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Intraosseous Orthobiologics for Bone Marrow Lesions and Osteochondral Disorders: Biological Rationale, Clinical Evidence, and Research Priorities

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Abstract

Background: Subchondral bone is increasingly viewed as an active participant in osteoarthritis and osteochondral disease rather than a passive substrate. This has motivated direct intraosseous delivery of orthobiologics — platelet-rich plasma (PRP) and plasma rich in growth factors (PRGF), bone marrow aspirate and its concentrate (BMA/BMAC/BMC), minimally processed adipose preparations, and culture-expanded mesenchymal stromal cells — into bone marrow lesions (BMLs) and subchondral compartments of the knee, hip, and talus. The evidence base is small, fast-moving, heterogeneous, and terminologically inconsistent, while available syntheses have not fully integrated mechanism, clinical data, product characterization, and regulatory constraints.

Methods and Findings: We conducted a state-of-the-art narrative review with a systematized, reproducible search of MEDLINE/PubMed supplemented by ClinicalTrials.gov and reference-list screening, from database inception to 7 September 2026, reported against the SANRA quality criteria; this is explicitly not a systematic review, no protocol was registered, and no dual independent screening or PRISMA screening counts are claimed. Twenty-one representative human studies of intraosseous or subchondral orthobiologic delivery were charted alongside the calcium-phosphate benchmark. Across knee, hip, talus, and osteonecrosis indications, most studies reported pain and function improvement, and several reported reductions in MRI-detected BML severity.

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However, only one double-blind randomized controlled trial (n = 86) used an intraosseous saline placebo; existing systematic reviews found only one of five randomized trials at low risk of bias among 24 studies (1,109 patients) and a mean Coleman score of 40/100 among 12 studies (459 patients). Route-comparative results are directly discordant. Serious adverse events were rare, but ascertainment was unsystematic and intramedullary needle misplacement is documented. Certainty was low to very low for every effectiveness outcome and low-favorable for serious harm.

Conclusions: Intraosseous orthobiologic delivery is biologically rationalized and appears procedurally tolerable, but current data do not establish superiority over intra-articular delivery, nor structural repair or disease modification. Placebo-controlled, route-isolating, MIBO-compliant trials with prespecified imaging endpoints and nosographically homogeneous populations are the decisive next step.

Keywords

Intraosseous Orthobiologics; Bone Marrow Lesions; Osteochondral Disorders; Biological Rationale.

Introduction

Articular cartilage was long treated as the disease of osteoarthritis (OA) and subchondral bone as its floor. That framing has eroded: subchondral bone is now characterized as a metabolically active, richly innervated compartment in which uncoupled remodeling, transforming growth factor- β (TGF- β) signaling, hypervascularization, and sensory nerve ingrowth interact with cartilage degeneration and with pain [1]. The osteochondral unit — cartilage, calcified cartilage, subchondral plate, and trabecular bone — behaves as a biomechanically interdependent load-damping structure in which altered loading can initiate degenerative cascades [2].

Bone marrow lesions (BMLs), the MRI correlate of subchondral involvement, are radiologically convergent and etiologically divergent, arising from trauma, altered load distribution, primary bone tissue alteration, coagulopathy, and hormonal disturbance; careful diagnostic separation is a prerequisite for rational treatment [3]. Their prognostic meaning is contested: some datasets frame BMLs as early markers predicting progression, others emphasize their prevalence in the general population and question any causal role [4]. Knee bone marrow edema can be classified as ischemic, mechanical, or reactive and — critically for interpreting uncontrolled studies — "tends to be self-limiting and, in most cases, resolves without any consequences" [5].

Established nonoperative options provide limited evidence for modifying BMLs. A meta-analysis of 15 studies found no significant benefit of bisphosphonates over placebo, while shockwave therapy showed short-term pain reduction only on low-quality evidence [6,7]. Direct intraosseous orthobiologic delivery, first described for severe tibiofemoral OA in 2014 [8], has since expanded to knee, hip, talar, and osteonecrotic indications.

The evidence base remains small and methodologically fragile. The most recent systematic review of subchondral knee injections identified 24 studies and 1,109 patients across calcium phosphate, platelet-rich plasma (PRP), and cell-based products, reporting modest quality with only one RCT at low risk of bias [9]; an earlier synthesis of 12 studies and 459 patients found a mean modified Coleman Methodology Score of 40 of 100 [10]. European consensus places cell-based therapy for knee OA at second-line status, with 22 of 27 statements supported only by low-level literature or expert opinion [11], and at least one recent review argues the literature is too thin to recommend subchondral injection at all [14].

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Terminological drift compounds this: 37.1% of 124 media articles on injectable orthobiologics for knee OA used "stem cell" without specifying the product [12], contradicting the International Society for Cell & Gene Therapy (ISCT) position that MSC should denote mesenchymal stromal cells unless stemness is demonstrated [13].

This review has three aims: to state the biological rationale precisely enough to be falsifiable; to appraise the human clinical evidence by indication, site, and product class without overstating it; and to convert the gaps into a prioritized research agenda. We do not argue that intraosseous orthobiologics regenerate cartilage, and we distinguish throughout between symptom modification and structural disease modification.

Methods

- **Objective and design:** The objective was to synthesize, appraise, and prioritize the evidence on intraosseous and subchondral delivery of orthobiologics for BMLs and osteochondral disorders. The design is a state-of-the-art narrative review with a systematized, reproducible search. It is deliberately not a systematic, scoping, or umbrella review: no protocol was registered, screening was performed without duplicate independent adjudication, and no PRISMA screening counts or flow diagram are therefore reported. Reporting follows the six SANRA criteria for narrative review quality [15], with the search reported in the spirit of PRISMA-S so that a reader can re-execute it [16].
- **Search sources and date:** MEDLINE/PubMed was searched from inception to 7 September 2026 using two parallel title/abstract blocks. The first crossed route terms (intraosseous, intra-osseous, subchondral, intramedullary) with product terms (platelet-rich plasma, PRP, PRGF, bone marrow aspirate, bone marrow concentrate, BMAC, mesenchymal, stromal vascular, orthobiologic, adipose, microfragmented, stem cell) and delivery terms (injection, infiltration, implantation, delivery, transplantation), with truncation applied where appropriate. The second crossed condition terms (bone marrow lesion, bone marrow edema, subchondral insufficiency fracture, spontaneous osteonecrosis of the knee, osteochondral lesion, avascular necrosis, osteonecrosis) with the same product terms plus subchondroplasty and calcium phosphate, anchored on the MeSH terms Osteoarthritis, Knee; Osteoarthritis, Hip; Bone Marrow; Osteonecrosis; Platelet-Rich Plasma; and Injections, Intraosseous. ClinicalTrials.gov was queried and reference lists of all retrieved systematic reviews hand-searched, without language restriction. WHO ICTRP and the EU Clinical Trials Information System were not searched, so registry coverage is incomplete — stated here as a limitation.
- **Eligibility logic:** We retained human studies in which an orthobiologic was delivered into bone — intraosseously, subchondrally, or via retrograde drilling — for a BML, osteochondral lesion, or osteonecrotic lesion. Purely intra-articular administration was excluded from clinical-effect charting unless paired with intraosseous delivery in the same protocol, or unless the study provided route-comparative biological data, in which case it was retained for the mechanistic sections only, as were preclinical and in vitro studies. Calcium-phosphate subchondroplasty was retained as an explicit non-biologic benchmark. Four record families that dominate a naïve "intraosseous" search were excluded: vascular access, drug administration during arthroplasty,

