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CURRENT CONCEPTS IN THE MANAGEMENT OF KNEE OSTEOARTHRITIS: BIO-LOGIC THERAPIES IN FOCUS — A NARRATIVE REVIEW

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ABSTRACT

Knee osteoarthritis (KOA) is the most common form of degenerative joint disease and a lead-ing cause of disability worldwide. It is characterized by progressive cartilage degradation, sub-chondral bone remodeling, synovial inflammation, and chronic pain, which together lead to significant functional impairment and reduced quality of life. The global prevalence of KOA is rising in parallel with aging populations and increasing obesity rates, posing a substantial soci-oeconomic burden. In recent years, growing attention has been directed toward biological therapies, which aim to modify disease progression rather than only alleviate symptoms. This narrative review summa-rizes current evidence on the use of platelet-rich plasma (PRP), hyaluronic acid (HA), and mes-enchymal stem/stromal cells (MSCs) for KOA, as well as emerging combination strategies. Literature was identified through PubMed and Scopus searches focusing on randomized trials, systematic reviews, and guideline statements.

Overall, PRP injections demonstrate superior short- to mid-term outcomes compared with HA in pain relief and functional scores, though results vary with preparation methods. HA remains widely used, particularly in early disease, but provides modest benefits. MSC therapies show promise in structural modification and long-term symptom improvement, though heterogeneity of protocols and limited high-quality trials restrict definitive conclusions. Combination and next-generation biologic approaches are under active investigation.

In conclusion, biological therapies represent a rapidly evolving frontier in KOA management. While evidence supports meaningful clinical benefit of PRP and potentially MSCs, lack of standardized protocols and robust long-term trials remain major limitations. Future research should focus on optimization, safety, cost-effectiveness, and integration into clinical guide-lines.

KEYWORDS

Knee, Osteoarthritis, PRP, Hyaluronic Acid, Stem Cells

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Introduction

Knee osteoarthritis (KOA) affects hundreds of millions of people worldwide and accounts for substantial years lived with disability. In most health systems, KOA care remains dominated by symptom management: education, exercise therapy, weight loss, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and—in advanced disease—arthroplasty. While these approaches are essential, they do not directly address the complex biological drivers of cartilage breakdown, subchondral bone remodeling, and synovial inflammation. Accordingly, there has been growing interest in biologic therapies that might restore a healthier joint microenvironment or even stimulate repair.

Interest in biologics coincides with greater recognition that KOA is not a single disease but a spectrum of phenotypes and endotypes. Mechanical overload, metabolic dysregulation, and low-grade inflammation interact over decades to produce heterogeneous symptom trajectories. This heterogeneity likely explains inconsistent outcomes seen with otherwise plausible interventions. A modern review of KOA should therefore examine both biology and therapy, and emphasize how patient selection and protocol details influence results.

This narrative review synthesizes evidence with a practical intention: to equip clinicians and trainees with a coherent framework for integrating biologics into staged, value-based management. We first outline epidemiology and disease burden, then expand on pathophysiology and phenotyping, including imaging and biomarker correlates. We next review HA, PRP, and MSC therapies in depth—mechanisms, protocols, trial evidence, safety, and economics—before proposing an algorithm and a research agenda.

Synovial fibroblasts and macrophages orchestrate low-grade inflammation through cytokine networks (e.g., IL-1β, TNF-α), while adipokines from the infrapatellar fat pad modulate nociception and matrix turnover. Biologic injectables may exert effects by interrupting these circuits and re-establishing homeostatic signaling [1].

At the tissue level, cross-talk between subchondral bone and cartilage appears pivotal. Increased remodeling and vascular channel formation in the subchondral plate facilitate exchange of inflammatory mediators, perpetuating catabolism within cartilage. Bone marrow lesions likely reflect this dysregulated interface and correlate with pain, providing a mechanistic target for both mechanical unloading and biologic therapies [13,3].

Future directions include phenotype-guided care pathways, real-world registries with automatic data capture, and adaptive trials comparing optimized PRP with next-generation cell-free products such as MSC-derived extracellular vesicles.

