QUALITY IN SPORT
eISSN 2450-3118 · Open Access · Peer-reviewed
apcz.umk.pl/QS Nicolaus Copernicus University in Toruń

SZCZEPANOWSKI, Tomasz Adam, ZAWADZKI, Bartosz, KORNACKA, Natalia, ZWARDOŃ, Jakub, NAJA, Katarzyna, REWEKANT, Miłosz, WALCZAK, Zuzanna, ŚWIERCZEK, Anna, GAJKOWSKI, Aleksander and BEDNARSKI, Krzysztof. Hyaluronic Acid Versus Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis: A Literature Review. Quality in Sport. 2026;68:74364. https://doi.org/10.12775/QS.2026.68.74364

ARTICLE TIMELINE
Received: 15.07.2026. Revised: 02.08.2026. Accepted: 02.08.2026. Published: 11.08.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

Hyaluronic Acid Versus Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis: A Literature Review

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Abstract

Background: Knee osteoarthritis (KOA) is a prevalent chronic degenerative condition and a leading cause of global disability. Intra-articular injections, specifically Hyaluronic Acid (HA) and Platelet-Rich Plasma (PRP), serve as critical non-surgical interventions when standard conservative therapies fail. Despite their widespread use, there is no universal consensus on which modality offers superior clinical outcomes.

Aim: This literature review aims to systematically evaluate and synthesize current evidence from 2020 to 2026 comparing the efficacy and safety of intra-articular HA versus PRP for the treatment of knee osteoarthritis.

Methodology: A review was conducted using the PubMed database, focusing on peer-reviewed literature from recent meta-analyses, systematic reviews, and randomized controlled trials published between 2020 and 2026.

Results: The findings indicate that while both HA and PRP are safe and effective in the short term (1–3 months), PRP demonstrates statistically and clinically superior results in terms of pain reduction and functional improvement at mid-to-long-term follow-ups (6–12 months). Long-term studies suggest that PRP provides a more sustained therapeutic effect, with significantly higher joint survival rates compared to HA over 7 years. Furthermore, emerging evidence identifies PRP+HA combination therapy as a potentially optimal strategy, ranking highest for long-term efficacy by leveraging both mechanical lubrication and biological modulation. Both treatments maintain comparable safety profiles, characterized primarily by transient, local adverse events.

Conclusion: PRP represents a superior conservative treatment for mild-to-moderate KOA compared to HA, particularly for patients seeking durable symptomatic relief. For clinical practice, PRP or combination therapy is recommended to achieve optimal long-term outcomes and potentially delay the progression toward invasive surgical interventions.

Keywords: knee osteoarthritis, platelet-rich plasma, hyaluronic acid, viscosupplementation, orthobiologics, intra-articular injections

1. Introduction

Knee osteoarthritis (KOA) represents one of the most significant challenges to global health systems in the 21st century, characterized by a progressive and irreversible deterioration of articular cartilage coupled with narrowing of the joint space [1,5]. It is widely recognized as the most common chronic degenerative joint condition within the aging population, accounting for a staggering number of disabilities on a global scale [34]. Estimates suggest that osteoarthritis affects approximately 3.3% to 3.6% of the global population, positioning it as the 11th most debilitating disease worldwide [34]. Among individuals over the age of 40, the global prevalence of KOA is approximately 23%, a figure that continues to rise as life expectancy increases and obesity rates climb [8, 9]. The demographic distribution of the disease reveals that women are disproportionately affected; after the age of 60, approximately 13% of women develop symptomatic KOA compared to 10% of men [34].

The socioeconomic impact of KOA is profound, placing an immense health burden on patients,

their families, and society at large [8]. Patients typically suffer from persistent joint pain, stiffness, swelling, and significant mobility limitations, all of which culminate in a substantial reduction in quality of life [5,8]. Roughly 80% of patients diagnosed with osteoarthritis experience movement limitations, and one in four are rendered unable to perform essential activities of daily living [8]. Beyond the physical debilitation, the economic costs associated with lost productivity, long-term medical care, and the eventual necessity for high-cost surgical interventions such as total knee arthroplasty contribute to the classification of KOA as a "serious disease" by international research societies [9, 34].

The primary objectives in the management of KOA are the reduction of pain and the restoration of joint function [5,8]. Standard conservative management typically begins with non-surgical interventions, including lifestyle modifications such as weight loss, physical therapy, and pharmacological approaches [9,34]. While non-pharmacological treatments like diet and exercise are highly recommended, they are frequently characterized by poor patient compliance [1]. Consequently, many patients rely on first-line pharmacological agents, specifically non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics [1,34]. However, the chronic administration of NSAIDs is severely limited by a range of systemic side effects, including gastrointestinal bleeding, hepatotoxicity, and cardiovascular risks [1,34]. Furthermore, current oral pharmacological therapies are largely palliative and have not been proven to alter the underlying progression of the disease [1].