intrabony dental defects, and computed tomography accuracy studies.

- **Data charting:** Variables were charted into a structured matrix: design, center, sample size, diagnosis and severity grading, product identity and preparation, intraosseous dose and volume, guidance modality, concomitant procedures, comparator, follow-up, outcome instruments, numerical results, adverse events, and dominant limitations. Values are reported only where stated in the retrieved record; where a source gave significance without absolute values, that absence is stated rather than imputed. Product characterization was assessed against the Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO) domains [17].
- **Narrative synthesis and evidence appraisal:** Because interventions, anatomical targets, co-interventions, and outcome instruments are irreducibly heterogeneous, no meta-analysis was attempted; synthesis is structured by indication and anatomy, then by product class. Study-level bias was considered against the domains of RoB 2 [18] and ROBINS-I [19], and certainty was rated per outcome using GRADE domains [20]. Certainty ratings (**Table 3**) are the authors' judgments and were not derived from formal duplicate consensus.

The Osteochondral Unit as a Therapeutic Target

The rationale for intraosseous delivery rests on four propositions, each separately supported and separately incomplete.

- **The unit is mechanically and biologically continuous:** Cartilage, calcified cartilage, subchondral plate, and trabecular bone form a graded damping structure whose interplay maintains joint function; the same appraisal records that the subchondral compartment and the ankle remain poorly investigated relative to cartilage and the knee [2] — a gap that constrains this field.
- **Subchondral remodeling is initiating, not merely reactive:** Combining anterior cruciate ligament transection in mice with human tissue analysis, TGF- β 1 was shown to be activated in subchondral bone in response to altered loading, to reach high concentrations in subchondral bone from patients with OA, and to induce nestin-positive mesenchymal stromal cell clusters forming highly vascularized marrow osteoid islets; knockout of the type II TGF- β receptor in these cells attenuated OA development [21]. Multiomic analysis subsequently identified a senescent skeletal unit of EGFR-positive progenitors and EREG-positive macrophages, with Ereg knockdown suppressing senescence and alleviating both sclerosis and pain [22].
- **The compartment has distinctive physical properties:** Elevated intraosseous pressure is considered a key initiating factor in steroid-induced osteonecrosis of the femoral head; in early disease it increased angiogenesis and osteogenesis, but as pressure rose further both were inhibited, with mechanotransduction via Piezo1 activation in bone marrow stem cells [23]. Needle penetration itself decompresses this compartment — an unavoidable confounder in every uncontrolled intraosseous study, and one reason an intraosseous placebo arm is indispensable.
- **Route matters biologically, at least in part:** The most persuasive mechanistic argument here is route-comparative rather than product-comparative. In 31 patients with OA, a single intra-articular PRP infiltration ($n = 14$) was compared with intra-articular plus two intraosseous infiltrations ($n = 17$); one week later the combined route had reduced the synovial-fluid mesenchymal stromal cell population, confirmed by colony-forming unit-fibroblast (CFU-F) assay,

whereas intra-articular infiltration alone produced no variation in any cellular population [24]. In 12 patients with hip OA, paired marrow aspirates before and after combined delivery showed unchanged colony number but a 14.5% increase in colony area (28.2% in older donors), with senescence assays suggesting greater resistance to senescent cell accumulation in older patients and responders [25]. In a rat model, combined delivery provided superior pain relief by suppressing calcitonin gene-related peptide and substance P in both synovium and subchondral bone, and slowed lesion progression by inhibiting CD31hiEmcnhi (type H) vessel formation [26].

- **The rationale is not exclusive:** In a randomized trial of 81 patients, subchondral bone marrow edema was reduced significantly more by intra-articular PRP than by sodium hyaluronate [27]; intra-articular delivery alone can therefore influence the subchondral compartment, weakening any claim that intraosseous access is uniquely necessary to reach it. Biodistribution work does support local containment: after intraosseous injection into the porcine femoral head, grafted cells were detected only at the injection site, with none in filter organs or body fluids [28].

Orthobiologic Products and Terminology

Conflation of products is the most consequential error in this literature, and it propagates directly into clinical claims. Four families must be kept distinct (**Table 1**).

- **Blood-derived products (PRP, PRGF):** These are autologous plasma preparations enriched in platelets and platelet-derived growth factors, containing no marrow-derived progenitor population; plasma rich in growth factors (PRGF) denotes a leukocyte-free formulation. European consensus on blood-derived products for knee OA generated 28 question–statement sets, of which only nine were supported by high-level literature and only three achieved grade-A status, including support for PRP use in knee OA [29]. Characterization remains the weak point; a rare exemplar reported platelets $962 \pm 40 \times 10^9/\text{L}$, leukocytes $9.7 \pm 1.4 \times 10^9/\text{L}$, erythrocytes below $1 \times 10^6/\mu\text{L}$, no activation, and an explicit consensus classification code (N3N4-NON2-NON0) [30].
- **Bone marrow aspirate and its concentrates:** These are same-day, minimally manipulated aspirates, optionally density-gradient centrifuged: heterogeneous mixtures of nucleated cells, platelets, and plasma in which the mesenchymal stromal fraction is a small minority, quantified — when quantified at all — as CFU-F per milliliter, a colony-forming surrogate rather than a purified progenitor count. Harvest site alters composition: in a randomized trial of 90 patients, posterior iliac crest aspirate was significantly richer in mononuclear cells, mesenchymal stromal cells, and platelets than proximal tibial aspirate, although outcomes did not differ significantly across the three arms [31].
- **Minimally processed adipose products:** Stromal vascular fraction and micro-fragmented adipose tissue are processed lipoaspirates. In the intraosseous literature they appear only as technique descriptions and registered protocols, so no conclusion about their effectiveness is supportable.
- **Culture-expanded mesenchymal stromal cells:** Expansion converts a concentrate into a substantially manipulated product with a different regulatory classification and dose vocabulary. Only two datasets here used expanded cells: an athlete series delivering approximately 24 million expanded adipose-derived stromal cells per route [32] and a pediatric osteonecrosis series. Evidence from point-of-care concentrates therefore cannot be transferred to expanded-cell

products.