For payers, standardized documentation of product characteristics and outcomes is pivotal. A minimal dataset including WOMAC/KOOS, time to rescue therapy, and return-to-activity metrics would align clinical care with evidence generation [4].

Implementation science principles matter: structured exercise prescriptions, adherence monitoring, and patient education deliver outsized returns regardless of injectable choice. Embedding PRP within such programs improves value by amplifying functional gains [29].

Health-economic value depends on achieving durable symptom control and functional gains that delay or reduce the need for surgery. Cost-utility models are most favorable for PRP in younger, active patients with mild-to-moderate disease when injections are embedded within a comprehensive non-operative pathway emphasizing exercise therapy and weight management. Robust real-world registries with standardized product descriptors would materially inform coverage policies [4].

Methods: Narrative Review Approach

The practical algorithm proposed integrates phenotype-informed selection, staged re-assessment at 8–12 weeks, and escalation to surgical options when biologics and conservative measures fail to meet patient goals.

Key limitations include the rapid evolution of PRP preparation technologies, heterogeneous MSC products, and publication bias favoring positive findings. We mitigated these risks by prioritizing high-quality trials and guideline statements and by explicitly describing areas of uncertainty [6].

Finally, there is a need to harmonize definitions of treatment response. Using a combination of absolute and relative change thresholds on validated scales (e.g., ≥15-20 point improvement on WOMAC pain) would improve cross-study comparability.

Another limitation is ecological validity: trials often exclude patients with significant malalignment, multiple comorbidities, or occupational knee loading. These real-world factors strongly influence outcomes. Pragmatic trials and registry-based randomization could better capture effectiveness in routine practice ([29]).

Publication bias remains a nontrivial concern, particularly for newer interventions where small positive studies are more likely to be reported than neutral or negative results. Prospective trial registration, adherence to CONSORT reporting, and full disclosure of funding sources help mitigate these issues but are inconsistently observed across the literature [4].

As a narrative review, our synthesis emphasizes clinical applicability and triangulates evidence from randomized trials, meta-analyses, and guidelines. We highlight convergent findings across designs rather than pooling effect sizes, which can be misleading when protocols and populations vary substantially [4].

We searched PubMed and Google Scholar without date restriction, prioritizing publications from the last 10–12 years. Study types emphasized included randomized controlled trials (RCTs), systematic reviews and meta-analyses, large observational cohorts, registry analyses, and guidelines or position statements from the Osteoarthritis Research Society International (OARSI), American Academy of Orthopaedic Surgeons (AAOS), and American College of Rheumatology/Arthritis Foundation (ACR/AF). Key terms included “knee osteoarthritis,” “hyaluronic acid,” “viscosupplementation,” “platelet-rich plasma,” “PRP,” “mesenchymal stem cell,” “MSC,” “stem cell concentrate,” “exercise therapy,” and “arthroplasty.”

The methodology for this review is summarized in Tables 1 and 2.

Table 1. Randomized trials of PRP vs HA.

Study (Year)	n (PRP/Comp)	Comparator	Protocol (inj#)	Follow-up	Key Outcomes
Dai et al.	154/148	HA	3 injections	6–12 mo	PRP > HA in pain/function
Belk et al.	—	HA/meta-analysis	1–3 injections	3–12 mo	PRP superior short- to mid-term
Campbell et al.	—	Multiple comps	Varied	Up to 12 mo	Favors PRP; heterogeneity noted
Anz et al.	90/90	BMAC	Single	12 mo	Equivalent at 1 year
Laudy et al.	—	Placebo/HA	Varied	Up to 12 mo	PRP benefit; protocol variability

Key characteristics of included studies are detailed in Table 2.

Table 2. Hyaluronic acid formulations and clinical outcomes.

Study (Year)	Product	n	Follow-up	Key Outcomes
Freitag et al.	Expanded MSC (BM)	102	24 mo	Improved pain/function; MRI signals
Koh et al.	Adipose-derived MSC	24	24 mo	Symptom improvement; cartilage signal
Shapiro et al.	BMAC	25	12 mo	Improved symptoms vs placebo
Chahla et al. (review)	BMAC	—	—	Systematic review: favorable but heterogeneous
Anz et al.	BMAC vs PRP	180	12 mo	Equivalence at 1 year

As a narrative review, we did not preregister a protocol or perform PRISMA-concordant selection. Instead, we curated studies for methodological rigor, clinical relevance, and recency. Where evidence was conflicting or heterogeneous, we highlight areas of consensus and uncertainty to guide shared decision-making.

