is a concentrated plasma fraction whose leukocyte content, platelet dose and activation state vary by an order of magnitude between preparations. Bone marrow aspirate concentrate delivers a mixed nucleated-cell population in which the mesenchymal fraction is a small minority. Adipose-derived products range from enzymatically digested stromal vascular fraction to mechanically micro-fragmented tissue that is not cell-selected at all. Culture-expanded mesenchymal stromal cells, umbilical-cord products, amniotic suspensions, autologous conditioned serum and hypertonic dextrose are grouped with them chiefly by route of administration rather than by mechanism. Treating this collection as a single intervention is a statistical convenience that clinical reasoning should resist.

Three questions matter for practice and are answerable from the published record. First, how large is the symptomatic benefit, and does it persist? Second, is the benefit a property of the biological product or of the comparison it is measured against — and how much of it survives blinding? Third, is there structural

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disease modification, or is the effect purely symptomatic? A fourth question follows from the answers: which specific indications and products have earned routine clinical use, which have earned use within registries, and which should still be confined to trials.

We therefore built a three-stream synthesis. Rather than restrict the analysis to a single product or a single joint, we extracted arm-level data from every randomised trial we could resolve in arthrosis, all controlled and uncontrolled clinical series we could resolve in lumbar degeneration, and an umbrella layer of 63 systematic reviews that allows the primary pooling to be checked against the published consensus. Every value in this paper is bound to the URL of the document it was read from, and the reference list of 244 entries is the complete set of those documents.

Methods

Design and reporting

This is a systematic review with three parallel quantitative streams, reported in accordance with PRISMA 2020. The protocol was not prospectively registered; a registration identifier is to be inserted prior to submission. Because all analysed data are previously published, ethical approval was not required.

Eligibility criteria

Stream 1 (arthrosis) included randomised controlled trials in which at least one arm received an intra-articular or peri-articular orthobiologic injection for degenerative joint disease of any joint, reporting a continuous pain or function outcome with a mean and a measure of dispersion at a defined follow-up. Stream 2 (lumbar degeneration) included randomised, quasi-randomised, prospective cohort and prospective single-arm studies of orthobiologic injection for discogenic low back pain, degenerative disc disease, lumbar radiculopathy or facet-mediated pain by any route. Stream 3 (umbrella) included systematic reviews, meta-analyses and network meta-analyses reporting at least one pooled quantitative estimate in either domain. Narrative reviews, case reports, surgical-augmentation studies without an injection arm and animal-only reports were excluded from the clinical streams; preclinical reviews were retained in the umbrella layer only for mechanistic context and were excluded from all pooled clinical estimates.

Data extraction and source binding

For every extracted row we recorded the study label, joint or spinal condition, modality, comparator, outcome instrument, follow-up in months, per-arm sample size, mean and standard deviation, study design, blinding status, and the source URL. Where a report gave a standard error, a 95% confidence interval or a change score rather than a final-value standard deviation, the row was flagged accordingly and the dispersion converted before pooling. Where a scale was oriented so that higher scores indicate better health (IKDC, KOOS, SF-36 physical component summary), the sign of the effect was reversed so that in all analyses a negative Hedges g favours the orthobiologic. Rows reporting medians with interquartile ranges, figure-only data or dispersion that could not be reconstructed were retained in the descriptive tables but excluded from pooling and are listed in the supplementary notes.

Statistical analysis

Effects were expressed as Hedges g with the small-sample correction applied to the standardised mean

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difference. To avoid within-study dependency, one estimate per study was carried into each pooled analysis, selected by a fixed preference hierarchy that favours the pain outcome, then function, then composite scores. Pooling used the DerSimonian–Laird random-effects estimator with inverse-variance weighting. Heterogeneity was quantified with Cochran Q, τ^2 and I^2, and each pooled estimate is accompanied by a 95% prediction interval, which describes the effect expected in a future comparable trial rather than the precision of the mean.

Pre-specified subgroup analyses at the 6-month timepoint examined orthobiologic class, comparator type, blinding status, completeness of product reporting and joint. Robustness was assessed with leave-one-out analysis across all 43 contributing trials, cumulative meta-analysis ordered by publication year, and random-effects meta-regression of effect size on the natural logarithm of total trial size. Small-study effects were tested with the Egger regression intercept and the Begg rank-correlation test, and the potential impact of missing studies estimated with the Duval and Tweedie trim-and-fill procedure. In the lumbar stream, 10 arm sizes not stated in the source report were imputed from the reported total randomised sample; no imputation was required in the arthrosis stream. All computation was performed in Python with independently implemented estimators rather than a packaged meta-analysis library, and the analysis script is available with the extracted data files.

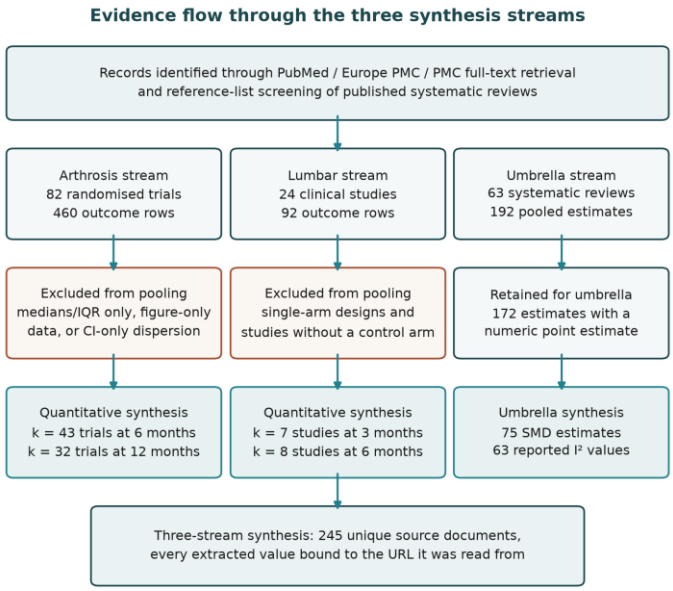

Figure 1: Flow of evidence through the three synthesis streams. Counts are unique studies and extracted outcome rows before and after the poolability filters described in Section 2.3.