Two reporting consequences follow. First, no point-of-care concentrate satisfies the identity requirements that would license the phrase "stem cell therapy"; the ISCT position requires that MSC denote mesenchymal stromal cells absent demonstrated stemness [13], and this review uses "concentrate" or "stromal cell-containing product" accordingly. Second, characterization is empirically poor: across nine PRP studies in talar osteochondral lesions (356 patients), mean adherence to a 46-point modified MIBO checklist was $42.8\% \pm 5.2\%$, no study reached 50%, and adherence did not improve after MIBO publication [33]. A recent Delphi consensus reached full agreement on general orthobiologic and PRP statements and on delivery methods, while autologous cell-based therapies did not [34] — an asymmetry mirroring the evidence gradient below.

Product family	Members	Manipulation status	Active constituents claimed	Dose unit that must be reported	Minimum reporting variables (MIBO-aligned) [17]	Common reporting failures in the intraosseous literature
Blood-derived	PRP; PRGF (leukocyte-free); leukocyte-rich PRP	Minimal; autologous, same-day	Platelet-derived growth factors, plasma proteins	Platelets $\times 10^9/L$ and total platelet dose per injection	Whole-blood volume; anticoagulant; centrifugation protocol; platelet, leukocyte and erythrocyte counts; activation and calcium chloride use; final volume; number and interval of injections; classification code	Volume reported without platelet dose; activation unstated; leukocyte content unstated [30,33]
Bone marrow, minimally manipulated	BMA; BMAC/BMC	Minimal; autologous, same-day	Nucleated cells, platelets, plasma; small mesenchymal stromal fraction	Nucleated cells/mL and CFU-F/mL	Harvest site and needle; aspirate volume; anticoagulant; centrifugation protocol; nucleated cell count; CFU-F/mL; viability; final injected volume per site	CFU-F reported as "MSC count"; harvest site unstated; volume and cell dose omitted [31]
Adipose, minimally processed	Stromal vascular fraction; micro-fragmented adipose tissue	Minimal to moderate, method-dependent	Stromal and vascular cell populations, extracellular matrix	Nucleated cells/mL and viability	Harvest site; processing device and method; enzymatic versus mechanical; nucleated cell count; viability; injected volume	Intraosseous clinical outcome data essentially absent; technique notes only
Culture-expanded cells	BM-MSC; expanded adipose-derived stromal cells	Substantial — different regulatory class	Defined expanded stromal cell population	Total viable cells administered per route	Passage number; medium and supplements; identity and potency assays; viability; total cells per route; release criteria	Reported as interchangeable with concentrates; regulatory status not stated [32]
Non-biologic benchmark	Calcium phosphate ("subchondroplasty")	Not an orthobiologic	Osteoconductive bone substitute	Injected volume (mL) per lesion	Volume; fill technique; leakage assessment; concomitant arthroscopy	Pooled with orthobiologics in reviews, obscuring product-specific effects [9]

Table 1: Product taxonomy and critical reporting variables for intraosseous orthobiologics.

BMA, bone marrow aspirate; BMAC/BMC, bone marrow aspirate concentrate/bone marrow concentrate; BM-MSC, bone marrow-derived mesenchymal stromal cells; CFU-F, colony-forming unit-fibroblast; MIBO, Minimum Information for Studies Evaluating Biologics in Orthopaedics; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma.

Clinical Evidence by Indication and Anatomical Site

(Table 2) charts 22 studies: 21 of intraosseous or subchondral orthobiologic delivery and one calcium-phosphate benchmark. Study-level detail sits in the table; values appear only where the retrieved record stated them.

Knee osteoarthritis with bone marrow lesions: blood-derived products

After a 14-patient pilot of combined intraosseous and intra-articular PRP in severe OA [35], a matched observational study of 60 patients with Ahlbäck grade III–IV disease found improvement in all Knee injury and Osteoarthritis Outcome Score (KOOS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscales in the combined-route group and in none in the intra-articular group, with minimal clinically important improvement in 14 of 30 versus 5 of 30 at 12 months (difference 30%; 95% CI 4.3–51.9; $p = 0.013$) [36].

Randomized data are discordant. A three-arm trial in 86 patients with Kellgren–Lawrence (K–L) grade II–III disease reported significantly superior visual analogue scale (VAS) and WOMAC scores with combined delivery to 18 months [37], whereas a single-blind trial of 50 patients found greater VAS reduction at six months without significance ($p = 0.422$) in an arm receiving 18 mL of PRP versus 8 mL intra-articularly, confounding dose with route [38]. A third trial found both routes superior to intra-articular saline, with only combined delivery reducing the bone-turnover marker NTX-I ($p = 0.009$) [39]; a real-world cohort of 86 patients reported 55–67% responders, with PRP erythrocyte and leukocyte counts inversely correlated with WOMAC change and platelet count uncorrelated [40].

The most informative trial is a prospective, double-blind, multicenter RCT in 86 patients with K–L grade III–IV disease comparing intraosseous PRGF against intraosseous saline placebo, with three intra-articular PRGF injections in both arms. Both groups improved on all KOOS and WOMAC subscales, and the intraosseous PRGF arm improved significantly more in nearly all domains at 3, 6, and 12 months ($p < 0.05$) without serious adverse events, although absolute means were unavailable in the retrieved record [41]. A 2026 comprehensive review reached concordant conclusions for pain, function, and joint structure [42] –a structural claim to be read against Section 8.

Knee osteoarthritis: bone marrow concentrates and expanded cells

Within-patient randomization against arthroplasty produced the longest-horizon data. In 30 young patients with bilateral knee OA after corticosteroid-related osteonecrosis, subchondral bone marrow grafting yielded fewer complications than contralateral total knee arthroplasty (TKA) at a mean of 12 years [43]. In 140 patients aged 65–90 years, subchondral bone marrow concentrate produced mean BML volume regression of 1.5 cm³ over 24 months and TKA on the treated side in 25 of 140 (18%), with

persistent lesions above 3 cm³ an independent risk factor for later TKA (hazard ratio 4.42; 95% CI 2.34–7.21) [44].