Global estimates from the Global Burden of Disease Study 2019 suggest that knee osteoarthritis accounts for over 40 million years lived with disability worldwide, with the steepest relative growth observed in low- and middle-income countries. Rising obesity prevalence in China and India is predicted to double KOA incidence by 2040, while in Europe and North America, aging demographics remain the dominant driver. Interestingly, regional occupational exposures—such as squatting in agrarian communities—contribute to phenotypic variation, underlining the need for context-specific guidelines. These international comparisons highlight the importance of tailoring prevention and management strategies to local health system resources and population risk profiles.

Epidemiology and Burden

KOA prevalence rises with age and is higher in women. Obesity is a dominant modifiable risk factor, magnifying knee joint load and amplifying systemic inflammation. Prior injuries, particularly anterior cruciate ligament and meniscal pathology, predispose to post-traumatic osteoarthritis. Manual occupations involving kneeling, squatting, or heavy lifting confer additional risk. The socioeconomic burden includes direct medical costs and indirect costs due to productivity loss, disability, and caregiver demands.

Beyond classical cartilage and synovial pathology, emerging work highlights the role of immunosenescence. Aging immune cells exhibit a senescence-associated secretory phenotype that perpetuates low-grade inflammation, sometimes termed "inflammaging." Neuroinflammatory changes within dorsal root ganglia and altered central pain processing further contribute to symptom severity disproportionate to radiographic findings. Moreover, gut microbiome composition has been linked to systemic inflammation and OA progression, suggesting a potential role for diet or microbiome-targeted interventions in future multimodal strategies. Collectively, these insights reinforce that KOA is not a single disease entity but a complex, systemic disorder with local and systemic drivers.

Importantly, KOA progression is not linear. Many patients experience episodic flares of synovitis and pain superimposed on a slowly evolving structural process. This temporal variability underscores the need for periodic reassessment and adaptive treatment plans.

Pathophysiology and Phenotypes

Pathogenesis reflects an interplay of biomechanical and inflammatory processes across joint tissues. Articular cartilage, rich in type II collagen and aggrecan, distributes load and minimizes friction. With aging and overload, chondrocytes exhibit senescence, mitochondrial dysfunction, and impaired autophagy, shifting toward a catabolic phenotype that elevates matrix metalloproteinases (MMPs) and aggrecanases (ADAMTS). Concurrently, synovium develops low-grade inflammation, secreting cytokines such as IL-1β and TNF-α that further suppress anabolic signaling.

Artificial intelligence (AI) tools applied to radiographs and MRI scans now enable automated quantification of joint space width, cartilage texture, and bone marrow lesions, often surpassing human reproducibility. Multi-omics biomarker research—including metabolomics, proteomics, and transcriptomics—has identified candidate panels that may discriminate fast vs slow progressors, although none are yet clinically validated. Integration of imaging and biomarker data into machine learning models could allow prediction of biologic responsiveness, a critical step toward precision OA therapy. These advances promise to bridge the gap between traditional radiographic grading and clinically relevant phenotyping.

Subchondral bone thickens and forms bone marrow lesions that correlate with pain and predict progression. Crosstalk between subchondral bone and cartilage, mediated by vascular channels and cytokines, may perpetuate degeneration. The infrapatellar fat pad and periarticular adipose tissue release adipokines that modulate inflammation and nociception.

Phenotypically, patients may be biomechanical-dominant (malalignment, meniscal deficiency), inflammatory-dominant (recurrent effusions, high C-reactive protein within normal range), or metabolic-dominant (obesity, insulin resistance). Many patients exhibit mixed features. Recognizing these patterns helps align expectations for biologic therapies.

Imaging and Biomarkers for Phenotyping

A practical clinical phenotype heuristic incorporates alignment (varus/valgus), synovitis (clinical or imaging), body mass index, and activity goals to guide selection among HA, PRP, and mechanical interventions.

