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General

Advances in hyaluronic acid therapy for knee osteoarthritis: monotherapy and combination strategies: an evidenced based review

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Knee osteoarthritis (KOA) is a chronic degenerative joint disease that lead to cartilage loss, inflammation, and disability. Intra-articular hyaluronic acid (HA) is widely used for its viscoelastic, anti-inflammatory, and chondroprotective properties; however clinical outcomes remain inconsistent. Recent studies have explored combining HA with biologic or pharmacologic agents, such as platelet-rich plasma (PRP), corticosteroids (CS), fibrinogen, botulinum toxin A, polydeoxyribonucleotide (PDRN), and stem cells, to enhance efficacy through multimodal mechanisms. Despite this, the comparative benefits and safety profiles of these emerging strategies remain unclear. This review aims to evaluate the clinical efficacy of intra-articular HA, used either alone or in combination with adjunctive agents, for the management of KOA. A comprehensive literature search was conducted across PubMed, Embase, the Cochrane Library, and Web of Science, covering the period from January 2010 to April 2025. A total of 70 studies were included, comprising 50 randomized controlled trials (RCTs) and 20 meta-analyses. High-quality evidence supports the modest yet clinically significant efficacy of HA monotherapy, especially in the early to moderate stages of KOA. Outcomes appear to be affected by factors such as molecular weight, crosslinking, and injection protocols. Among combination strategies, the combination of HA and PRP demonstrates the most consistent synergistic benefits across various outcome domains. Short-term improvements are also observed with the combination of HA and CS. Emerging combinations involving fibrinogen, botulinum toxin A, peripheral blood stem cells and polydeoxyribonucleotide show early promise but remain under investigation.

INTRODUCTION

Knee osteoarthritis (KOA) is a progressive and common joint disease, affecting nearly 25% of individuals over 50, and is a leading cause of disability worldwide.[1-5] In addition to articular cartilage degeneration, KOA also affects periarticular soft tissues. Progressive erosion of the capsular-ligamentous compartment may predispose patients to myotendinous lesions, worsening disability and functional decline. These musculoskeletal complications demonstrate the broader systemic impact of KOA beyond the joint itself.[6] As life expectancy and obesity rates continue to rise, the incidence of KOA is expected to increase further, emphasizing the urgent need for effective, scalable, and personalized non-surgical treatments.[1,5,7]

Intra-articular hyaluronic acid (HA) is a well-established non-operative therapy for KOA, particularly in the early to moderate stages. HA exerts mechanical effects by restoring the viscosity of synovial fluid and biological effects through anti-inflammatory and chondroprotective pathways. Clinical studies have demonstrated that HA injections may improve pain and function in selected patients. For instance, a comprehensive network metaanalysis conducted by Han et al[8] included 43 RCTs and 5,554 patients. The study revealed that HA significantly reduced pain compared to a placebo (SMD 0.94, 95% CI 0.09–1.78) and was associated with a low rate of adverse events. These results highlight the favorable balance of clinical benefits and tolerability in KOA management.[8] Moreover, Bahrami et al[9] found that a single injection of cross-linked high-molecular-weight (HMW) HA was as effective as three weekly injections of linear low-molecular-weight (LMW) HA in improving pain and function at 2 and 6 months, with the exception of better stiffness outcomes in the LMW group at 2 months. Nevertheless, real-world effectiveness remains variable, and clinical practice guidelines differ in their recommendations.[1,10]

Despite its widespread use, HA monotherapy may only provide short-term benefits, especially in patients with advanced KOA or active synovitis. Comparative studies indicate that symptom relief may decrease after 3 to 6 months, and treatment response is affected by HA molecular weight,

cross-linking, and the patient's specific inflammatory burden.[9,11-18] These limitations have generated interest in improving HA efficacy through combination therapies.