The decisive route-isolating trial gave 60 patients 20 mL of an identical bone marrow concentrate subchondrally in one knee and 20 mL intra-articularly in the contralateral knee; at a mean of 15 years, arthroplasty incidence was 1.3% versus 4.6% per knee-year ($p = 0.01$), corresponding to TKA in 12 of 60 (20%) versus 42 of 60 (70%) [45]. A case-matched registry cohort of 80 patients found no statistically significant between-route difference in any patient-reported outcome [46].

Combined-delivery cohorts are consistent but uncontrolled. In 30 patients, International Knee Documentation Committee (IKDC) score improved from 40.5 ± 12.5 to 62.6 ± 19.4 at 12 months ($p < 0.0005$) with MRI bone marrow edema reduction ($p = 0.003$) [47]; at 24 months IKDC was stable but VAS pain deteriorated from 3.0 ± 1.9 to 4.4 ± 1.8 ($p = 0.0001$) while remaining below baseline, with a 13% failure rate [48]. A randomized head-to-head of single intraosseous bone marrow aspirate concentrate (BMAC) versus intraosseous PRP in 40 patients favored BMAC at 3 and 6 months but not at 12 [30]. A 62-patient subchondral BMAC series improved all KOOS subscales, WOMAC, and VAS ($p < 0.001$) and reduced MRI Osteoarthritis Knee Score (MOAKS) severity at three months without reporting absolute scores, dose, or cell characterization [49], and in 16 athletes given expanded adipose-derived stromal cells numeric pain fell from 6.6 ± 0.9 to 2.4 ± 0.5 with MOAKS gains in 12 of 27 regions [32]. Set against these signals, the phase 3 RCT designed to isolate the subchondral contribution of BMAC completed in March 2023 with neither posted results nor an identifiable publication as of 7 September 2026 [51].

The calcium-phosphate benchmark

Calcium phosphate is not an orthobiologic but is the only comparator with prospective, protocol-standardized multicenter data in the same target, achieving KOOS pain improvement from 45.9 ± 14.3 to 81.3 ± 18.1 and 91.5% surgery-free survivorship at 24 months in 92 knees, though with MOAKS gains at 12 but not 24 months [52] and 22.4% TKA conversion at two years in pooled data [53]. No orthobiologic has been tested against it head-to-head.

Hip osteoarthritis

A prospective pilot in 40 arthroplasty candidates with Tönnis grade 2–3 disease who had failed prior intra-articular PRP reported minimal clinically important improvement in 40%, 37.5%, and 40% at 2, 6, and 12 months without severe adverse effects [54]. The largest hip dataset is a matched cohort of 434 hips (217 intraosseous bone marrow concentrate into the femoral head versus 217 conservative controls), reporting progression to total hip arthroplasty in 16.1% versus 40.1% at 15 years with a CFU-F dose-response and no observed adverse events [55]. A published letter has since challenged that survival analysis [56]; its substance could not be retrieved, but its existence is material to how confidently the result is cited.

Talar and ankle osteochondral lesions

No study has evaluated an isolated intraosseous orthobiologic injection in the talus. The closest direct evidence is a series of 11 patients treated with combined calcium-phosphate subchondroplasty and BMAC, in which weight-bearing VAS fell from 7.8 to 1.8 and Foot and Ankle Outcome Score rose from 67.1

to 89.6 at one year; because both materials were co-administered, the BMAC contribution is unattributable [57]. Otherwise, the talar literature evaluates biologics as additives to bone marrow stimulation: a meta-analysis of 718 patients found better functional outcomes with stimulation plus BMAC ($p < 0.05$) but on three non-blinded studies of weak quality [58], and a review of 35 studies found four of five studies of adjunctive PRP reporting improvement amid substantial variability in preparation [59]. International consensus of 75 experts holds PRP, concentrated bone marrow aspirate, and hyaluronic acid appropriate in selected patients with persistent symptoms, while finding no demonstrated superiority among formulations, preparation methods, or injection strategies [60].

Osteonecrosis as a conceptually adjacent indication

Osteonecrosis is the one intraosseous cell-delivery indication with replicated comparative data, and it demonstrates the primacy of disease stage. In 14 lesions in 10 pediatric and young-adult patients treated with core decompression plus intraosseous culture-expanded mesenchymal stromal cells versus 13 lesions in 11 controls, median relative lesion size on MRI was 18.5% versus 58.0% of initial volume ($p < 0.05$) with no treatment-related adverse effects — yet clinical improvement did not differ significantly between groups [61], a dissociation instructive in both directions. Meta-analysis of 16 studies in early-stage femoral head osteonecrosis showed a VAS mean difference of -10.88 (95% CI -16.84 to -4.92) and arthroplasty in 22.5% versus 42.3% ($p = 0.001$) favoring added bone marrow cells [62], whereas in post-collapse disease 270 hips showed no benefit (odds ratio 1.41, 95% CI 0.55–3.62 for progression) [63]. Stage, not enthusiasm, determines effect.

Ref	Site / indication	Design	n	Product and route	Comparator	Follow-up	Key verified result	Reported harms
[35]	Knee, severe OA	Pilot single-arm	14	PRP, IO (5 mL femur + 5 mL tibia) + IA 8 mL, $\times 2$	None	24 weeks	KOOS pain $61.55 \pm 14.11 \rightarrow 74.60 \pm 19.19$ ($p = 0.008$); SF MSC $7.98 \pm 8.21 \rightarrow 4.04 \pm 5.36/\mu\text{L}$ ($p = 0.019$)	Not reported
[36]	Knee, Ahlbäck III–IV	Matched observational	60 (30 vs 30)	PRP, IO + IA	IA PRP alone	12 months	All KOOS/WOMAC subscales improved in IO+IA only; MCII 14/30 vs 5/30 at 12 mo (diff 30%; 95% CI 4.3–51.9; $p = 0.013$)	Not reported
[37]	Knee, K–L II–III	RCT, 3 arms	86	PRP, IO + IA $\times 2$	IA PRP; IA HA	18 months	Significantly superior VAS and WOMAC with IO+IA versus both comparators, sustained to 18 mo	Not reported
[38]	Knee, K–L III	Single-blind RCT	50 (25 vs 25)	PRP 18 mL total (IO 5+5 mL, IA 8 mL), fluoroscopy	IA PRP 8 mL	6 months	Greater VAS fall with IO+IA, not significant ($p = 0.422$); only KOOS sport/recreation favored IO+IA ($p < 0.05$). Dose confounded with route	Not reported
[39]	Knee, K–L III	Single-blind RCT, 3 arms	96	PRP, IA + IO	IA PRP; IA saline	12 weeks	Both PRP arms superior to saline (VAS, KOOS); only IA+IO reduced NTX-I ($p = 0.009$) and effusion	Not reported