Results

Characteristics of the evidence base

The arthrosis stream comprised 82 randomised trials contributing 460 extractable outcome rows. The knee dominated (69 trials, 84% of the stream), followed by the hip (6), with single or near-single trials in the temporomandibular joint, shoulder, ankle, hand and lumbar facet joint. PRP and its leukocyte-defined variants accounted for 46 trials, adipose-derived products for 15, bone marrow products for 10, dextrose

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prolotherapy for 7, and umbilical-cord, amniotic, exosome and autologous conditioned serum products for one trial each. 45 trials were double-blind. Product characterisation was complete in 45 trials (55%), partial in 34, and absent in 3.

Orthobiologic product	Randomised trials	Outcome rows
PRP (unspecified leukocyte content)	37	190
Leukocyte-poor PRP	6	34
Leukocyte-rich PRP	3	19
Adipose-derived MSC	7	29
Micro-fragmented adipose tissue	6	40
Stromal vascular fraction	2	10
Bone marrow aspirate concentrate	6	40
Bone marrow-derived MSC (culture-expanded)	4	37
Hypertonic dextrose prolotherapy	7	33
Umbilical cord MSC	1	8
Amniotic suspension allograft	1	9
MSC-derived exosomes	1	5
Autologous conditioned serum	1	6
Total	**82**	**460**

Table 1: Composition of the arthrosis evidence stream by product class. Trials contributing more than one product arm are counted once per class.

The lumbar stream was markedly smaller and methodologically weaker: 24 studies, 92 outcome rows, of which 10 were prospective single-arm series and only 10 were randomised controlled trials. Intradiscal delivery predominated (16 studies) over transforaminal (3), epidural interlaminar (2) and intra-articular facet (1) routes. Discogenic low back pain was the commonest indication (10 studies), followed by degenerative disc disease (6) and radiculopathy (6). 11 studies had no control arm at all and were therefore excluded from every pooled estimate.

Indication	Studies	Delivery route	Studies
Discogenic low back pain	10	Intradiscal	16
Radiculopathy	6	Transforaminal	3
Degenerative disc disease	6	Other or not stated	2
Mixed	1	Epidural, interlaminar	2
Facet	1	Intra-articular facet	1

Table 2: Composition of the lumbar degeneration evidence stream. The two columns are independent cross-tabulations of the same 24 studies, not a paired breakdown.

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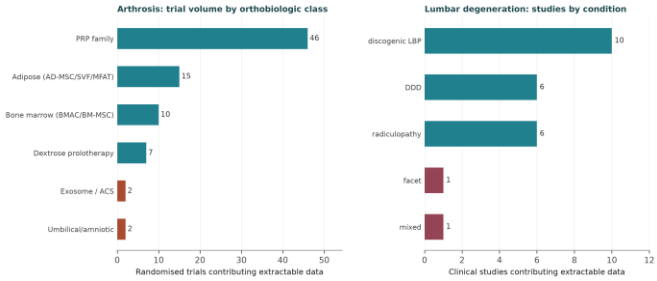

Figure 2: Evidence volume by orthobiologic class in arthrosis (left) and by spinal indication in lumbar degeneration (right). The asymmetry between the two domains is the single most important structural feature of this literature.

Pooled effect in arthrosis

Across all products and comparators, orthobiologic injection produced a moderate reduction in pain and improvement in function that was statistically robust and did not attenuate over the first year. At 6 months, the timepoint with the largest contributing set, the pooled Hedges g was -0.47 (-0.66 to -0.27) (k = 43, p = < 0.0001). The 3-month and 12-month estimates were of similar magnitude, and the 12-month estimate was numerically the largest of the three. Heterogeneity was substantial to considerable at every timepoint (I^2 83–91%), and the prediction intervals cross zero at all three timepoints — meaning that although the mean effect is reliably negative, a future trial drawn from this population could plausibly report no benefit.

Follow-up	k	Pooled Hedges g (95% CI)	p	I^2 (%)	τ^2	95% prediction interval
3 months	32	-0.44 (-0.77 to -0.12)	0.0081	91.2	0.799	-2.30 to +1.41
6 months	43	-0.47 (-0.66 to -0.27)	< 0.0001	83.4	0.336	-1.64 to +0.71
12 months	32	-0.53 (-0.78 to -0.27)	< 0.0001	88.1	0.431	-1.89 to +0.84

Table 3: Random-effects pooled effect of orthobiologic injection versus comparator in arthrosis. Negative values favour the orthobiologic. One pain-preferred estimate per study.

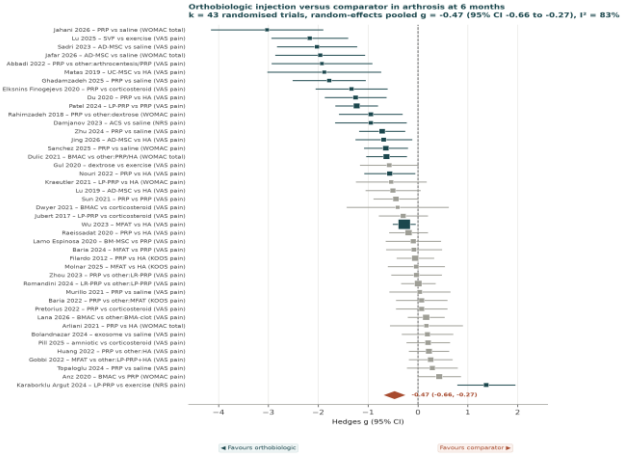

Figure 3: Forest plot of all randomised comparisons contributing to the 6-month arthrosis estimate, ordered by effect size. Marker area is proportional to inverse-variance weight; teal denotes a confidence interval excluding the

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null. The diamond is the random-effects pooled estimate.

The effect depends more on the comparator than on the product

The most consequential finding of this analysis is not the size of the pooled effect but its dependence on the control arm. Against saline or sham injection, the pooled effect was large (-0.97 (-1.54 to -0.41), k = 10, p = 0.00075). Against hyaluronic acid it was small to moderate but precise and significant (-0.42 (-0.66 to -0.18), k = 11, I^2 = 59%, the lowest heterogeneity of any comparator subgroup). Against corticosteroid it was null (-0.29 (-0.79 to +0.20), p = 0.2451), and against other active biological comparators it was also null (-0.24 (-0.53 to +0.04), p = 0.0963). The saline-referenced effect is roughly four times the effect measured against an active comparator.