Candidate serum and synovial biomarkers—including COMP, CRP within normal range, and specific collagen neoepitopes—could enrich clinical trials by identifying endotypes. Harmonized collection and reporting standards will accelerate translation to practice [1].

Beyond structural grading, identifying inflammatory activity is clinically useful. Ultrasound-detected synovial hypertrophy and Doppler signal correlate with pain flares, suggesting a window in which anti-inflammatory biologics such as PRP may be particularly helpful. Bone marrow lesions on MRI track with pain and progression, highlighting the importance of biomechanics and load management [13].

Radiography remains first-line to document joint-space loss and osteophytes; however, structural severity explains only part of pain variance. MRI provides comprehensive evaluation of cartilage, menisci, synovitis, and subchondral bone. Quantitative MRI techniques—such as T2 mapping and dGEMRIC—offer research tools for cartilage composition. Ultrasound is valuable for detecting effusions and synovitis and for guiding injections. Biomarkers (e.g., CRP, cartilage oligomeric matrix protein, neoepitope fragments) may eventually stratify patients for biologic responsiveness.

Because biologics act primarily on the joint microenvironment, imaging and biomarker phenotyping may identify responders. For example, PRP appears most effective in earlier radiographic grades with active synovial inflammation but preserved cartilage thickness, whereas MSC approaches may suit focal cartilage loss with relatively contained mechanical derangement.

Hyaluronic Acid (Viscosupplementation)

Hyaluronic acid (HA) is a high-molecular-weight glycosaminoglycan that contributes to the viscoelastic and lubricating properties of synovial fluid. In KOA, synovial HA is reduced in concentration and molecular weight, impairing lubrication and shock absorption. Intra-articular HA, termed viscosupplementation, aims to restore these properties and exert anti-inflammatory effects via CD44-mediated pathways.

Formulations vary by molecular weight (low, intermediate, high) and cross-linking, with dosing schedules from one to five injections. Clinical trials report heterogeneous outcomes. Meta-analyses often find small to moderate effect sizes versus placebo, with greater benefit in less advanced KOA and high-molecular-weight products. However, high-quality, sham-controlled trials sometimes show minimal differences, leading to divergent guideline positions.

Safety is favorable. The most frequent adverse events are transient injection-site reactions or flares. Pseudoseptic reactions are rare and self-limited. Compared with corticosteroids, HA has a slower onset but potentially longer tail of benefit. Cost considerations and patient preference frequently influence selection.

From a biological standpoint, HA likely reduces synovial inflammation and boundary friction, improves mechanotransduction at the cartilage surface, and may modulate nociception by altering joint fluid rheology. These mechanisms may explain selective benefit in phenotypes with synovial irritation rather than gross mechanical derangement.

Platelet-Rich Plasma (PRP)

Platelet-rich plasma (PRP) is an autologous concentrate typically achieving a 3–5-fold increase in platelet count over baseline whole blood. After activation, platelets release a cocktail of growth factors and cytokines—including PDGF, TGF-β, VEGF, IGF-1, HGF, and SDF-1—that can dampen synovial inflammation, enhance matrix synthesis, and influence peripheral nociception. PRP may also modulate macrophage polarization toward an anti-inflammatory phenotype.

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Preparation protocols vary widely: single-spin versus double-spin centrifugation, leukocyte-rich (LR-PRP) versus leukocyte-poor (LP-PRP), activation with calcium chloride or thrombin versus in situ activation, and use of anticoagulants such as citrate. Clinical regimens range from a single injection to series of two or three injections spaced 1–4 weeks apart. Such heterogeneity complicates meta-analysis and guideline formulation.

Across multiple RCTs and meta-analyses, PRP demonstrates superior improvement in pain and function over placebo and HA in mild-to-moderate KOA, with effect sizes typically peaking at 3–6 months and persisting up to 12 months in many cohorts. Benefits appear greatest in younger patients with lower Kellgren–Lawrence grade and shorter symptom duration. Comparisons with corticosteroids suggest a slower onset but longer durability for PRP.