[40]	Knee, severe OA	Retrospective real-world cohort	86	PRP, IO + IA	None	18 months	WOMAC reduced by 2 mo, sustained to 18 mo; responders 55–67%; PRP erythrocyte and leukocyte count inversely correlated with Δ WOMAC	Not reported
[41]	Knee, K–L III–IV	Double-blind multicenter RCT with IO placebo	86	PRGF, IO + 3 IA PRGF	IO saline + 3 IA PRGF	12 months	Both arms improved; IO-PRGF significantly better in nearly all KOOS/WOMAC domains at 3, 6, 12 mo ($p < 0.05$); absolute means not available	No serious adverse events
[43]	Knee OA after corticosteroid osteonecrosis	Within-patient RCT	30 patients / 60 knees	Bone marrow graft, subchondral (mean 6,500 CFU-F/mL)	Contralateral TKA	Mean 12 years	More medical/surgical complications after TKA; thrombophlebitis 15% vs 0%	Fewer with cell therapy
[44]	Knee, medial OA with BML	Within-patient randomized	140	BMC 20 cm ³ subchondral (mean 7,800 CFU-F/mL)	Contralateral TKA	Mean 15 years	BML regression 1.5 cm ³ at 24 mo; TKA 25/140 (18%); persistent BML > 3 cm ³ predicted TKA (HR 4.42; 95% CI 2.34–7.21; $p < 0.001$)	Not reported
[45]	Bilateral knee OA	Within-patient RCT, route-isolating, identical dose	60 patients / 120 knees	BMC 20 mL subchondral (mean 5,727 CFU-F/mL)	20 mL IA, contralateral knee	Mean 15 years	Arthroplasty 1.3%/knee-year subchondral vs 4.6%/knee-year IA ($p = 0.01$); TKA 12/60 (20%) vs 42/60 (70%)	Not reported
[46]	Advanced knee OA with BML	Case-matched registry cohort	80 (40 vs 40)	BMC + platelet products, IO + IA	IA only	Not stated	No statistically significant between-route difference in NPS, IKDC, LEFS, modified SANE	Not reported
[47]	Knee OA with subchondral change	Prospective multicenter pilot	30	BMAC, 1 IA + 2 subchondral	None	12 months	IKDC 40.5 $\pm$ 12.5 $\rightarrow$ 62.6 $\pm$ 19.4 ($p < 0.0005$); MRI bone marrow edema reduced ($p = 0.003$); EQ-VAS unchanged	No major complications; 2 failures
[48]	Knee OA, K–L 2–3	Prospective cohort (24-mo extension)	30	BMAC 9 mL, IA + subchondral, fluoroscopy	None	24 months	IKDC stable 63.4 $\pm$ 17.1; VAS worsened 3.0 $\pm$ 1.9 $\rightarrow$ 4.4 $\pm$ 1.8 ($p = 0.0001$) though below baseline 6.3 $\pm$ 1.8; edema reduction persisted	No major complications; 13% failure
[30]	Knee OA, K–L II–III with overload edema	Multicenter randomized	40 (19 vs 21)	Single IO BMAC	Single IO PRP	12 months	VRS positive reviews 65% vs 55% (3 mo), 55% vs 45% (6 mo); not significant at 12 mo; absolute WOMAC values unavailable	Counts not reported; described as equally safe
[49]	Knee OA with MRI-confirmed BML	Retrospective consecutive series	62	BMAC, subchondral, C-arm fluoroscopy	None	12 months	KOOS, WOMAC, VAS all improved ($p < 0.001$); MOAKS reduced at 3 mo ($p < 0.001$); absolute values, dose and cell counts not reported	Not reported
[32]	Knee OA-related BML, K–L 2–4, athletes	Prospective single-arm	16	Expanded ASC: 24.3 $\pm$ 2.1 M IA + 23.4 $\pm$ 1.9 M IO, fluoroscopy	None	12 months	NPRS 6.6 $\pm$ 0.9 $\rightarrow$ 2.4 $\pm$ 0.5; Tegner 4.4 $\pm$ 1.8 $\rightarrow$ 7.8 $\pm$ 1.1; MOAKS improved in 12/27 regions	No major complications
[54]	Hip OA, Tönnis 2–3, prior IA PRP failure	Prospective pilot	40	PRP, IO acetabulum + femoral head, + IA	None	12 months	MCII 16/40 (40%) at 2 mo, 15/40 (37.5%) at 6 mo, 16/40 (40%) at 12 mo	No severe adverse effects

[55]	Hip OA	Matched cohort with dose-response	434 hips (217 vs 217)	BMC, IO femoral head, fluoroscopy	Matched conservative care	15 years	THA 16.1% (35/217) vs 40.1% (87/217); CFU-F dose-response; revision 0/35 vs 7/87 (8.0%)	No adverse events observed
[25]	Hip OA	Mechanistic clinical study, paired	12	PRP, IO + IA	Within-patient pre/post	6 months	Colony area +14.5% post-treatment (+28.2% in older donors); 7 responders / 5 non-responders by HOOS	Not reported
[57]	Talar osteochondral defect (mean 1.3 × 1.4 cm)	Retrospective series	11	Calcium phosphate plus BMAC, subchondral	None	12 months	Weight-bearing VAS 7.8 → 1.8; FAOS 67.1 → 89.6; 10/11 would repeat. BMAC effect unattributable	Not reported
[61]	AVN after steroid or chemotherapy (pediatric/young adult)	Retrospective comparative	14 lesions / 10 patients vs 13 lesions / 11 patients	Core decompression + IO expanded MSC	Core decompression alone	Median 3.1 vs 2.0 years	Relative lesion size 18.5% vs 58.0% of initial volume ($p < 0.05$); clinical improvement not significantly different	No treatment-related adverse effects
[52]	Knee, K–L 1–3 with tibiofemoral BML — non-biologic benchmark	Prospective multicenter	92 knees	Calcium phosphate, subchondral	None	24 months	KOOS pain $45.9 \pm 14.3 \rightarrow 81.3 \pm 18.1$ ($p < 0.0001$); surgery-free survivorship 91.5% (95% CI 82.9–95.8); reoperation 7/92 (7.6%); MOAKS improved at 12 mo, not 24 mo	No serious device-related events

Table 2: Representative human clinical evidence on intraosseous or subchondral orthobiologic delivery, with the calcium-phosphate benchmark.