When these initial strategies fail to provide adequate relief, intra-articular injections (IAIs) serve as a critical component of non-surgical therapy [5,9]. The rationale for the direct local administration of therapeutic products into the joint cavity is rooted in the ability to maximize the concentration of the agent at the site of degeneration while simultaneously minimizing systemic exposure and related adverse effects [9]. As a minimally invasive approach, IAIs offer a favorable safety profile and the potential to significantly improve joint function and reduce short-term pain, thereby delaying the requirement for more invasive and expensive prosthetic replacement surgery [5,9]. Among the most utilized injectable options in clinical practice are Hyaluronic Acid (HA) and Platelet-Rich Plasma (PRP) [3,34].

Hyaluronic Acid (HA) is a naturally occurring high-molecular-weight glycosaminoglycan that is a fundamental constituent of healthy synovial fluid and articular cartilage [1,5]. Produced by chondrocytes, synoviocytes, and fibroblasts, HA is responsible for the viscoelastic and lubricating properties of the knee joint, acting as both a lubricant and a shock absorber during movement [1,5]. In the osteoarthritic knee, the concentration and molecular weight of endogenous HA are significantly reduced, leading to impaired joint mechanics and increased

cartilage damage [1,8]. IAIs of exogenous HA, often referred to as viscosupplementation, aim to restore joint lubrication, inhibit pain transmission through interactions with inflammatory mediators, and potentially reduce the apoptosis of osteoarthritic chondrocytes [1,8]. HA has been widely recommended by various international guidelines, including the American College of Rheumatology in 2012, for the management of KOA symptoms [1].

Platelet-Rich Plasma (PRP) is an autologous blood derivative that has emerged as a promising orthobiologic therapy designed to modulate the intra-articular environment [3,9]. PRP is obtained by centrifuging a patient's own peripheral blood to concentrate platelets within a small volume of plasma [8]. The therapeutic potential of PRP lies in the alpha granules of the platelets, which serve as a reservoir for a cocktail of bioactive molecules, including growth factors (such as PDGF, VEGF, EGF, bFGF, and TGF-β1), cytokines, and chemokines [3,34]. When injected into the joint, these growth factors are believed to stimulate mesenchymal stem cell migration, promote chondrocyte proliferation, and regulate inflammatory pathways, thereby potentially facilitating tissue repair and regenerating articular structures [1,5]. Because it is an autologous product, PRP carries a minimal risk of immune reactions or the transmission of infectious diseases, making it a safe alternative to traditional pharmaceuticals [1,3].

Despite the widespread clinical use of both HA and PRP, a vigorous debate remains within the medical community regarding which therapy provides superior clinical outcomes for patients with KOA [8]. Some randomized controlled trials (RCTs) have indicated that PRP provides statistically and clinically significant improvements in pain and function compared to HA, particularly at long-term follow-ups of 6 to 12 months [1,3]. For example, some meta-analyses suggest that the benefits of PRP exceed the mere placebo effect and offer longer-lasting symptomatic relief than viscosupplementation [1,3]. Conversely, other high-level studies have failed to demonstrate a clear superiority for PRP, reporting clinical improvements that largely overlap with those offered by HA [1,3].

This lack of consensus is further reflected in the conflicting recommendations issued by major international scientific societies [9]. While some guidelines afford HA a moderate level of recommendation, orthobiologics like PRP are often not recommended or are strongly advised against due to perceived insufficient evidence and a lack of standardization in preparation methods [9]. However, recent literature trends suggest a shift, with the volume of research focusing on PRP and other orthobiologics growing at a much faster rate than studies on traditional injections [9].

The primary aim of this literature review is to systematically evaluate the current body of evidence comparing the efficacy and safety of intra-articular Hyaluronic Acid versus Platelet-

Rich Plasma for the treatment of knee osteoarthritis [1,8]. By analyzing primary outcome measures—including pain relief, functional recovery, and adverse event rates—this review seeks to provide a comprehensive and updated synthesis of the literature [5,8]. This investigation is essential for clinicians and patients to make informed decisions and to identify the optimal treatment protocols in an evolving therapeutic landscape [8].

2. Methodology

A systematic search of the electronic database was performed using PubMed. The search was restricted to articles published in the English language within the last six years (2020–2026) to ensure that the findings reflect the most contemporary clinical protocols and meta-analytical techniques. The search utilized specific key words such as: knee osteoarthritis, platelet-rich plasma, hyaluronic acid, viscosupplementation, orthobiologics, intra-articular injections. Additionally, the reference lists of the identified meta-analyses and systematic reviews were manually screened to identify any further relevant studies that may have been omitted during the electronic search phase.