Combination strategies that include HA and other intra-articular agents, such as plateletrich plasma (PRP), corticosteroids (CS), or polydeoxyribonucleotide (PDRN), have demonstrated promising synergistic effects. For instance, Yu et al[19] reported that patients who received a combination of HA and PRP experienced significantly greater improvements in

WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) pain scores, with a mean reduction of 5.58 points, as well as functional scores compared to those treated with HA or PRP alone. The rationale for combination therapy is based on its ability to modulate both humoral and cellular immune responses, promote angiogenesis, and inhibit inflammatory cytokines, which may prolong symptom relief and delay structural progression of KOA.[19]

However, the existing literature lacks a comprehensive synthesis that compares HA monotherapy to combination regimens across various levels of KOA severity. Most available trials and reviews focus on single interventions or fail to provide direct comparisons between strategies, leading to fragmented guidance for clinical decision-making.[1,10] Variations in trial design, HA formulations, and outcome measures complicate interpretation. This narrative review aims to synthesize evidence on the clinical efficacy of intra-articular HA, whether used alone or in combination, for KOA management. We analyze RCTs and meta-analyses published from 2010 to 2025, highlighting mechanisms of action, comparing HA formulations, evaluating combination strategies, and discussing implications for personalized treatment in clinical practice.

METHODS

A comprehensive literature search was conducted across major electronic databases - PubMed, Embase, Web of Science, and the Cochrane Library – covering the period from January 2010 to April 2025. The search strategy combined Medical Subject Headings (MeSH), Emtree terms, and relevant keywords, including "hyaluronic acid," "hyaluronan," "knee osteoarthritis," "platelet-rich plasma," "intra-articular injection," "viscosupplementation," and "corticosteroids." Boolean operators (AND, OR) were applied to optimize search sensitivity and specificity. Reference lists of included studies were also manually screened for additional eligible articles.

Studies were included if they met the following criteria: (1) original clinical research conducted in humans, including RCTs and meta-analyses; (2) evaluation of intra-articular HA, either as monotherapy or in combination with PRP or CS; and (3) outcomes addressing pain relief, functional improvement (e.g., WOMAC, VAS, IKDC), or treatment safety. Exclusion criteria were (1) animal or *in vitro* studies without direct clinical relevance, (2) publications not in English, or (3) studies focused on non-knee joints or non-KOA conditions.

Following initial screening and eligibility assessment, a total of 70 studies were included in this review. These comprised 50 RCTs and 20 meta-analyses. PRISMA flow diagram of study selection process is presented in Figure 1. Although this review utilizes a narrative synthesis approach rather than a formal systematic review, the inclusion process is summarized in a diagram for transparency. The methodological framework adheres to the SANRA (Scale for the Assessment of Narrative Review Articles) guideline, emphasizing defined inclusion criteria, a comprehensive search strategy, and structured thematic synthesis.

MECHANISM OF ACTION OF HYALURONIC ACID

HA improves joint biomechanics by restoring the viscoelasticity of synovial fluid. In patients with KOA, the breakdown of endogenous HA leads to reduced lubrication and shock absorption within the joint, exacerbating cartilage wear. Exogenous HA injection compensates for this deficiency by increasing synovial fluid viscosity, reducing mechanical friction, and enhancing shock-buffering capacity during weight-bearing activity.[17,20,21]

HA exerts biological effects through anti-inflammatory and cartilage-protective pathways. It binds to CD44 receptors on chondrocytes and synoviocytes, resulting in the downregulation of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and suppression of matrix metalloproteinases (MMP-1, 3, 9, and 13), enzymes involved in extracellular matrix degradation. Additionally, HA promotes the synthesis of proteoglycans and type II collagen, supporting the structural maintenance of articular cartilage.[17,21]

Immunologically, HA modulates synovial inflammation by altering cellular infiltration and cytokine activity. Histological evidence shows that HA reduces mononuclear cell infiltration and synoviocyte hyperplasia in KOA joints, reflecting its immunomodulatory effects on local inflammation.[20] Furthermore, intra-articular HA has been shown to decrease synovial concentrations of MMP-9, an enzyme associated with inflammation-induced cartilage breakdown and angiogenesis.[17]