By product class, adipose-derived preparations produced the largest significant effect (-0.75 (-1.23 to -0.27), k = 9) and PRP a moderate one (-0.46 (-0.73 to -0.19), k = 24). Bone marrow products — BMAC and culture-expanded BM-MSC — showed no pooled benefit at 6 months (-0.07 (-0.49 to +0.35), k = 5, p = 0.7396). This is a genuinely negative result for the most invasive and most expensive product class in the category, and it is consistent with the recent randomised-only synthesis reporting that autologous BMAC and MSC did not outperform sham for primary pain and function endpoints in spondylosis [230].

Blinding mattered. Double-blind trials produced a larger pooled effect (-0.61 (-0.89 to -0.32), k = 25) than trials that were not double-blind (-0.30 (-0.56 to -0.03), k = 18) — the opposite of the usual direction, and almost certainly a confound: double-blind trials in this literature are overwhelmingly the placebo-controlled ones, so the blinding subgroup is partly a restatement of the comparator subgroup. Effects were similar in the knee (-0.45 (-0.67 to -0.24), k = 36) and in non-knee joints (-0.55 (-0.98 to -0.13), k = 7), and trials with complete product characterization reported slightly larger effects (-0.51 (-0.78 to -0.24)) than those with partial reporting (-0.39 (-0.66 to -0.12)).

Subgroup	k	Pooled Hedges g (95% CI)	p	I^2 (%)
By orthobiologic class				
UC-MSC/amniotic	2	-0.77 (-2.81 to +1.27)	0.4608	91
Adipose	9	-0.75 (-1.23 to -0.27)	0.0024	87
PRP	24	-0.46 (-0.73 to -0.19)	0.0010	85
Other	2	-0.35 (-1.46 to +0.77)	0.5411	84
Bone marrow	5	-0.07 (-0.49 to +0.35)	0.7396	72
By comparator				
Saline/sham	10	-0.97 (-1.54 to -0.41)	0.00075	88
Exercise/conservative	3	-0.44 (-2.38 to +1.49)	0.6527	96
Hyaluronic acid	11	-0.42 (-0.66 to -0.18)	0.00051	59

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Corticosteroid	5	-0.29 (-0.79 to +0.20)	0.2451	72
Other active	14	-0.24 (-0.53 to +0.04)	0.0963	81
By blinding				
Double-blind	25	-0.61 (-0.89 to -0.32)	< 0.0001	85
Not double-blind	18	-0.30 (-0.56 to -0.03)	0.0319	80
By joint				
Knee	36	-0.45 (-0.67 to -0.24)	< 0.0001	85
Non-knee joints	7	-0.55 (-0.98 to -0.13)	0.0102	65
By completeness of product reporting				
full	28	-0.51 (-0.78 to -0.24)	0.00020	86
partial	15	-0.39 (-0.66 to -0.12)	0.0045	75

Table 4: Subgroup analyses at the 6-month timepoint. Subgroups are not mutually exclusive across panels; each panel re-partitions the same 43 trials.

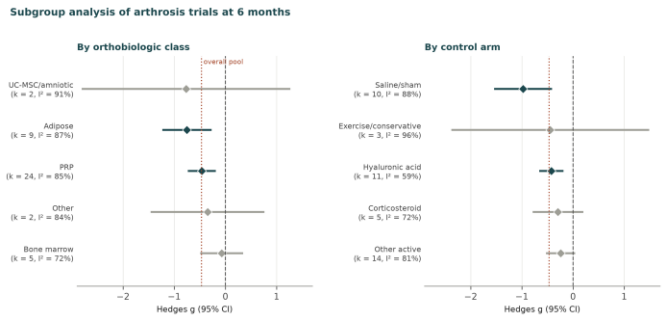

Figure 4: Subgroup estimates at 6 months by orthobiologic class (left) and control arm (right). Grey denotes a confidence interval crossing the null; the dotted vertical line is the overall pooled estimate.

Robustness, small-study effects and durability

The pooled estimate was insensitive to any single trial. Across all 43 leave-one-out iterations the pooled g ranged from -0.505 to -0.425 and remained statistically significant in every iteration. Cumulative meta-analysis ordered by year showed the estimate settling close to its final value early: by 2019 with only 5 trials the cumulative g was -0.57, against a final value of -0.47. Twelve subsequent years and 38 further trials narrowed the interval without moving the point estimate — the signature of a literature that is accumulating precision rather than resolving uncertainty about mechanism.

Small-study effects were unambiguous on formal testing. The Egger regression intercept was -3.675 (SE 1.048, t = -3.51, df = 41, p = 0.0011) and the Begg rank-correlation test gave τ = -0.395 (z = -3.74, p = 0.00019). Both indicate that smaller trials in this literature report systematically larger benefits. The Duval and Tweedie trim-and-fill procedure nevertheless imputed 0 missing studies and left the adjusted estimate unchanged at -0.468 (-0.664 to -0.273). We report this divergence rather than resolving it: trim-and-fill assumes asymmetry arises from suppression of null results in the right tail, and here the asymmetry is driven by an extreme left tail of small trials with very large effects, which the algorithm is

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not designed to correct. Meta-regression of effect size on log total sample size pointed the same way without reaching significance (β = +0.262, SE 0.153, t = 1.71, p = 0.0946, R^2 = 6.7%). At 12 months the asymmetry tests were borderline (Egger p = 0.0515; Begg p = 0.0517).

Durability was favourable. Among the 23 trials reporting both a 6-month and a 12-month outcome, the mean effect moved from -0.57 to -0.65 — no decay, and a slight deepening. This is one of the more clinically reassuring findings in the dataset and distinguishes orthobiologics from intra-articular corticosteroid, whose benefit is characteristically short-lived.