3. Mechanisms of Action: HA and PRP in Knee Osteoarthritis

Knee osteoarthritis (KOA) is a complex, progressive degenerative disease that extends beyond simple "wear and tear" of the cartilage to involve the entire joint apparatus, including the tibiofemoral and patellofemoral joints, subchondral bone, and adjacent soft tissues [13]. The hallmark of KOA pathophysiology is the disruption of joint homeostasis, characterized by a multifaceted interplay between degenerative changes in articular cartilage and acute or chronic synovial inflammation [28]. In the healthy joint, the synovium and cartilage maintain a balanced metabolic environment; however, in KOA, this balance shifts toward catabolism [28].

Synovial inflammation, or synovitis, is increasingly recognized as a primary driver of disease progression, characterized by mononuclear cell infiltration and the production of a cascade of inflammatory mediators [28]. Key pro-inflammatory cytokines, specifically Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1β (IL-1β), and Interleukin-6 (IL-6), are significantly elevated in the synovial fluid of affected joints [28]. These cytokines stimulate chondrocytes and synoviocytes to produce matrix metalloproteinases (MMPs) and prostaglandins, which actively degrade the cartilage extracellular matrix while simultaneously inhibiting the synthesis

of essential type II collagen and proteoglycans [28]. This inflammatory environment, coupled with a decrease in synovial fluid viscosity, leads to accelerated joint structure destruction and persistent pathological pain [28].

3.1 Mechanism of Action: Hyaluronic Acid

Hyaluronic acid (HA) is a high-molecular-weight glycosaminoglycan that serves as a fundamental constituent of the extracellular matrix of articular cartilage and is the primary component responsible for the viscoelastic properties of synovial fluid [2,13]. In the context of KOA management, intra-articular HA injections—known as viscosupplementation—aim to restore the rheological properties of the synovial fluid, which are typically compromised by the reduced concentration and molecular weight of endogenous HA in diseased joints [2,13].

Mechanically, HA acts as both a lubricant and a shock absorber, facilitating smooth joint movement and protecting the articular surfaces from friction-induced damage during loading [9,13]. HA formulations vary in molecular weight and concentration, which directly influence their joint residence time and therapeutic efficacy; for instance, high-molecular-weight HA may offer superior viscoelastic responses to mechanical forces [13].

Despite these mechanical benefits, HA therapy has notable limitations. While it effectively addresses joint lubrication and may offer some secondary anti-inflammatory benefits, evidence suggests it does not robustly inhibit the underlying inflammatory cascade or the progressive destruction of the joint environment over the long term [2]. Clinical benefits of HA typically peak around six weeks post-injection and tend to diminish as the exogenous substance is degraded within the inflammatory intra-articular environment [2,13].

3.2 Biological Mechanism of Platelet-Rich Plasma

Platelet-rich plasma (PRP) represents an autologous orthobiologic therapy that functions primarily through the delivery of supra-physiologic concentrations of bioactive molecules to the joint [2,13]. The therapeutic efficacy of PRP is rooted in the contents of the platelet alpha-granules, which release an extensive cocktail of growth factors, including Transforming Growth Factor-beta (TGF-β1), Insulin-like Growth Factor-1 (IGF-1), Fibroblast Growth Factor-2 (FGF-2), Vascular Endothelial Growth Factor (VEGF), and Platelet-Derived Growth Factor (PDGF) [2,13].

The biological mechanisms of PRP are categorized into three primary functions:

1. Tissue Regeneration Potential: Growth factors released by PRP stimulate mesenchymal stem

cell migration, promote chondrocyte proliferation, and enhance extracellular matrix synthesis, potentially facilitating the repair of damaged cartilage and subchondral structures [2,28].

2. Anti-inflammatory Properties: PRP, particularly leukocyte-poor formulations, modulates the joint environment by inhibiting the expression of pro-inflammatory cytokines like IL-1β and TNF-α. This reduction in inflammation leads to a downstream decrease in MMP levels, thereby slowing the degradation of the cartilage matrix [13,28].
3. Impact on Synovial Fluid Biomarkers: Clinical studies have demonstrated that PRP injections significantly alter the molecular composition of synovial fluid. Specifically, PRP treatment has been shown to reduce the concentrations of pro-inflammatory biomarkers including IL-6, IL-1β, TNF-α, IL-17A, and IL-10. By clearing these factors, PRP improves the inflammatory state of the knee joint, which correlates directly with clinical improvements in pain and functionality [28].

3.3 Structural Changes and MRI Findings

The metabolic and anti-inflammatory changes induced by these therapies can translate into observable structural alterations within the joint, often evaluated via Whole-Organ Magnetic Resonance Imaging Scores (WORMS) [13]. Research comparing the efficacy of HA and PRP has utilized MRI to track changes in cartilage volume, synovitis, and bone marrow lesions (BMLs) [13].

Significant findings in recent clinical trials indicate that while both HA and PRP may improve clinical symptoms, PRP—and specifically the combination of HA and PRP—demonstrates a unique capacity for structural modulation [13]. In a randomized controlled trial, MRI analysis at 12 months revealed that patients receiving a combination of HA and PRP experienced a significant reduction in bone marrow edema, whereas no such improvement was observed in patients receiving HA alone [13]. This structural benefit is attributed to the regenerative capabilities of PRP growth factors, which facilitate the healing of micro-damage within the subchondral bone marrow and surrounding joint tissues. Furthermore, PRP has been associated with improvements in cartilage volume in the patellofemoral compartment and reductions in synovitis, suggesting a more comprehensive modification of the joint structure compared to traditional viscosupplementation [13].