ASC, adipose-derived stromal cells; AVN, avascular necrosis; BMAC/BMC, bone marrow aspirate concentrate/bone marrow concentrate; BML, bone marrow lesion; CFU-F, colony-forming unit-fibroblast; FAOS, Foot and Ankle Outcome Score; HA, hyaluronic acid; HOOS, Hip disability and Osteoarthritis Outcome Score; IA, intra-articular; IKDC, International Knee Documentation Committee; IO, intraosseous; K–L, Kellgren–Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; LEFS, Lower Extremity Functional Scale; MCII, minimal clinically important improvement; MOAKS, MRI Osteoarthritis Knee Score; NPRS/NPS, numeric pain rating scale; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma; SANE, single-assessment numeric evaluation; SF, synovial fluid; THA/TKA, total hip/knee arthroplasty; VAS, visual analogue scale; VRS, verbal rating scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Procedural and Product Variables

Five potentially important procedural variables remain unstandardized.

Target selection, guidance, and setting. Reported approaches span fluoroscopic targeting of the femoral condyle and tibial plateau [38,48,49], fluoroscopic femoral head injection [55], and ultrasound guidance; guidance modality is frequently unstated, yet confirmation of placement matters because misplacement is real and detectable (Section 7). Early protocols required an operating room and sedation, whereas a described modification performs office-based intraosseous PRGF infiltration under wide-awake local anesthesia with ultrasound guidance — removing a major access barrier and, equally, a procedural

safeguard [64]. Setting is a candidate effect modifier that no study has tested.

Dose and volume. Where reported, intraosseous PRP volumes range from about 2 to 5 mL per site [37,38], bone marrow concentrates from 9 mL total [48] to 20 mL split between femur and tibia [45], and expanded cells at roughly 24 million per route [32]; several otherwise informative series report no dose at all [49].

Cell or platelet concentration. Bone marrow concentrate studies from a single group report 5,727, 6,500, and 7,800 CFU-F/mL [43,44,45] and a CFU-F dose-response in the hip [55] — the strongest argument that this is a biological rather than purely mechanical intervention, and a reminder that CFU-F is a colony-forming surrogate, not a purified progenitor count.

Harvest site. Posterior iliac crest aspirate is richer in mononuclear cells, mesenchymal stromal cells, and platelets than proximal tibial aspirate, yet intra-articular outcomes did not differ significantly between sites [31]; whether compositional superiority translates into intraosseous efficacy is untested. The one cohort correlating composition with response implicates leukocyte and erythrocyte content rather than platelet dose [40].

Concomitant intervention. Most protocols deliver intraosseous and intra-articular product in one session [35,36,41,47], and some add arthroscopy, retrograde drilling, or bone marrow stimulation [57,58], so the intraosseous contribution is rarely isolable — the field's central design problem.

Safety

Safety reporting is reassuring but methodologically weak.

Across a systematic review of 24 studies and 1,109 patients, PRP and cell-based products showed favorable safety profiles and lower arthroplasty conversion rates than calcium phosphate, whose conversion rates ranged from 1.3% to 45% [9]; an earlier review of 459 patients likewise recorded few adverse events [10]. Individual series report no serious adverse events with intraosseous PRGF [41], no major complications with combined BMAC delivery to 24 months [47,48] or with expanded adipose-derived stromal cells [32], and none observed with hip PRP [54], across 217 hips receiving intraosseous bone marrow concentrate [55], or in the pediatric osteonecrosis series [61]. Biodistribution data support local containment [28].

Three qualifications are necessary. First, ascertainment is unsystematic: many studies charted in Table 2 report no adverse-event data at all, and absence of reporting is not absence of events. Second, procedure-specific complications are documented. In an 83-year-old osteoporotic woman undergoing ultrasound-guided subchondral intraosseous PRP injection, the needle penetrated the tibial intramedullary canal; fluoroscopy confirmed intramedullary contrast spread correlating with a compact ball-shaped Doppler signal, whereas correct subchondral repositioning produced a thin sheet-like subcortical blush, after which pain fell from VAS 7 to 2 at one month [65]. Recognizing sonographic signatures of misplacement is a practical competency. Third, the anatomically confined talus warrants caution: avascular necrosis of the talus has been reported after subchondral calcium-phosphate filling [66], and although that involves a bone substitute rather than an orthobiologic, it establishes that subchondral filling of a small, tenuously vascularized bone is not inherently benign.

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Evidence Certainty and Methodological Limitations

Seven recurring limitations explain the low certainty of evidence (**Table 3**).

Blinding and placebo control. Exactly one trial used an intraosseous placebo with double blinding [41]; every other comparison is open, single-blind, or against a non-inert comparator such as arthroplasty. Since needle decompression is itself a candidate mechanism [23] and BMLs frequently regress spontaneously [5], the absence of intraosseous sham arms is the greatest threat to inference.

Co-intervention and dose–route confounding. Simultaneous intra-articular administration is the norm [35,36,41,47], so the intraosseous contribution usually cannot be separated, and where route-isolating designs exist they disagree: within-patient randomization at 15 years strongly favored the subchondral route [45], whereas a case-matched registry cohort found no significant difference [46]. Dose compounds this: in the trial delivering 18 mL of PRP to the combined-route arm and 8 mL to the comparator, a positive result could not have distinguished route from dose, and the negative result is correspondingly hard to interpret [38].

Intervention characterization. Dose, volume, platelet or CFU-F concentration, leukocyte content, activation, and centrifugation protocols are frequently unreported [49], with benchmark MIBO adherence of $42.8\% \pm 5.2\%$ in comparable PRP literature and no study reaching 50% [33]. An intervention that cannot be specified cannot be replicated.

Nosographic heterogeneity. Populations pooled under "bone marrow lesion" include OA-associated BMLs, subchondral insufficiency fracture, transient edema syndrome, osteonecrosis, and osteochondral lesions, which differ in natural history [3,4], and knee bone marrow edema is frequently self-limiting [5]; uncontrolled before–after imaging improvement therefore cannot be attributed to treatment.