Analysis	Scope	Result	Interpretation
Leave-one-out analysis	43 iterations	g range -0.505 to -0.425	Significant in every iteration
Cumulative meta-analysis	43 trials by year	-0.57 by 2019 → -0.47 final	Estimate stable for over a decade
Egger regression (6 mo)	k = 43	intercept -3.68, t = -3.51, p = 0.0011	Strong small-study asymmetry
Begg rank correlation (6 mo)	k = 43	τ = -0.395, z = -3.74, p = 0.00019	Confirms asymmetry
Trim-and-fill (6 mo)	k = 43	0 studies imputed; adjusted g -0.468	No correction applied; see text
Meta-regression on log(n) (6 mo)	k = 43	β = +0.262, p = 0.0946, R^2 = 6.7%	Direction consistent, not significant
Egger regression (12 mo)	k = 32	intercept -2.58, p = 0.0515	Borderline
Durability, 6 vs 12 months	23 paired trials	mean g -0.57 → -0.65	No attenuation at one year

Table 5: Sensitivity, publication-bias and durability analyses for the arthrosis stream.

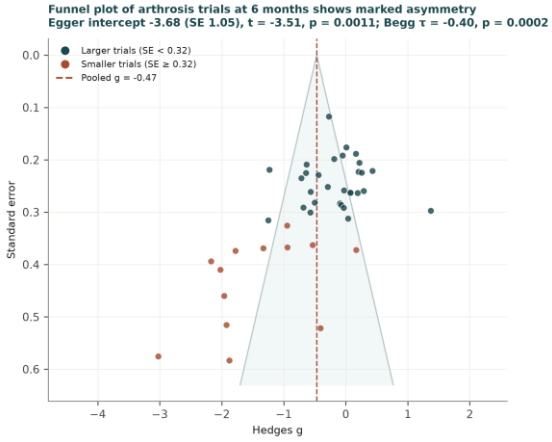

Figure 5: Funnel plot of the 6-month arthrosis comparisons. The shaded region is the pseudo 95% confidence region around the pooled estimate. The excess of small trials in the lower left is the source of the significant Egger and Begg statistics.

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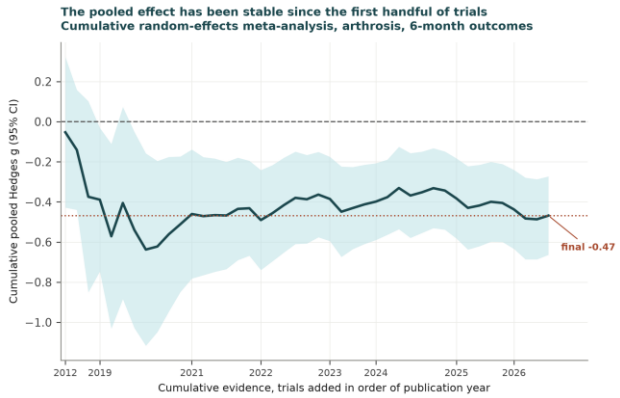

Figure 6: Cumulative random-effects meta-analysis of the 6-month arthrosis outcome, trials entered in order of publication year. The shaded band is the cumulative 95% confidence interval.

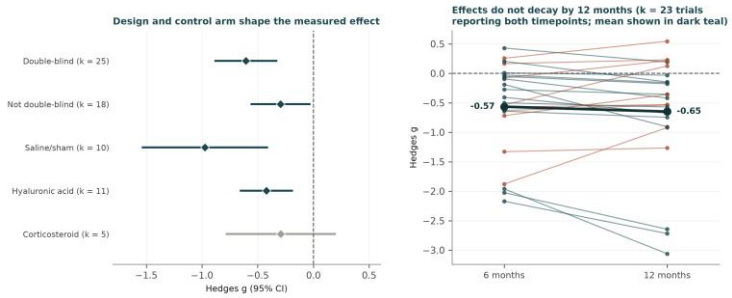

Figure 7: Left: pooled effect by blinding status and by control arm, showing that design choices move the measured effect more than product choices do. Right: paired 6-month and 12-month effects in the 23 trials reporting both, with the mean trajectory in dark teal.

Lumbar degeneration: a thin controlled evidence base

The lumbar stream cannot support the same analytic weight as the arthrosis stream, and the honest presentation of that limitation is itself a finding. Of 24 studies extracted, only 8 contributed a controlled comparison at 6 months and only one at 12 months. The 6-month pooled estimate was large (-0.96 (-1.57 to -0.36), p = 0.0019) but rests on a very small and heterogeneous set (I^2 = 89%, τ^2 = 0.647) whose prediction interval spans -3.07 to +1.15. The single controlled 12-month estimate, from the RESPINE allogeneic bone marrow MSC trial, was -0.29 (-0.56 to -0.01) [148] — far smaller than the 6-month pool and a reasonable reminder that early large effects in this domain have not generally been sustained.

Effects differed sharply by route. Epidural and perineural delivery produced the largest and least stable estimate (-1.34 (-2.50 to -0.18), k = 5, I^2 = 93%), whereas intradiscal delivery produced a smaller but far more consistent one (-0.50 (-0.87 to -0.12), k = 3, I^2 = 44%). By modality, PRP-family products drove the large epidural signal (-1.77 (-3.31 to -0.22), k = 4) while cell therapies produced a modest, homogeneous and significant effect (-0.34 (-0.62 to -0.06), k = 2, I^2 = 10%). Given that the epidural estimate rests on 5 studies with I^2 above 90%, the cell-therapy estimate is the more trustworthy of the two despite being the smaller.

Analysis	k	Pooled Hedges g (95% CI)	p	I^2 (%)

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All controlled, 3 months	7	-0.74 (-1.26 to -0.23)	0.0049	84
All controlled, 6 months	8	-0.96 (-1.57 to -0.36)	0.0019	89
All controlled, 12 months	1	-0.29 (-0.56 to -0.01)	0.0401	n.a.
By route, 6 months				
Epidural/perineural	5	-1.34 (-2.50 to -0.18)	0.0236	93
Intradiscal	3	-0.50 (-0.87 to -0.12)	0.0091	44
By modality, 6 months				
PRP family	4	-1.77 (-3.31 to -0.22)	0.0250	93
Cell therapy	2	-0.34 (-0.62 to -0.06)	0.0168	10
Other	2	-0.38 (-1.22 to +0.46)	0.3765	82

Table 6: Pooled effects in lumbar degeneration, restricted to studies with a control arm. Single-arm series were excluded from all estimates.