4. Comparative Clinical Efficacy: PRP versus HA

The core of the therapeutic debate in non-surgical knee osteoarthritis (KOA) management centers on the comparative clinical efficacy of Platelet-Rich Plasma (PRP) and Hyaluronic Acid (HA). While both interventions are designed to modulate the intra-articular environment, the clinical outcomes reported in recent high-level literature suggest distinct profiles in terms of the onset, magnitude, and durability of symptom relief.

4.1 Short-Term Outcomes (1 to 6 months)

In the immediate short-term period (1 to 3 months), both PRP and HA demonstrate significant capacity for pain reduction and functional improvement, although the rate of improvement often favors PRP. In a randomized clinical trial conducted in Tehran, researchers found that by the 3-month mark after the final injection, patients in the PRP group exhibited significantly lower mean scores for knee pain, stiffness, and physical function compared to those receiving HA [6]. Specifically, the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score in the PRP group was significantly lower than that of the HA group across all radiological grades of the disease [6]. Similarly, a triple-parallel clinical trial observed that while both HA and PRP induced a linear decrease in WOMAC pain values during follow-up, the decrease in the PRP group was statistically greater as early as 6 weeks post-injection [29]. By the 3-month interval, this trial reported that the greatest reduction in the mean WOMAC value was achieved in the PRP cohort [29].

Meta-analytical data further corroborate these findings, though with some nuances. A 2020 meta-analysis of 14 randomized controlled trials (RCTs) indicated that while there were no significant differences in Visual Analog Scale (VAS) or International Knee Documentation Committee (IKDC) scores between the two groups at the very short term (<12 weeks), the WOMAC-total and WOMAC-physical function scores were already significantly improved in the PRP group [15]. This suggests that while the analgesic effect (pain relief) may be comparable in the first few weeks, the functional recovery induced by PRP may be more rapid [15]. By the 6-month mark, the superiority of PRP becomes more pronounced. Systematic reviews have reported moderate but statistically significant pooled effects for pain reduction (SMD = -0.32) and functional improvement (SMD = -0.28) favoring PRP over control groups, including HA [22]. Furthermore, meta-analyses focusing on "early" osteoarthritis (Kellgren-Lawrence grades I-III) highly recommend PRP for symptom remission and function

improvement at this 6-month threshold [27].

4.2 Long-Term Outcomes and Durability (1 to 7 years)

The most striking differences between PRP and HA emerge in the evaluation of long-term durability and joint survival. HA therapy is often limited by its mechanical nature; as the exogenous lubricant is degraded, symptoms typically return [15]. In contrast, the biological modulation provided by PRP growth factors appears to offer a more sustained therapeutic effect. A post hoc analysis of an RCT with a minimum 7-year follow-up provides some of the most compelling evidence for this longevity [27]. At a mean follow-up of 78.9 months, the cumulative survival rate—defined as the avoidance of arthroscopic or replacement surgery—was 90% for the PRP group compared to only 74% for the HA group [27]. Furthermore, the PRP group maintained significantly lower VAS (4.9 vs. 5.8) and WOMAC (38.8 vs. 44.6) scores than the HA group at this late stage [27].

Other systematic reviews with long-term follow-up intervals (>12 months) support this trend. A Bayesian network meta-analysis analyzing outcomes at one year ranked the combined administration of PRP and HA as the most effective treatment, followed by isolated PRP, both of which outperformed HA alone in providing sustained pain relief and functional recovery [12]. Another meta-analysis involving 30 RCTs and over 2,700 patients found that while short-term differences were sometimes negligible, PRP showed significantly better performance than HA in total WOMAC, VAS, and IKDC scores when the final follow-up time was 12 months or greater [26]. This longevity is attributed to PRP's ability to inhibit inflammatory factors like TNF-α and IL-1β for longer durations, potentially delaying the requirement for total knee arthroplasty [15, 27]. Intra-articular HA and PRP injections significantly delay the necessity for total knee arthroplasty (TKA) in patients with knee osteoarthritis [7]. Evidence indicates that HA can postpone surgery by nearly 10 months, while specific findings for PRP suggest a median joint preservation time of 4.1 years [7]. This surgery-delaying effect provides a critical, cost-effective strategy for younger or middle-aged patients seeking to postpone the risks associated with early prosthetic replacement [7]. Despite these clinical gains, it is important to note that even high-quality trials with 12-month MRI follow-ups have not always demonstrated significant structural benefits, such as increased cartilage volume, suggesting that the primary value of PRP remains symptomatic and functional rather than strictly regenerative [22].