The therapeutic efficacy of HA is influenced by its molecular weight. HMW HA demonstrates superior rheological properties, longer intra-articular residence time, and stronger interaction with CD44 receptors compared to LMW formulations. This translates to more sustained anti-inflammatory and chondroprotective effects.[21,22]

Additionally, formulation characteristics such as origin, cross-linking, and injection protocol play a critical role in clinical outcomes. Products vary in their molecular structure, source (avian-derived *vs*. bacterial fermentation), and dosing regimens. Cross-linked HA has formulation differences that have been linked to variations in therapeutic durability and patient tolerance.[9,20,23,24]

Taken together, these mechanisms highlight the multifaceted role of HA in KOA treatment and underscore the importance of selecting appropriate formulations tailored to the disease stage and patient profile.

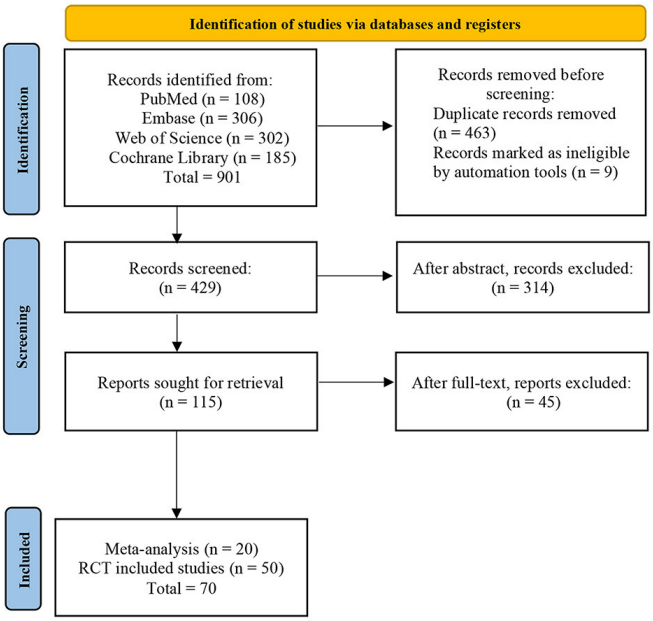

Figure 1. PRISMA flow diagram of study selection process

A total of 901 records were retrieved from four electronic databases (PubMed, Embase, Web of Science, and Cochrane Library). After removing 463 duplicates and 9 entries marked as ineligible by automation tools, 429 records were screened. Out of these, 314 were excluded based on abstract review. The full texts of 115 articles were assessed, and 45 were excluded for not meeting the inclusion criteria. Ultimately, 70 studies were included in the final synthesis, consisting of 50 randomized controlled trials (RCTs) and 20 meta-analyses.

CLINICAL EFFICACY OF HA IN KOA

SHORT-TERM EFFICACY WITHIN A 3-MONTH PERIOD

The short-term efficacy of intra-articular HA in KOA remains limited and inconsistent.[25-28]

Several high-quality meta-analyses have shown minimal or no clinical benefit during the first 1-3 months post-injection. Jevsevar et al[10] analyzing 79 RCTs and including 56 in their network meta-analysis, reported no significant improvement in pain or function versus placebo at 6 weeks, with an effect size (-0.05) below the minimal clinically important difference (MCID). Colen et al[29] found that HA offered only marginal benefit over placebo (VAS difference -10.2 mm), while Wang et al[30] found comparable efficacy between HA and CS at 1 month, but demonstrated superior pain relief with HA at 3 and 6 months. Supporting these findings, RCTs by Askari et al[31] and Tammachote et al[32] showed that CS provided faster pain relief than HA within 3 months. Similarly, according to Khan et al,[33] CS provided rapid pain relief within the first 2 weeks but its effectiveness diminished after 6 weeks. In contrast, HA acted more slowly but offered sustained improvement from week 6 to the third month in the treatment of KOA.[33] While Kesiktas et al[16] observed significant short term pain reduction with HA within the first month, its effects particularly for resting pain were not sustained at 3 months. However, in a randomized controlled trial by Küçükakkaş et al,[34] after one month of treatment, both patient groups receiving PRP and HA injections showed significant improvement in clinical symptoms. Specifically, VAS scores at rest and during movement decreased markedly compared to baseline, and WOMAC scores were also significantly reduced in both groups. Structurally, only the HA group demonstrated a statistically significant increase in lateral femoral cartilage thickness. In contrast, the PRP group did not exhibit any significant changes in cartilage thickness at this time point. These findings suggest that while both treatments are effective in improving early clinical symptoms, HA may have a superior impact on cartilage structure during the initial post-injection phase.[34] Overview of RCTs using intra-articular HA monotherapy for KOA is shown in Table 1.