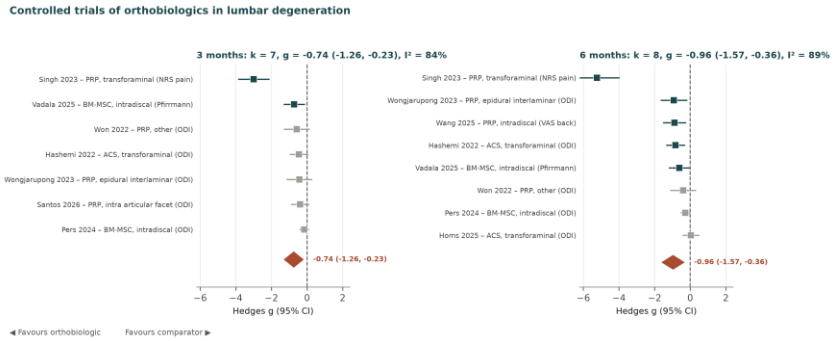

Figure 8: Forest plots of the controlled lumbar comparisons at 3 months (left) and 6 months (right). The width of the individual intervals, rather than the position of the diamonds, is the message.

Umbrella layer: what the published syntheses report

To situate our primary pooling against the wider literature we extracted 192 pooled estimates from 63 systematic reviews, meta-analyses and network meta-analyses. Of the 172 estimates with a numeric point value, 116 (67%) were statistically significant and 128 favoured the orthobiologic against 10 favouring the comparator, with 54 null. That distribution is itself informative: a literature in which four fifths of pooled estimates are positive and almost none are negative is a literature in which the reporting filter is doing visible work.

Heterogeneity in the umbrella layer mirrored our own. Of the 63 estimates reporting I^2, the median was 56% and 48% exceeded 75%, the conventional threshold for considerable heterogeneity. Among the 75 estimates expressed as a standardised mean difference the median value was -0.20, consistent in magnitude with our own 6-month pooled estimate of -0.47. Among the 12 knee-OA estimates expressed as a mean difference in VAS pain the median was -2.88 points on a 0–100 or 0–10 scale depending on the review — a range so wide that the metric is not poolable across reviews.

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Review	Comparison	Outcome	Metric	Pooled estimate (95% CI)	I^2 (%)
Xiong 2023	PRP vs control, mixed MSK	VAS pain	MD	-1.03 (-1.16 to -0.90)	87
Wu 2020	PRP vs hyaluronic acid, knee OA	WOMAC total	MD	-20.69 (-24.50 to -16.89)	94
Li 2025	PRP vs hyaluronic acid, knee OA, 12 mo	WOMAC pain	MD	-1.14 (-2.09 to -0.20)	n.a.
Du 2025	PRP + HA vs PRP alone, knee OA	WOMAC total	MD	-1.77 (-2.20 to -1.34)	10
Sadeghirad 2024	MSC vs control, knee OA, 6 mo	VAS pain	MD	-0.74 (-1.16 to -0.33)	n.a.
Wang 2020	MSC vs control, knee OA	WOMAC total	MD	-7.22 (-12.97 to -1.47)	n.a.
Xiao 2024	UC-MSC vs control, knee OA	WOMAC total	MD	-25.85 (-41.50 to -10.20)	n.a.
Cao 2025	MSC vs control, knee OA, 12 mo	WOMAC total	MD	+10.31 (+0.96 to +19.67)	n.a.
Wang 2022	Hypertonic dextrose vs control, knee OA, 6 mo	WOMAC total	MD	+13.77 (+6.75 to +20.78)	90
Sax 2022	PRP vs control, knee OA	MRI cartilage	SMD	-0.01 (-0.19 to +0.18)	n.a.
Kong 2024	MSC exosomes vs control, animal OA models	OARSI score	MD	-3.54 (-4.30 to -2.79)	98

Table 7: Representative pooled estimates from the umbrella layer, chosen to span product classes, directions of effect and levels of heterogeneity. Sign conventions follow each review as published; note that WOMAC-total estimates from Cao 2025 and Wang 2022 are reported on scales where a positive value favours the intervention. Full source citations: Xiong 2023 [181], Wu 2020 [185], Li 2025 [187], Du 2025 [183], Sadeghirad 2024 [193], Wang 2020 [200], Xiao 2024 [197], Cao 2025 [192], Wang 2022 [207], Sax 2022 [188], Kong 2024 [205].

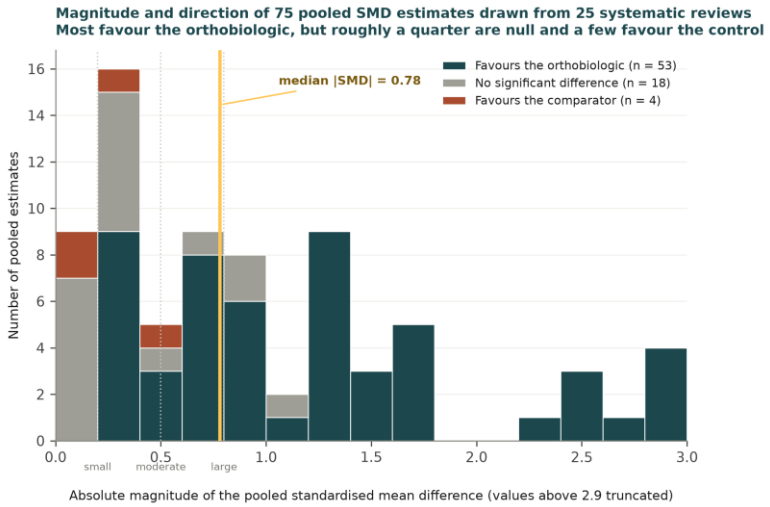

Figure 9: Magnitude and direction of the pooled standardised mean differences reported across the umbrella layer, coloured by the direction each review itself reported. A small number of very large values are truncated at 2.9 for display.