Safety is favorable given autologous origin. Post-injection soreness and swelling are common and self-limited; serious adverse events are rare. Leukocyte content may influence tolerability, with LP-PRP associated with fewer inflammatory flares, though head-to-head evidence is limited.

Outstanding questions include optimal platelet concentration, the role of leukocytes, activation strategies, and injection number and spacing. Standardized reporting—detailing baseline platelet counts, fold concentration, leukocyte content, and final volume—would substantially improve interpretability.

Key research gaps include head-to-head trials of LP-PRP vs LR-PRP at fixed platelet doses, standardized responder definitions incorporating function and quality-of-life, and biomarker-imaging correlates that predict which endotypes derive the greatest benefit [1,12].

Adverse events after PRP are predominantly transient pain flares and effusions that resolve with conservative care. Infection is rare with standard asepsis. Reported serious events are exceedingly uncommon in published RCTs and cohort studies, supporting the overall safety of the modality [14].

Longitudinal registries indicate that responders to an initial PRP series may maintain benefits with a single booster injection at 9–12 months, though controlled data are limited. From a pathway perspective, PRP integrates best when layered atop a robust exercise program and weight management, rather than replacing these foundational elements [4].

Clinical technique matters: ultrasound guidance can improve accuracy in challenging knees, while peri-procedural counseling about 24–48 hours of rest, followed by a graded return to activity, appears to reduce post-injection discomfort and sets expectations. Concomitant use of NSAIDs around the time of injection is debated; many protocols avoid them for several days to minimize interference with platelet function [6].

Evidence synthesis consistently demonstrates that PRP outperforms HA for pain and function in mild-to-moderate KOA, particularly at the 6- to 12-month horizon. The magnitude of benefit tends to be moderate and clinically meaningful, with the largest gains seen in younger patients and earlier radiographic grades. Heterogeneity remains substantial, yet sensitivity analyses restricting to LP-PRP and multi-dose protocols often show more coherent signals [15,16].

Recent head-to-head trials indicate that leukocyte-poor PRP provides more consistent symptom improvement and fewer post-injection flares than leukocyte-rich formulations. Mechanistically, PRP reduces nuclear factor-κB (NF-κB) activation in synovial macrophages and increases expression of lubricin, a key boundary lubricant, which may explain both anti-inflammatory and chondroprotective effects. A 2023 multicenter RCT with 480 participants demonstrated clinically meaningful improvement in KOOS pain at 12 months with PRP versus saline, reinforcing its role as a front-line biologic for early KOA. Despite these encouraging findings, further standardization of preparation and reporting remains essential for cross-study synthesis and payer acceptance.

Mechanistic rationale for PRP includes modulation of synovial macrophage phenotype, reduction in NF-κB signaling, and promotion of chondrocyte matrix synthesis via PDGF, TGF-β, and IGF-1. Leukocyte-poor formulations may attenuate pro-inflammatory cytokine spikes compared with leukocyte-rich mixes, which has practical relevance for tolerability in sensitive joints. Moreover, platelet alpha-granules release occurs within hours to days, suggesting that a series of injections could maintain a favorable intra-articular milieu during the critical healing window [17,14].

Dosing strategy is another source of variance. Many positive trials employed a short series of two to three injections spaced one to two weeks apart, while others used a single injection paradigm. Although head-to-head dose-response RCTs are scarce, pragmatic protocols frequently report better durability with multi-dose schedules, particularly in earlier Kellgren–Lawrence grades. Establishing a standard dosing framework would strengthen meta-analytic synthesis and payer evaluations [15,16].

Protocol heterogeneity and reporting transparency remain central obstacles to interpreting clinical outcomes for platelet-rich plasma (PRP) (see Protocol Standardization and Reporting - Deep Dive).

Mesenchymal Stem Cells (MSC)

Mesenchymal stem cell (MSC) therapies encompass a continuum from minimally manipulated concentrates—such as bone marrow aspirate concentrate (BMAC) and micro-fragmented adipose tissue—to culture-expanded products derived from bone marrow, adipose, or perinatal tissues. Mechanistically, MSCs exert paracrine immunomodulation and secrete trophic factors that may enhance endogenous repair, reduce synovial inflammation, and promote cartilage matrix synthesis.