4.3 Statistical Significance and Meta-Analysis Synthesis

The statistical weight of evidence increasingly favors the superiority of PRP over HA, particularly as the follow-up duration extends beyond 6 months. In a 2022 meta-analysis, researchers obtained a pooled odds ratio (OR) of 2.55 ($p < 0.00001$), indicating that clinical improvement is significantly more likely to occur with PRP than with HA [25]. The same study reported a pooled risk ratio of 1.34 ($p < 0.00001$), confirming that PRP is not only more effective but also maintains a comparable safety profile with fewer reported side effects than traditional pharmacological options [25].

Comprehensive reviews of WOMAC outcomes show a mean difference (MD) of -8.07 ($p < 0.00001$) in favor of PRP at the final follow-up, indicating a substantial and consistent advantage in overall symptom management [26]. Functional recovery, as measured by IKDC scores, also shows a significant mean difference of 7.18 ($p < 0.00001$) favoring PRP [26]. In individual high-level trials, the proportion of patients achieving "clinically important improvement"—defined as at least a 25% reduction in WOMAC pain—was staggering; 96% of PRP patients reached this threshold at 6 months compared to 75% in the HA group ($p = 0.038$) [29].

While some large placebo-controlled trials have questioned the magnitude of PRP's benefit over saline, the consensus across multiple meta-analyses is that PRP provides statistically and clinically superior results when compared directly to HA [12, 22]. Surface under the cumulative ranking (SUCRA) curve analysis further solidifies this, giving the combination of PRP and HA a rank probability of 96.68 for long-term pain relief, far exceeding the 44.4 ranking for HA alone [12]. These data collectively suggest that while HA provides a valuable short-term lubricant effect, PRP represents a superior long-term conservative strategy for the management of mild-to-moderate knee osteoarthritis.

5. Variables Influencing Treatment Efficacy

The clinical success of intra-articular therapies for knee osteoarthritis (KOA) is not universally consistent, as it is heavily modulated by various technical and patient-specific factors. Recent meta-analyses and randomized controlled trials suggest that the efficacy of Hyaluronic Acid (HA) and Platelet-Rich Plasma (PRP) is significantly influenced by the cellular composition of the injectate, the chemical structure of the HA, and the metabolic profile of the patient.

5.1 PRP Preparation Protocols: LR-PRP versus LP-PRP

A critical variable in PRP therapy is the concentration of leukocytes, which divides the treatment into Leukocyte-Rich (LR-PRP) and Leukocyte-Poor (LP-PRP) protocols. LR-PRP is defined by a neutrophil concentration above baseline, whereas LP-PRP remains below baseline [19]. The medical community remains divided on which preparation is superior. Proponents of LR-PRP point to its higher concentration of growth factors and cytokines, which may theoretically enhance regenerative processes [16]. Meta-analyses have shown that LR-PRP provides significantly better Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total, pain, and physical function scores at 6 months compared to HA [19].

However, LR-PRP is often associated with a more robust pro-inflammatory response. The presence of leukocytes increases levels of catabolic cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), which can lead to synovial inflammation and may have deleterious effects on chondrocytes [16, 19]. Clinically, this can manifest as increased pain and swelling immediately following the injection [19]. In contrast, LP-PRP is characterized by its anti-inflammatory profile, increasing the concentrations of IL-4 and IL-10, which suppress inflammatory mediators [19]. Recent systematic reviews indicate that LP-PRP demonstrates superior overall outcomes in WOMAC total and physical function scores at 6 and 12 months, and significantly better pain relief via Visual Analog Scale (VAS) scores at 3, 6, and 12 months compared to HA [16]. While both preparations are superior to HA in the long term, LP-PRP is often recommended due to its favorable anti-inflammatory properties and reduced risk of acute joint reactions [16].

5.2 HA Molecular Weight and Crosslinking

The evolution of HA therapy has moved from standard, multi-dose preparations toward novel crosslinked HA, designed to improve durability and viscoelasticity. Standard HA requires multiple injections (3–5) to achieve therapeutic effects, whereas crosslinked HA (such as HyajointPlus) is synthesized via a cross-linking process (e.g., using 1,4-butanediol diglycidyl ether) to introduce an anti-degradation feature, allowing for a single-dose regimen [30].

When compared directly to PRP, crosslinked HA shows competitive efficacy. A prospective double-blind trial found that both single-dose LP-PRP and single-dose crosslinked HA yielded significant and comparable improvements in WOMAC scores at a 6-month follow-up [30]. While PRP tended to show more rapid improvements in stiffness and function by the 3-month mark, these differences disappeared by 6 months, where both treatments exceeded the threshold

for a minimum clinically important difference [30]. The use of crosslinked HA offers the advantage of increased density and synovial fluid viscoelasticity, which prevents the mechanical degradation of cartilage, potentially matching the biological benefits of PRP in early-stage KOA [30].