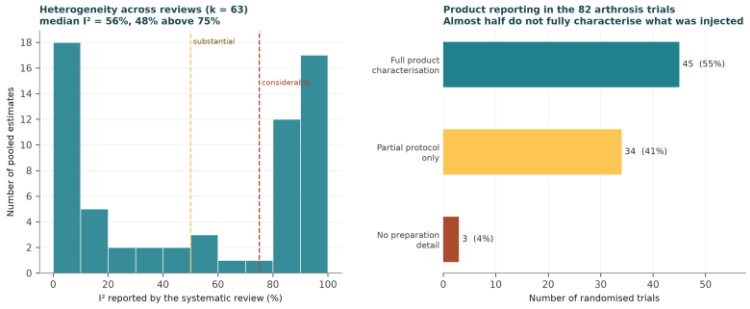

Figure 10: Left: distribution of I^2 values reported by the systematic reviews, which is strikingly bimodal. Right: completeness of product characterisation across the 82 arthrosis trials.

Safety

Safety is the strongest part of the orthobiologic evidence base, and it is the reason a tiered framework is possible at all. The Cochrane review of stem-cell injection in knee OA found serious adverse events in 5 of 219 placebo recipients and 4 of 242 stem-cell recipients, risk ratio 0.72 (95% CI 0.20 to 2.64), I^2 = 0%, across 7 trials and 461 participants [194]. A pooled analysis of BMAC across 6 randomised trials and 860 patients found overall complication rates of 41.91% with BMAC versus 41.25% with comparators (p = 0.85), a number-needed-to-harm of 152, and no difference in early or late complications [203]. In 844 intra-articular culture-expanded BM-MSC procedures followed for a mean of 21 months, 4 serious adverse events occurred: one infection after marrow aspiration, one pulmonary embolism, and two tumours remote from the injection site adjudicated as unrelated [233].

The signal is not uniformly benign. A meta-analysis of 16 MSC trials in 807 patients reported a relative risk of 2.67 (95% CI 1.19 to 5.99) for any adverse event and 1.58 (95% CI 1.04 to 2.38) for knee pain or swelling, both at low certainty [193]. Network meta-analyses rank placebo as safest and adipose-derived MSC least favourably [199], and a dual network analysis assigned cell-based injections a 100% Bayesian probability of higher adverse-event rates than cell-free comparators [239]. In the lumbar domain the events that

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matter are procedural rather than biological: no discitis occurred in the randomised intradiscal BMAC trial, although the report cites three previously published post-procedural cases [157], and the randomised intradiscal BM-MSC trial recorded four serious adverse events in the treatment arm and three in the sham arm, none adjudicated as ectopic tissue growth [147]. Across the entire extracted literature we found no controlled signal for tumourigenesis or ectopic tissue formation attributable to an injected orthobiologic.

Source	Scope	Endpoint	Finding	Ref.
Cochrane, stem cells in knee OA	7 trials, 461 patients	Serious adverse events	RR 0.72 (0.20 to 2.64), I^2 = 0%	[194]
MSC in knee OA	16 trials, 807 patients	Any adverse event	RR 2.67 (1.19 to 5.99), low certainty	[193]
BMAC, pooled RCTs	6 trials, 860 patients	Overall complications	41.91% vs 41.25%, p = 0.85; NNH 152	[203]
Culture-expanded BM-MSC	8 studies, 844 procedures	Serious adverse events	4 events; 2 remote tumours judged unrelated	[233]
Network meta-analysis, knee OA	16 RCTs, 1005 patients	Adverse-event ranking	Placebo safest (P = 74.9); AD-MSC least favourable (P = 13.3)	[199]
Cell-based vs cell-free	Dual network meta-analysis	Adverse events	Bayesian probability 100% vs 0%; SUCRA 98.2% vs 1.8%	[239]
PRP + HA vs PRP alone	11 RCTs, 1023 patients	Adverse events	RR 0.41 (0.35 to 0.48), I^2 = 12%	[183]
Umbilical cord MSC	8 studies, 688 participants	Treatment-related events	No serious events; mild and transient	[196]
Hypertonic dextrose prolotherapy	5 studies, 319 patients	Severe adverse events	None reported in any included study	[207]
Autologous conditioned serum	5 RCTs, 741 patients	Complications	24.8% with ACS vs 24.4% with saline	[212]
Intradiscal MSC	7 RCTs	Adverse events, SAEs, mortality	No significant difference versus sham or placebo	[220]
Intradiscal BM-MSC, randomised	DREAM trial	Serious adverse events	4 in MSC arm vs 3 in sham; no ectopic growth	[147]

Table 8: Safety evidence across the orthobiologic category. Procedural adverse events dominate; no controlled tumourigenic or ectopic-growth signal was identified.

Structural and mechanistic endpoints

Symptomatic benefit is not accompanied by demonstrable structural repair. Pooled MRI cartilage thickness and structural change after PRP in knee OA gave a standardised mean difference of -0.01 (95%

CI -0.19 to +0.18, p = 0.91) [188], and a separate synthesis reported a Hedges g of 0.079 (p = 0.723) for cartilage thickness across four studies and 0.217 (p = 0.281) for overall cartilage content across three randomised trials [189]. Pooled whole-organ MRI scores after stem-cell injection showed no significant difference from control across 16 studies and 875 patients [236], although cell-source subanalyses have reported imaging advantages for adipose over bone marrow sources at one year [234] and network ranking favours umbilical-cord products for whole-organ score improvement [198].

The most consequential mechanistic finding in the entire dataset is a partitioning analysis of intra-articular MSC injection in knee OA across 8 randomised trials and 467 patients, which attributed approximately 63% of pain reduction and 61% of functional improvement at 6 months to contextual, placebo-related factors rather than to the specific treatment effect, with corresponding figures of about 50% and 66% at 12 months [204]. Read alongside our own comparator subgroup analysis — where the effect against saline is roughly four times the effect against an active comparator — this converges on a coherent interpretation: a substantial proportion of the measured benefit of orthobiologic injection is attributable to the act of injecting, the procedural ritual surrounding it, and regression to the mean, rather than to the biological content of the syringe. Preclinical work with MSC-derived exosomes shows unambiguous histological and molecular cartilage protection in animal models [205,244], which makes the absence of a human structural signal a question about delivery, dose and residence time rather than about biology.