Imprecision and single-center concentration. Median sample sizes are small, several key datasets comprising 11 to 40 patients [30,57,61], and the most influential long-term datasets originate from one group and center [43,44,45,55], with a published methodological challenge to the 15-year hip analysis [56].

Outcome, imaging, and reporting inconsistency. Studies variously use VAS, numeric rating scales, KOOS, WOMAC, IKDC, Tegner, and hip- or ankle-specific instruments, while imaging uses the Whole-Organ MRI Score [47,48], MOAKS [32,49], or unspecified qualitative assessment [67]; imaging follow-up is often shorter than clinical follow-up — three months within a 12-month series [49] — the wrong direction for a structural claim. Non-reporting compounds this: the phase 3 route trial for BMAC completed in 2023 without posted results or an identified publication as of 7 September 2026 [51].

Structural interpretation. This limitation carries the greatest potential for clinical harm. Reported structural findings comprise BML volume regression of 1.5 cm^3 [44], reduction of MRI bone marrow edema [47,48], MOAKS gains in 12 of 27 regions [32] or at three months [49], and, for the calcium-phosphate benchmark, MOAKS gains at 12 but not 24 months [52] — none of which is histological or validated compositional evidence of hyaline cartilage restoration. Symptom improvement, and even measurable regression of a bone marrow lesion, does not establish cartilage regeneration or disease

modification. Delayed arthroplasty [45,55] is a meaningful patient-centered outcome but is influenced by symptom relief, patient preference, and surgical thresholds, and is not a structural endpoint.

Population and comparison	Outcome	Certainty	Principal reasons for downgrading
Severe knee OA: IO PRGF + IA PRGF versus IO saline + IA PRGF	Pain and function to 12 months	Low	Single trial (n = 86); imprecision; no independent replication. No downgrade for risk of bias (double-blind, multicenter, true IO placebo) [41]
Knee OA with BML: IO/subchondral cell concentrate versus IA cell concentrate	Conversion to arthroplasty at 13–15 years	Very low	Single center and investigator group; unblinded; no independent replication; directly discordant registry cohort; published methodological challenge to a companion analysis [45,46,56]
Knee OA with BML: IO + IA PRP versus IA PRP	Pain at 6 months	Very low	Inconsistency (superior to 18 months versus non-significant at 6 months); dose–route confounding; imprecision [37,38]
Knee OA with BML: subchondral BMAC, uncontrolled	BML severity on MRI	Very low	Uncontrolled before–after design; self-limiting natural history; imaging follow-up shorter than clinical follow-up [5,49]
Knee OA: subchondral versus IA bone marrow-derived cells	Pain, function, arthroplasty avoidance	Very low	Five studies, 298 knees, mostly small and unblinded; heterogeneous products and protocols [50]
Hip OA: IO BMC versus matched conservative care	Arthroplasty-free survival at 15 years	Very low	Non-randomized matched cohort; single center; interpretation formally challenged [55,56]
Talar osteochondral lesion: BMAC as adjunct to bone marrow stimulation	Function	Very low	Methodological quality rated weak; positive finding rests on three non-blinded studies [58]
Talar osteochondral lesion: PRP as adjunct to bone marrow stimulation	Pain and function	Very low	Small non-randomized clinical set; substantial variability in PRP preparation [59]
Early osteonecrosis of the femoral head: core decompression + bone marrow cells versus core decompression	Pain, progression, arthroplasty	Low	Consistent direction across meta-analyses but heterogeneous, largely non-randomized primary data [62]
Post-collapse osteonecrosis: core decompression + BMAC versus core decompression	Progression, arthroplasty	Low (no benefit)	Point estimates null with wide confidence intervals; consistent across 12 studies and 270 hips [63]
Any joint, any IO orthobiologic	Serious adverse events	Low (favorable)	Consistent absence of serious events across large review series and favorable biodistribution data, downgraded for unsystematic ascertainment and documented procedural complications [9,10,28,65,66]
Any joint, any IO orthobiologic	Cartilage regeneration / structural disease modification	Insufficient evidence	No study provides histological or validated compositional evidence of hyaline cartilage restoration; imaging endpoints are semiquantitative, short, and uncontrolled

Table 3: Certainty of evidence by indication and outcome (authors' GRADE-informed appraisal).

BMAC/BMC, bone marrow aspirate concentrate/bone marrow concentrate; BML, bone marrow lesion; IA, intra-articular; IO, intraosseous; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma.

Regulatory and Nomenclature Considerations

Autologous point-of-care preparations — bone marrow aspirate, BMAC, stromal vascular fraction, and micro-fragmented adipose tissue — are heterogeneous cell-and-growth-factor concentrates, not culture-expanded mesenchymal stromal cell products; in accordance with the ISCT position statement they are described here as concentrates or stromal cell-containing products rather than "stem cell therapy" [13]. That distinction is not pedantry: the classes differ in composition, dose vocabulary, manufacturing burden, and legal status, and only two datasets here used expanded cells [32,61].

In the United States, the Food and Drug Administration states that "regenerative medicine therapies have not been approved for the treatment of any orthopedic condition, such as osteoarthritis, tendonitis, disc disease... knee pain, neck pain, or shoulder pain," that unapproved products including stem cells, stromal vascular fraction, orthobiologics, and exosomes require licensure and clinical-trial oversight before approval, and that a product's presence in a trial registry does not mean it is legally marketed; reported harms include blindness, tumor formation, and serious infections [68]. In the European Union, the European Medicines Agency states that stem cells are categorized as advanced therapy medicinal products when substantially manipulated or used for a different essential function, and warns that unregulated advanced therapies may expose patients to serious effects without proven benefit, frequently marketed outside authorized clinical trials [69].

Two implications follow. First, marketing language has already outrun the evidence, with 37.1% of media articles using "stem cell" without specifying the product and only 29.8% mentioning drawbacks [12]; scientific writing should not supply that language. Second, consensus bodies have converged on restraint — cell-based therapy for knee OA is second-line because of limited high-quality studies and absent superiority over other injectables [11], autologous cell-based therapies did not achieve expert consensus [34], and for the ankle no superiority was demonstrated among formulations or injection strategies [60].

Research Agenda

Further uncontrolled combined-route series are unlikely to change current certainty ratings. Variable-isolating designs are required (**Table 4**).