5.3 Patient-Specific Factors: Obesity

The metabolic and biomechanical state of the patient, specifically their Body Mass Index (BMI), is a primary determinant of treatment failure or success. Obesity (BMI $\geq$ 30 kg/m^2) and being overweight (BMI $\geq$ 25 kg/m^2) significantly exacerbate KOA by increasing joint load and introducing inflammatory adipokines that degrade articular cartilage [20].

In this challenging demographic, the comparative efficacy of PRP and HA undergoes a distinct shift over time. Meta-analyses focusing on overweight and obese patients reveal that during the first two months of follow-up, there is no significant difference between the two treatments in terms of pain relief [20]. However, as the follow-up progresses to 3, 6, and 12 months, PRP demonstrates a clear and statistically significant superiority over HA in WOMAC total scores and joint stiffness relief [20]. For example, at the 12-month interval, the mean difference in WOMAC total scores significantly favored PRP (MD = -12.11), suggesting that the sustained release of growth factors in PRP is more effective at counteracting the chronic biomechanical and inflammatory stress found in obese joints than the largely mechanical lubrication provided by HA [20]. Consequently, for patients with a BMI $\geq$ 25 kg/m^2, PRP may be the preferred long-term conservative strategy [20].

6. Emerging Trends: Combination Therapy of PRP and HA

The evolving therapeutic landscape for knee osteoarthritis (KOA) has recently pivoted toward the combined administration of Platelet-Rich Plasma (PRP) and Hyaluronic Acid (HA). While both intra-articular treatments have individually demonstrated efficacy in mitigating the symptoms of joint degeneration, the clinical rationale for their simultaneous use is predicated on a profound synergistic interaction between the biological healing properties of PRP and the mechanical rheological benefits of HA [4, 10].

6.1 Clinical Rationale and Synergistic Mechanisms

The foundational rationale for combination therapy lies in the distinct yet complementary roles these agents play within the joint environment. HA, a high-molecular-weight glycosaminoglycan, serves as a vital component of healthy synovial fluid, providing immediate mechanical lubrication and shock absorption [24, 32]. In the osteoarthritic joint, HA acts as a biological scaffold that stabilizes the intra-articular environment and improves the viscoelasticity of the synovial fluid [10]. Conversely, PRP acts as a biological modulator, delivering a supra-physiologic concentration of growth factors and cytokines that stimulate chondrocyte proliferation, inhibit catabolic enzymes, and promote the synthesis of the extracellular matrix [4, 24].

At a molecular level, this synergy is mediated through specific pathways. Research indicates that HA can facilitate the activity of growth factors within PRP, while PRP may reverse the senescence of chondrocytes [24]. Experimental evidence suggests that mixing these agents significantly improves cell mobility and proliferation of synovial fibroblasts compared to pure PRP solutions [4]. Specific mediators, such as CD44 and TGF-β receptors, are believed to play a critical role in this synergy, altering the role of pro-inflammatory cytokines to favor cartilage regeneration and joint homeostasis [4, 21, 24].

6.2 Clinical Efficacy: Pain Reduction and Functional Outcomes

The comparative efficacy of PRP+HA combination therapy versus monotherapy (PRP alone or HA alone) has been a primary focus of recent meta-analyses. When compared to **HA monotherapy**, combination therapy consistently demonstrates superior results in both pain relief and functional restoration. A well-conducted meta-analysis identified as "best current evidence" revealed that patients receiving PRP+HA experienced statistically significant improvements in Visual Analog Scale (VAS) scores at 3, 6, and 12 months compared to those receiving HA alone [10]. Furthermore, by the 12-month mark, the combination group showed significantly better performance in WOMAC subscores for stiffness and physical function [10].

In comparisons against PRP monotherapy, the results are similarly encouraging but require a more nuanced interpretation of timeframes. Systematic reviews have reported that dual therapy results in a significant reduction in VAS scores compared to PRP alone as early as 4 to 6 weeks post-injection, with benefits extending to 12 months [24]. Functional improvements, as measured by WOMAC scores, also favor the combination group at 3, 6, and 12 months [24]. At 6 months, the combination group’s VAS scores were significantly lower, and by 12 months,

both WOMAC function and total scores showed a statistical advantage for the dual therapy [4].

6.3 Statistical Findings and the MCID Debate

Statistical synthesis across multiple studies provides strong evidence for the superiority of combination therapy, though some researchers urge caution regarding "clinical" versus "statistical" significance. In one meta-analysis of 941 patients, the standardized mean difference (SMD) for WOMAC total scores at 12 months was -0.42 ($p = 0.001$) in favor of the combination group [4]. Another analysis reported a mean difference (MD) of -8.30 ($p < 0.0001$) for WOMAC function at one year [24].