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Early-phase clinical trials and prospective cohorts report improvements in pain and function and, in some studies, MRI signals suggestive of cartilage quality enhancement. However, variability in cell source, processing methods, cell dose, and delivery techniques (simple intra-articular injection versus combination with scaffolds) limits generalizability. Regulatory frameworks differ across jurisdictions, affecting availability and trial design.

Safety data are encouraging overall, with transient local reactions most common and serious events rare; nonetheless, long-term surveillance is essential. At present, MSC approaches should be considered investigational outside trials or registries. Shared decision-making must emphasize uncertainties, potential costs, and realistic expectations for symptom relief versus structural modification.

Regulatory frameworks strongly influence MSC availability: while culture-expanded cells are restricted to trials in the United States and European Union, several Asian countries permit clinical use under hospital exemptions. Costs vary dramatically—from under $2,000 for minimally manipulated adipose products to over $10,000 for culture-expanded cells—posing equity challenges. Long-term registry data are needed to justify coverage decisions and clarify durability of effect. Additionally, differences in cell source, viability, and dosing strategies underscore the need for harmonized manufacturing standards if MSCs are to transition from experimental therapy to mainstream care.

Combination and Emerging Biologic Strategies

Extracellular vesicles derived from MSCs (exosomes) have emerged as a promising cell-free biologic, delivering microRNAs and proteins that recapitulate many MSC paracrine effects with superior safety and scalability. Early phase I trials suggest favorable tolerability and signal of efficacy. Similarly, gene therapy approaches targeting IL-1 receptor antagonism or enhancing TGF-β signaling are under investigation. Bioengineered 3D scaffolds seeded with MSCs or chondrocytes represent another frontier, offering structural support for focal cartilage repair within the broader OA joint. These novel strategies illustrate the rapid pace of innovation in biologic therapeutics.

Combination strategies seek synergy—for example, PRP plus HA to couple anti-inflammatory growth factors with lubrication, or MSCs delivered with scaffolds to enhance retention and chondrogenesis. Preclinical data and small clinical series show promise, but robust RCTs are scarce. Other emerging modalities include extracellular vesicles (exosomes) derived from MSCs, which may capture key paracrine effects in a cell-free product with favorable safety and logistics.

Gene therapy approaches targeting catabolic mediators (e.g., IL-1 receptor antagonism) or enhancing anabolic signaling are in early-stage investigation. As delivery vectors and safety profiles improve, these strategies might complement or partially replace cell-based approaches.

Safety, Counseling, and Regulatory Considerations

Adverse events across biologic injections are generally mild and transient, dominated by post-injection pain and swelling. Infection risk is low with standard asepsis. For HA, pseudoseptic reactions are rare; for PRP and MSC, systemic events are uncommon. Clinicians should counsel patients regarding temporary activity modification after injection and warning signs that warrant evaluation.

Regulatory oversight varies: viscosupplementation products are approved in many regions; PRP is typically regulated as a minimally manipulated autologous blood product; MSC therapies may require stringent regulatory approval when culture-expanded. These frameworks influence access, cost, and standardization, and should be considered when counseling patients.

Implementation and Health Economics

Implentation and cost-effectiveness of biologic therapies remain major issues. Comparative data are summarized in tables 3 and 4.

Implementation and cost-effectiveness are summarized in Tables 3 and 4; narrative interpretation follows below.

Table 3. Guideline positions across societies.

Society	Core Non-Pharm	NSAIDs	IA Steroids	HA	PRP	MSC
OARSI (2019)	Strongly recommended	Use as tolerated	Conditional/short-term	Conditional/select	Insufficient/variable	Insufficient
AAOS (2021)	Foundational	Risk-stratified	Short-term option	Against routine use	Insufficient evidence	Investigational
ACR/AF (2020)	Strongly recommended	Topical strong; oral conditional	Conditional for flares	Conditional/low certainty	No strong rec.	Not recommended outside trials

Table 4. Cost and implementation considerations.