Source	Population	Endpoint	Finding	Ref.
Sax 2022	PRP, knee OA	MRI cartilage thickness or structure	SMD -0.01 (-0.19 to +0.18), p = 0.91	[188]
Prodromidis 2022	PRP, knee OA	Cartilage thickness (4 studies)	Hedges g 0.079, p = 0.723	[189]
Xie 2024	Stem cells, knee OA	Pooled WORMS (16 studies, 875 patients)	No significant difference versus control	[236]
Jeyaraman 2021	MSC by cell source	WORMS at 1 year	Favours AD-MSC (p < 0.001) over BM-MSC (p = 0.041)	[234]
Chen 2024	Network of MSC sources	WORMS ranking	UC-MSC best for WORMS (SUCRA 94.1%)	[198]
Yin 2025	MSC, knee OA (8 RCTs, 467 patients)	Contextual-effect partitioning	~63% of pain and 61% of function gain at 6 months attributable to contextual factors	[204]
Kong 2024	MSC exosomes, animal OA	OARSI histological score	MD -3.54 (-4.30 to -2.79), I^2 = 98%	[205]
Wang 2025	MSC exosomes, rat knee OA (28 studies)	Histology and molecular markers	Improved OARSI, Mankin, ICRS; collagen II and IL-10 up, IL-1β, IL-6, MMP-13, TNF-α down	[244]

Table 9: Structural, imaging and mechanistic endpoints. Human structural benefit is not demonstrated despite consistent preclinical cartilage protection.

An Evidence-Tiered Framework for Clinical Use

A tiered framework is only useful if the tiers are defined by something other than enthusiasm. We define them by two axes that the data above can actually populate: whether safety is established in controlled series, and whether efficacy is established against a clinically meaningful comparator rather than against saline. This produces three tiers with sharply different clinical implications.

Tier 1 — proven safety and robust efficacy evidence — contains leukocyte-defined PRP for knee osteoarthritis, where the pooled effect against hyaluronic acid is significant, precise and the least heterogeneous subgroup in the dataset (-0.42 (-0.66 to -0.18), k = 11, I^2 = 59%), and hypertonic dextrose prolotherapy for knee OA, which carries a Strength of Recommendation Taxonomy grade B and a clean safety record across 319 patients [206,207]. Even here the American Academy of Orthopaedic Surgeons clinical practice guideline treats PRP as an evidence gap requiring better characterisation and subgroup stratification rather than as a graded recommendation [242].

Tier 2 — proven safety with growing but incomplete efficacy evidence — contains adipose-derived products for knee OA, which produced the largest significant class effect in our analysis (-0.75 (-1.23 to -0.27), k = 9) but rank least favourably on adverse events in network comparison [199]; hip and ankle osteoarthritis, where the direction of effect matches the knee but the trial count does not; and PRP for lumbar radicular and facet-mediated pain, graded Level III with moderate recommendation strength by the two most recent interventional-pain guideline syntheses [225,226,243].

Tier 3 — established safety but limited efficacy evidence, appropriate for registries and trials rather than routine care — contains autologous bone marrow products for arthrosis, where our pooled estimate is null (-0.07 (-0.49 to +0.35), p = 0.7396) and randomised-only synthesis finds no advantage over sham [230]; intradiscal cell therapy, where the controlled 12-month evidence reduces to a single trial [148]; MSC-derived exosomes, which have compelling preclinical data [205,244] and one small human randomised trial in our dataset; and every application in which the only available comparison is against saline.

Indication and product	Efficacy evidence	Safety evidence	Clinical implication
Tier 1 — proven safety, robust efficacy evidence			
PRP, knee osteoarthritis	g -0.42 (-0.66 to -0.18) vs hyaluronic acid; k = 11, I^2 = 59%	No severe events; adverse events fewer with PRP + HA than PRP alone	Routine clinical use; document platelet dose and leukocyte content
Hypertonic dextrose prolotherapy, knee OA	SORT grade B; positive pooled WOMAC total at 6 months	No severe dextrose-related events in 319 patients	Routine use where PRP is unavailable or unaffordable
Tier 2 — proven safety, growing efficacy evidence			
Adipose-derived products (AD-MSC, SVF, MFAT), knee OA	g -0.75 (-1.23 to -0.27); k = 9, I^2 = 87%	Least favourable adverse-event ranking among injectables	Use with explicit consent regarding uncertainty; prefer registry enrolment
Hip and ankle osteoarthritis, any product	Non-knee joints pooled g -0.55 (-0.98 to -0.13); k = 7	No distinct safety signal identified	Reasonable second-line use; effect size not joint-specific
PRP, lumbar radicular and facet pain	Level III evidence, moderate recommendation strength (GRADE)	No severe adverse events across 416 patients	Selected patients after failed conservative care
Tier 3 — established safety, limited efficacy evidence			
Bone marrow products (BMAC, BM-MSC), arthrosis	g -0.07 (-0.49 to +0.35), p = 0.7396; k = 5	Complication rate equivalent to	Registry or trial context only; not first-line despite cost and invasiveness

		comparators; NNH 152	
Intradiscal cell therapy, degenerative disc disease	Cell therapy pooled g -0.34 (-0.62 to -0.06) at 6 months; one controlled 12-month estimate	No excess serious adverse events versus sham	Trial or registry only
MSC-derived exosomes, any indication	Strong preclinical histological benefit; minimal human randomised data	Human safety data insufficient to characterise	Investigational only
Any indication studied only against saline or sham	Saline-referenced pooled g -0.97 (-1.54 to -0.41) versus -0.24 (-0.53 to +0.04) against active comparators	Not applicable	Interpret as unproven until an active-comparator trial exists

Table 10: Evidence-tiered framework for orthobiologic use in arthrosis and lumbar degeneration. Tiers are defined by safety establishment and by efficacy against a clinically meaningful comparator, not by mechanistic plausibility. Supporting citations are given in the corresponding text of Section 4.

Discussion

Principal findings

Orthobiologic injection produces a moderate, durable and statistically robust symptomatic benefit in arthrosis — pooled Hedges g -0.47 at 6 months and -0.53 at 12 months — that is smaller than the field's rhetoric and larger than its harshest critics allow. Three qualifications transform how that number should be used. First, it is comparator-dependent to a degree that is difficult to reconcile with a purely pharmacological mechanism. Second, it is not accompanied by structural change on imaging. Third, it is not uniform across product classes: the most invasive and expensive class, autologous bone marrow, is the one with no pooled benefit.