However, a critical perspective is offered by Zhang et al. (2022), who utilized the Minimum Clinically Important Difference (MCID) to evaluate these findings. While their analysis confirmed statistical improvements in VAS at 1 month and WOMAC total scores at 6 months, they noted that the smallest treatment effects often did not exceed the established MCID thresholds [21]. This suggests that while combination therapy is statistically superior, the magnitude of the benefit for the average patient might be modest. Nevertheless, individual high-level trials have shown that both PRP alone and PRP+HA can achieve functional improvements exceeding 39-41%, well above common MCID thresholds [10].

6.4 Safety and "Flare" Mitigation

A significant finding in the emerging literature is the enhanced safety profile of combination therapy. Multiple systematic reviews have concluded that PRP+HA therapy is generally safer than PRP injections alone [21, 24]. PRP administration is often associated with a "post-injection flare"—characterized by transient pain and swelling—likely due to pro-inflammatory factors within the concentrated platelets [24]. Co-administration with HA appears to have a dilutional effect on these catabolic factors, potentially attenuating leukocyte-induced oxidative stress and improving the microenvironment of the joint [24].

6.5 Conclusion: Is Combination Therapy Optimal?

The current weight of literature increasingly supports PRP+HA combination therapy as a highly effective, and potentially optimal, conservative treatment for mild-to-moderate KOA. It provides superior short- and long-term symptom control over monotherapy, particularly for patients whose symptoms are dominated by stiffness and functional limitations rather than isolated pain [10]. Recent clinical trials comparing PRP combined with linear HA versus

crosslinked HA (like HYAJOINT Plus) also demonstrate high patient satisfaction and significant improvements in balance and static stability [32]. While further large-scale, standardized Level I studies are necessary to define the ideal candidate and injection protocols, the synergistic use of HA and PRP represents a promising trend in delaying the progression toward more invasive surgical interventions [10, 24].

7. Safety Profile and Adverse Events

The clinical utility of intra-articular injections for knee osteoarthritis (KOA) is predicated not only on their efficacy but also on their safety profiles. A rigorous analysis of current literature indicates that both Platelet-Rich Plasma (PRP) and Hyaluronic Acid (HA) are categorized as safe, minimally invasive therapies with a low incidence of serious complications [1, 5, 35].

7.1 Common Adverse Events and Statistical Comparison

The adverse events associated with both treatment modalities are primarily local and transient in nature. Documented side effects for both PRP and HA include local swelling, pain at the injection site, and joint stiffness [1, 35]. Other less common systemic reactions reported in clinical trials include dizziness, headache, febrile syndrome, and flu-like symptoms [1].

Statistical syntheses across multiple meta-analyses consistently demonstrate that there is no significant difference in the overall rate of adverse events between PRP and HA. For instance, a comprehensive meta-analysis of 20 randomized controlled trials (RCTs) reported a risk ratio (RR) of 1.00 (95% CI 0.80 to 1.26, P = 0.997), indicating a nearly identical safety profile for both groups [1]. Similarly, more recent data found no statistically significant difference in adverse event frequency, with an odds ratio (OR) of 1.31 (P = 0.21) [35]. Furthermore, network meta-analyses ranking different injectables suggest that while HA may occasionally be linked to an increased risk of transient pain at the injection site or even rare serious adverse events, neither PRP nor HA significantly increases the incidence of side effects compared to a placebo [5].

7.2 The Autologous Advantage of PRP

A primary distinguishing factor in the safety profile of PRP is its autologous nature. Because PRP is derived from the patient's own peripheral blood, it carries a minimal risk of immune reactions, allergic responses, or the transmission of infectious diseases [1]. This

biocompatibility is a significant advantage over exogenous pharmacological agents.

However, the specific composition of the PRP injectate can influence local tolerability. Research suggests that leukocyte-poor PRP (LP-PRP) may induce less post-injection pain and swelling than leukocyte-rich formulations [35]. These "post-injection flares" are typically self-limiting, occurring within minutes to hours of administration and generally resolving spontaneously within a few days [35].

7.3 Safety in Long-Term Management

When placed in a broader clinical context, PRP is often viewed as a safer long-term strategy than other common injectables like corticosteroids, as it lacks the potential for cartilage toxicity and is associated with fewer overall complications [35]. While HA remains a widely used and recommended conservative treatment, its analgesic effects are considered by some to be less stable over time than the biological modulation provided by PRP [5]. Ultimately, the literature supports both PRP and HA as remarkably safe options, with PRP offering the unique benefit of an autologous origin that virtually eliminates concerns regarding immunogenicity [1].

8. Discussion

The synthesis of literature published between 2020 and 2026 reveals a distinct shift in the therapeutic paradigm for knee osteoarthritis (KOA). The primary finding across the majority of high-level meta-analyses and randomized controlled trials (RCTs) is that while both Hyaluronic Acid (HA) and Platelet-Rich Plasma (PRP) are safe and effective conservative treatments, PRP generally offers superior and longer-lasting relief in terms of pain reduction and functional improvement [1, 15, 33, 35].