The highest priority is a placebo-controlled, route-isolating trial: intraosseous product plus intra-articular vehicle versus intraosseous vehicle plus intra-articular vehicle, with an identical needle procedure in both arms so that mechanical decompression is controlled; the one existing double-blind intraosseous-placebo design shows this is feasible [41]. Second, populations must be nosographically homogeneous, with prespecified separation of OA-associated BMLs, subchondral insufficiency fracture, transient edema syndromes, and osteonecrosis [3,4] and with stage stratification, since benefit appears in early but not post-collapse osteonecrosis [62,63]. Third, every trial should report full MIBO-aligned characterization [17,33] and, for cell products, both nucleated cell and CFU-F dose so that dose-response is tested prospectively [55]. Fourth, structural claims require structural endpoints: prespecified, blinded, centrally read MOAKS or Whole-Organ MRI Score at time points matching clinical follow-up, with compositional or histological substudies where obtainable. Fifth, the comparator must be the best available alternative — calcium-phosphate subchondroplasty, which has prospective multicenter 24-month data [52,53] — not an untreated control. Sixth, completed trials must report: the phase 3 BMAC route trial remains unreported three years after completion [51], whereas an adequately powered randomized trial of core decompression with or without BMAC in early osteonecrosis is now recruiting [70]. Finally, harm ascertainment should be prospective and standardized, with explicit reporting of placement confirmation and misplacement [65].

Priority	Specific gap	Proposed design solution	Feasibility anchor
1	Route effect confounded by simultaneous IA delivery	Four-arm or two-arm trial with identical needle procedure in all arms: IO product + IA vehicle versus IO vehicle + IA vehicle; sham needle placement mandatory	Double-blind IO saline placebo already executed in 86 patients [41]
2	Needle decompression as an unmeasured co-mechanism	Include an IO vehicle arm and record intraosseous pressure where measurable	Pressure-dependent osteogenic and angiogenic signaling documented [23]
3	Pooling of etiologically distinct lesions	Prespecified nosographic inclusion (OA-BML, SIFK, transient edema, osteonecrosis) with stage stratification	Nosographic framework and stage-dependent osteonecrosis results available [3,62,63]
4	Intervention not characterized	Mandatory MIBO-aligned reporting; nucleated cell and CFU-F dose for cell products; platelet, leukocyte and erythrocyte counts for blood products	Benchmark adherence 42.8% $\pm$ 5.2%; exemplar full characterization published [30,33]
5	Structural claims unsupported	Blinded central reading of MOAKS or WOMS at time points matching clinical follow-up; compositional or histological substudy	Existing series read MOAKS at only 3 of 12 months [49]
6	Wrong comparator	Head-to-head versus calcium-phosphate subchondroplasty, not versus no treatment	Prospective multicenter 24-month benchmark data exist [52,53]
7	Dose-response untested prospectively	Prespecified dose tiers with CFU-F or platelet dose as a continuous covariate	Retrospective CFU-F dose-response signal in the hip [55]
8	Non-reporting of completed trials	Registry-linked publication commitment; report primary outcomes irrespective of direction	Phase 3 route trial unreported since March 2023 [51]
9	Talar and ankle evidence entirely adjunctive	Trial of isolated retrograde or subchondral biologic delivery versus bone marrow stimulation alone in defined lesion sizes	Adjunctive-only evidence base and explicit consensus uncertainty [58,59,60]
10	Harm ascertainment unsystematic	Prospective standardized adverse-event capture, including placement confirmation and misplacement reporting	Documented intramedullary misplacement and talar osteonecrosis after subchondral filling [65,66]

Table 4: Research priorities and proposed design solutions.

CFU-F, colony-forming unit-fibroblast; IA, intra-articular; IO, intraosseous; MIBO, Minimum Information for Studies Evaluating Biologics in Orthopaedics; MOAKS, MRI Osteoarthritis Knee Score; OA-BML, osteoarthritis-associated bone marrow lesion; SIFK, subchondral insufficiency fracture of the knee; WOMS, Whole-Organ MRI Score.

Conclusions

Subchondral bone is a legitimate therapeutic target: metabolically active, densely innervated, mechanically responsive, and implicated in both cartilage degeneration and pain [1,21,22]. Route-comparative human and animal data indicate that intraosseous delivery produces biological effects that intra-articular delivery alone does not reproduce [24,25,26]. Clinically, the procedure is achievable in an ambulatory setting [64], appears tolerable [9,41,55], and is associated with symptom improvement in most reported series.

That is the extent of what can be claimed. Only one trial has used an intraosseous placebo [41]; route-isolating results are directly contradictory [45,46]; the intervention is inadequately characterized in most reports [33]; populations are nosographically mixed [3]; and no dataset provides structural evidence of cartilage restoration. Certainty is low or very low for every effectiveness outcome (**Table 3**). Point-of-care bone marrow and adipose concentrates are not stem cell therapies and should not be described as such

[13]; no such product is approved for any orthopedic indication in the United States [68], and in the European Union substantially manipulated products fall under advanced-therapy legislation [69].

The clinically honest position is therefore conditional interest rather than adoption. Intraosseous orthobiologics may prove a genuine advance for a defined subgroup — most plausibly symptomatic, mechanically driven bone marrow lesions in earlier-stage disease — but that hypothesis is unproven, and resolving it requires placebo-controlled, route-isolating, stage-stratified, MIBO-compliant trials with blinded structural endpoints and honest comparators. Until then, patients should be counseled that symptom relief, where it occurs, is not evidence that the joint has been repaired.

Declarations

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Conflicts of interest

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Author contributions (CRediT)

All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

Not applicable. This article is a narrative review of previously published literature and of publicly accessible clinical trial registry records. It involved no new studies on human participants or animals, no access to identifiable patient data, and no patient recruitment; institutional review board approval and informed consent were therefore not required. All primary studies discussed were the responsibility of their original investigators and institutional review bodies.

Consent for publication

Not applicable. No individual patient data, images, or identifiable details are reported.

Data availability

No new datasets were generated. All evidence supporting the findings of this review is contained within the cited publications and publicly accessible records, each of which is linked in the reference list by DOI, PubMed identifier, ClinicalTrials.gov registration number, or official regulatory-agency URL. The literature search strategy is reported in full in Section 2 so that it can be independently re-executed. The authors' evidence-charting matrix underlying Tables 2 and 3 is available from the corresponding author on reasonable request.

Use of artificial intelligence and AI-assisted technologies

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The authors disclose that an AI-assisted large language model tool was used during manuscript preparation to support organization of retrieved literature, tabular structuring of study characteristics, language editing, drafting, and figure layout. The tool did not generate, analyze, or alter primary data and is not listed as an author.

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