None of this makes orthobiologics ineffective. A moderate, durable reduction in pain with a benign safety profile is a clinically valuable thing in a disease for which the alternatives are repeated corticosteroid, chronic non-steroidal anti-inflammatory exposure, or arthroplasty. But it reframes what is being sold. The honest claim is symptomatic relief comparable to or modestly better than hyaluronic acid, with a favourable safety profile and no demonstrated disease modification. The claim of cartilage regeneration is not supported by human imaging data.

The comparator problem and contextual effects

The gap between the saline-referenced effect (-0.97 (-1.54 to -0.41)) and the active-comparator effect (-0.24 (-0.53 to +0.04)) is the central interpretive problem in this literature. Intra-articular saline is not an inert control: needle placement, joint distension, capsular stretch and the theatre of a technical procedure all produce measurable analgesia. When a formal partitioning analysis attributes roughly 63% of the 6-month pain reduction after MSC injection to contextual factors [204], and when our own data show the effect shrinking to null against corticosteroid, the parsimonious reading is that a large fraction of what patients experience after an orthobiologic injection would also follow a well-performed injection of something else. Trials that compare an orthobiologic against saline are therefore measuring the wrong thing, and the field's continued production of them is the main reason the evidence base has grown in size without growing in usefulness.

Product heterogeneity and reporting

Only 45 of 82 arthrosis trials (55%) fully characterised the product they injected. In a category where

platelet dose varies by an order of magnitude between preparations, where leukocyte content plausibly determines whether the effect is anti-inflammatory or pro-inflammatory, and where a bone marrow concentrate may contain a mesenchymal fraction differing hundredfold between operators, incomplete reporting makes the pooled estimate an average over an undefined set of interventions. Our finding that trials with complete characterisation report slightly larger effects (-0.51 (-0.78 to -0.24) versus -0.39 (-0.66 to -0.12)) is consistent either with better products or with better trials, and the data cannot distinguish these. Minimum reporting standards — platelet concentration and absolute dose, leukocyte and erythrocyte content, activation method, injection volume, and for cell products the nucleated cell count and colony-forming-unit assay — would cost nothing and would transform the interpretability of the next decade of trials.

Quality of life, function and the wider health context

The clinical value of a moderate analgesic effect in arthrosis is not confined to the joint. Degenerative joint disease reduces physical activity, and reduced physical activity is associated with adverse cardiometabolic outcomes in longitudinal cohorts. An intervention that restores tolerable weight-bearing activity therefore has a plausible pathway to benefits beyond the treated joint, even in the absence of structural repair. That pathway is a hypothesis, not a finding: none of the trials in this dataset measured cardiovascular or mortality endpoints, and follow-up beyond 24 months was essentially absent. Clinicians may reasonably frame orthobiologic injection as a way to keep patients moving, but should not represent downstream systemic benefit as demonstrated.

The same caution applies to combination regimens. Adjunctive nutritional and pharmacological strategies are frequently bundled with orthobiologic injection in commercial practice. No trial in this dataset randomised such a combination against the injection alone, so any incremental benefit of the bundle is unmeasured. Where such adjuncts are used, they should be presented as independent choices with their own evidence base, not as part of the injection protocol.

Future directions

Four developments would change the tiers in Table 10. First, active-comparator trials: an adequately powered orthobiologic versus corticosteroid trial with 12-month follow-up would settle the question our null corticosteroid subgroup only raises (-0.29 (-0.79 to +0.20), k = 5). Second, cell-free products: MSC-derived exosomes reproduce the histological benefits of cell therapy in animal models [205,244] without the manufacturing, storage and regulatory burden of live cells, and they are the most likely route to an off-the-shelf product. Third, allogeneic and dose-defined cell products: a randomised-only synthesis found that allogeneic mesenchymal precursor cells produced durable improvement where autologous BMAC and MSC did not [230], which if replicated inverts the field's current preference for autologous harvesting. Fourth, patient stratification: the persistent I^2 of 83% in a category this large is unlikely to be pure noise, and inflammatory-phenotype, radiographic-severity and synovitis-based stratification are the obvious candidates for explaining it.

Limitations

Several limitations bear directly on interpretation. Pooling across products, joints, comparators and outcome instruments produces an estimate whose heterogeneity (I^2 = 83%) exceeds the threshold at

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which a single summary is conventionally advisable; we report it because the subgroup structure is more informative than the mean, not because the mean is the answer. Standardised mean differences across different instruments assume comparable responsiveness, which is unlikely to hold exactly between, for example, VAS pain and IKDC. Selection of one estimate per study by a fixed hierarchy discards information, though it avoids the greater error of double-counting. Risk of bias was captured only through blinding status and reporting completeness rather than through a full domain-level tool. The lumbar stream is too small to support confident conclusions and we have presented it as such. Trials reporting medians and interquartile ranges or figure-only data were excluded from pooling, which may itself introduce selection. Finally, the strong Egger and Begg asymmetry combined with a trim-and-fill estimate of 0 missing studies is an unresolved internal inconsistency that we report rather than reconcile; readers should treat the pooled effect as an upper bound.

Conclusion

Across 82 randomised trials in arthrosis, 24 clinical studies in lumbar degeneration and 63 systematic reviews, orthobiologic injection emerges as a safe intervention with a moderate, durable symptomatic effect that is largest where it is least meaningfully controlled. The pooled 6-month effect of -0.47 does not decay by 12 months, does not depend on which joint is treated, and does not translate into structural change on imaging. It does depend, heavily, on what the product is compared against and on whether the patient and assessor could tell which arm they were in. The most invasive product class in the category shows no pooled benefit at all.

The clinical conclusion is not that orthobiologics should be abandoned but that they should be positioned accurately: as a well-tolerated symptomatic option with a durability advantage over corticosteroid and an efficacy profile comparable to hyaluronic acid, offered with explicit acknowledgement that disease modification is not demonstrated. The research conclusion is sharper. This field does not need more saline-controlled trials of under characterized products. It needs active-comparator trials of dose-defined products in stratified populations, and it needs every trial to report the six numbers that describe what was actually injected.

Declarations

Not applicable. This study analysed previously published data only.

Availability of data and materials

All extracted data rows, with their source bindings, and the analysis scripts used to produce every figure and table are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

[MHK, CAPMR] conceived and designed the study. All authors read, revised and approved the final manuscript.

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