Parameter	Options	Clinical Considerations
Platelet fold-increase	2–7× baseline	Dose-response unclear; >5× may not add benefit
Leukocytes	LR-PRP vs LP-PRP	LP-PRP may reduce post-injection flares
Activation	CaCl2/thrombin vs in situ	Influences growth factor release kinetics
Injections	1 vs 2–3	Series (2–3) often used for durability
Interval	1–4 weeks	Commonly 2-week spacing
Volume	3–8 mL	Patient comfort; joint capacity

Health system context shapes uptake: in many European countries, PRP remains an out-of-pocket expense, whereas in parts of Asia it is partially reimbursed under regenerative medicine frameworks. Cost-utility analyses converge on PRP being most favorable in younger, active patients where surgical delay yields high economic savings. MSC therapies currently lack sufficient cost-effectiveness data, and most insurers classify them as experimental. Transparent cost reporting in trials and registries will be essential to guide equitable access. The future of biologic adoption will therefore depend not only on efficacy and safety, but also on economic and policy frameworks that ensure sustainability.

From a health-economic perspective, high-value care begins with exercise therapy and weight loss, which deliver consistent benefits at low cost. Biologic injections incur procedural and product costs that vary widely. Cost-utility for PRP is most favorable in younger, active patients with early-stage disease when injections defer or reduce the need for surgery. HA may be cost-effective in selected phenotypes, whereas MSC therapies presently lack robust cost-effectiveness data.

Payers increasingly seek standardized protocols and registry-based outcomes to support coverage decisions. Clinicians can facilitate learning by participating in registries and reporting detailed preparation parameters and outcomes.

Practical Algorithm for Integrating Biologics

Patient selection benefits from a phenotype-informed lens. Individuals with earlier radiographic changes, intermittent synovitis, and preserved alignment may experience greater benefit from PRP, whereas those with lubrication-dominant symptoms and activity-related crepitus can reasonably trial HA. In the presence of substantial malalignment or meniscal deficiency, mechanical optimization via bracing or osteotomy may be prerequisite to any biologic intervention [6].

A pragmatic integration strategy is phenotype-informed. All patients begin with education, exercise therapy, and weight optimization. For mild-to-moderate symptoms with earlier radiographic grade and synovial features, PRP offers the best balance of safety and mid-term benefit; HA may be considered when lubrication and synovial comfort are primary goals or when PRP is unavailable. Short-course corticosteroids are reserved for inflammatory flares.

In patients with focal malalignment or mechanical overload, bracing and targeted physiotherapy are prioritized; surgical realignment (HTO) may be appropriate before or instead of biologics. When conservative measures and injectables fail, timely referral for arthroplasty avoids prolonged disability. Throughout, reassessment at 8–12 weeks ensures course correction based on response.

Protocol Standardization and Reporting — Deep Dive

Deep-dive considerations for biologic protocols emphasize transparent reporting of baseline hematology, preparation steps, and final injectate characteristics. Clinicians should document centrifugation force and time, platelet and leukocyte counts before and after processing, activation methods, and injectate volume. In research settings, aligning outcomes to core knee OA sets (pain, function, quality of life) and including objective measures (e.g., imaging or biomarker panels) will permit more informative synthesis and facilitate phenotype-guided analyses. Standard operating procedures and proficiency training reduce variability and may improve real-world effectiveness. Patient education about expectations, timelines of benefit, and the continued importance of exercise and weight management is critical for durable outcomes.

Minimum reporting items should include baseline whole-blood platelet and leukocyte counts, the fold-increase achieved in the final product, the presence or absence of leukocytes (LP-PRP vs LR-PRP), activation method (exogenous vs in situ), anticoagulant used, and injected volume. These items materially influence the biological payload released after injection and plausibly explain the variability observed across trials [17,14].

Limitations

This narrative review is subject to selection bias and cannot provide pooled effect estimates. Rapidly evolving literature—particularly for PRP protocols and MSC products—means that new evidence may refine recommendations. Future work should prioritize standardized reporting, long-term outcomes, and phenotype-guided trials.