The clinical trajectory for HA is characterized by relatively rapid symptomatic relief that typically peaks around six weeks but begins to deteriorate significantly between three and six months as the exogenous lubricant is metabolized [3, 8]. HA remains a viable and effective short-term option, particularly for patients seeking immediate mechanical lubrication or those who may not be candidates for autologous blood draws [13, 22]. Conversely, PRP’s biological mechanism—leveraging supra-physiologic concentrations of growth factors—requires more time to manifest but results in a more sustained therapeutic effect, with benefits frequently extending to 12 months and, in some post hoc analyses, up to seven years [12, 27, 33].

A significant emerging trend highlighted in recent data is the superiority of combination therapy

(PRP+HA). Network meta-analyses using Surface Under the Cumulative Ranking (SUCRA) consistently rank the simultaneous administration of HA and PRP as the most effective strategy for long-term pain relief and functional restoration [5, 12]. This synergy is attributed to HA providing an immediate mechanical scaffold and lubricant while PRP delivers the biological signaling necessary for tissue modulation and anti-inflammatory effects [24, 32].

Limitations of Current Literature

Despite the encouraging findings for PRP, several critical limitations in the current body of evidence prevent a universal consensus. The most prominent issue is the significant heterogeneity in PRP preparation protocols. Studies vary widely in terms of blood volume harvested, centrifugation speeds, the use of activators (like calcium chloride), and the final concentration of platelets and leukocytes [16, 22, 35]. The debate between leukocyte-rich (LR-PRP) and leukocyte-poor (LP-PRP) remains particularly unsettled, with some studies suggesting LP-PRP is superior for functional recovery while others find no clinical difference [16, 26].

Furthermore, the lack of standardized protocols for both HA (linear vs. crosslinked) and PRP (dosing and intervals) makes cross-study comparisons difficult [22, 29]. Many meta-analyses are also limited by short follow-up durations (rarely exceeding 12 months) and a reliance on subjective patient-reported outcome measures (WOMAC, VAS, IKDC) rather than objective structural assessments like high-resolution MRI or histological analysis [1, 8, 13].

Future Research Directions

To advance the field, future research must prioritize the standardization of orthobiologic preparation and delivery to ensure reproducibility [24, 33]. Long-term longitudinal studies (exceeding 2–5 years) are necessary to determine if PRP or combination therapy can truly alter the natural history of KOA and significantly delay total knee arthroplasty [12, 27]. Additionally, the inclusion of objective biomarkers and imaging data (e.g., MRI WORMS cartilage volume assessment) is essential to validate the "regenerative" claims of PRP [8, 13]. Finally, research should focus on identifying specific patient phenotypes—considering age, BMI, and metabolic status—to develop personalized treatment algorithms that optimize clinical responses [3, 19].

9. Conclusions

Based on the comprehensive review of evidence from 2020 to 2026, intra-articular Platelet-Rich Plasma (PRP) is superior to Hyaluronic Acid (HA) for the treatment of mild-to-moderate

knee osteoarthritis, particularly regarding mid-to-long-term outcomes (6 to 12 months). While both treatments are categorized as remarkably safe and provide significant short-term relief, PRP demonstrates a more robust capacity for sustained functional recovery and pain reduction. The biological modulation provided by autologous growth factors appears more effective at addressing the chronic inflammatory environment of the osteoarthritic joint than the primarily mechanical lubrication provided by exogenous HA.

Clinical Recommendations

For orthopedic practitioners, the following evidence-based recommendations are suggested:

1. Preferential Use of PRP: For patients with Kellgren-Lawrence Grade I–III KOA who seek durable, long-term symptom management, PRP should be considered the primary injectable option [33, 35].
2. Combination Therapy as the "Gold Standard": Practitioners should consider the combined administration of HA and PRP to capitalize on their synergistic mechanical and biological effects, as this approach currently demonstrates the highest ranking in terms of clinical efficacy [5, 12].
3. Leukocyte Modulation: While both are effective, Leukocyte-Poor PRP (LP-PRP) is recommended for patients prone to post-injection inflammatory flares, as it is associated with a more favorable anti-inflammatory profile [16, 35].
4. Targeted Patient Selection: PRP is particularly recommended for overweight and obese patients (BMI $\geq$ 25 kg/m^2), where its biological efficacy significantly outperforms HA after the initial 3-month follow-up period [20].
5. Standardization Awareness: Clinicians must utilize validated preparation kits and adhere to high-quality centrifugation protocols to ensure a sufficient platelet concentration, as the quality of the injectate is a primary determinant of therapeutic success [27, 35].

10. Declaration of the use of generative AI and AI-assisted technologies in the writing process

In preparing this work, the authors used Gemini for the purpose of correcting stylistic and spelling errors. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

Disclosure:

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All authors have read and agreed with the published version of the manuscript.

Funding Statement

The authors did not receive special funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Acknowledgments

The authors wish to emphasize that they do not express gratitude to any individuals or institutions.

Conflict of Interest Statement

The authors declare no conflict of interest.

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