Guideline Landscape and Areas of Consensus/Disagreement

Guideline positions remain polarized: the American Academy of Orthopaedic Surgeons (AAOS) issued a strong recommendation against routine HA use, citing minimal benefit over placebo in sham-controlled trials, whereas the Osteoarthritis Research Society International (OARSI) and the European Society for Clinical and Economic Aspects of Osteoporosis and OA (ESCEO) endorse conditional use in selected phenotypes. This divergence reflects heterogeneity in trial design and outcome measures. Clinicians must reconcile these conflicting recommendations by focusing on patient-centered outcomes, such as short-term symptom relief and return to activity. Importantly, understanding formulation differences (molecular weight, cross-linking) is key to interpreting variable trial outcomes and aligning therapy with patient phenotype.

For cost and implementation details, see Implementation and Health Economics

Checklist for PRP Protocol Reporting (for Clinicians and Researchers)

• Safety: adverse event definitions, monitoring period, management of post-injection flares.

• Outcomes: standardized instruments (e.g., WOMAC, KOOS), time points (e.g., 3, 6, 12 months), return-to-activity metrics, rescue therapy documentation.

• Concomitant care: NSAID avoidance policy, activity modification plan, structured exercise program.

• Injection protocol: number of injections, interval, volume per injection, guidance (landmark vs ultrasound), target compartment(s).

• Final injectate characteristics: platelet fold-increase, leukocyte status (LP vs LR), red blood cell contamination, activation method, anticoagulant, volume.

• Processing details: device/kit, centrifugation force (g) and duration (min), single vs double spin.

• Baseline hematology: whole-blood platelet and leukocyte counts; hemoglobin.

As standardization advances and registries mature, the field can move toward precision care wherein patients are matched to the biologic most likely to help them at a particular disease stage. Such a framework aligns clinical outcomes with value, by minimizing non-response and focusing resources where the probability of meaningful improvement is highest.

In summary, biologic therapies are best conceptualized not as stand-alone cures but as components of a multimodal pathway that begins with education, exercise, and weight management. PRP currently offers the most reproducible symptom benefit for appropriately selected patients, HA provides a safe option for lubrication-dominant pain, and MSC interventions remain promising yet investigational. Transparent protocol reporting and phenotype-guided selection are the levers most likely to raise the average clinical yield [4,6].

Clinical Scenarios and Decision-Making

Scenario 1 (Younger, active, early KOA): A 48-year-old runner with KL-2 medial compartment KOA, intermittent effusions, BMI 27, and mild varus alignment. Initial management emphasizes neuromuscular exercise and weight optimization. Given inflammatory flares and preserved cartilage thickness, a series of two PRP injections two weeks apart is reasonable. Expected trajectory: gradual improvement by week 6–8, peak at 3–6 months, with consideration of a booster at 9–12 months if decline begins [15,14].

Scenario 2 (Lubrication-dominant symptoms): A 62-year-old office worker with KL-3 KOA, no large effusions, prominent crepitus, and activity-related stiffness. Adherence to strengthening and aerobic exercise remains critical. HA may be trialed for short- to mid-term comfort with a favorable safety profile; PRP can be discussed but expectations moderated, as benefits are less consistent in advanced radiographic disease [11,10].

Scenario 3 (Mechanical overload): A 55-year-old tradesperson with KL-3 varus KOA, meniscal deficiency, and tibiofemoral malalignment. Bracing and targeted physiotherapy are prioritized; if disability persists, high tibial osteotomy may address the root cause. Biologic injections are adjunctive at best and unlikely to compensate for sustained malalignment [6].

Conclusions

Biologic therapies occupy an increasingly important middle space between conservative care and surgery in KOA. Among available options, PRP has the most consistent clinical signal for symptom improvement in mild-to-moderate disease; HA offers a safe, selective option with mixed efficacy; and MSC therapies remain promising yet investigational. Success hinges on careful patient selection, protocol transparency, and integration with high-value foundational care.

A precision, multimodal future—grounded in phenotype and endotype assessment, standardized biologic preparations, and rigorous registries—offers the best path to meaningful, durable improvement for patients with knee osteoarthritis.

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Conflicts of Interest

The author declares no conflicts of interest related to this manuscript.

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