These outcomes may be explained by HA's delayed biological activity, requiring time to modulate inflammation and restore viscoelasticity. In contrast, CS act rapidly. Therefore, HA may not be ideal for immediate symptom relief and should be considered for longer-term therapeutic goals.

MID-TERM EFFICACY OF HA WITHIN A 3- TO 6-MONTH PERIOD

HA demonstrates greater clinically meaningful benefits during this mid-term period, particularly between 3 and 6 months after injection.[25,29,35,36,41,45,47,49,50]

Several meta-analyses and RCTs report pain and functional improvements exceeding MCID thresholds, suggesting that this timeframe is optimal for HA to exert therapeutic effects. A systematic review by Altman et al[50] found that HMW HA provided significant pain and function improvements at 3–6 months, often surpassing the MCID. Similarly, Migliorini et al[22] showed that HMW and ultra-high-molecular-weight (uhMW) formulations achieved the greatest

Table 1. Overview of RCTs using intra-articular HA monotherapy for KOA

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
1. Shimizu et al, 2010, Japan[17]	To compare the efficacy of HA and CS based on clinical scores and joint biomarkers in KOA.	RCT, 2 groups (HA, CS)	Total: 51 - HA: 26 - CS: 25	Mean age: 75.9 ± 5.9 (HA), 75.3 ± 4.9 (CS); Gender: 78.1% female (HA), 73.4% female (CS); KL grade II–III	HA: 25 mg (2.5 ml, i.a.), once/week for 5 weeks; CS: dexamethasone 4 mg (1 ml, i.a.), single injection with the option for an additional dose	Baseline, 5 weeks and 6 months	VAS pain, clinical assessment scores, synovial fluid biomarkers (HA, MMP-9, Chondroitin 4-/6-sulfate, TIMP-1)	No AEs reported	Both HA and CS improved clinical scores; HA increased HA levels and decreased MMP-9 in synovial fluid, suggesting protective effects on articular cartilage.
2. Navarro-Sarabia et al, 2011, Spain[24]	To compare the efficacy and safety of repeated injections of HA against a placebo, and to assess its effect on disease progression over a 40-month period.	RCT, 2 groups (HA, placebo)	Total: 306 - HA: 153 - Placebo: 153	Mean age: 63.0 ± 8.2 (HA), 63.9 ± 8.9 (Placebo); Gender: 83.7% female (HA), 83.7% female (Placebo); KL grade II–III	HA: 2.5 ml of 1% HA (900 kDa,), 4 cycles of injections (i.a.); Placebo: 2.5 ml saline; 1-week intervals between injections (i.a.)	Baseline, 7, 14, 21, 27, 34, and 40 months	VAS pain, function, patient global assessment (OARSI 2004), paracetamol/ NSAID use	HA: 15/153 (9.8%); Placebo: 14/ 153 (9.1%); Mild-moderate AEs only, no serious AEs reported	Repeated HA IA injections improved symptoms of KOA and demonstrated a lasting effect up to one year after the final cycle. The HA group showed a higher responder rate (80.5%) compared to the placebo group (65.8%) at 40 months (p = 0.004).
3. Leighton et al, 2013, Canada, UK, Sweden[35]	To compare cross-linked HMW HA gel for the treatment of KOA against methylprednisolone acetate.	RCT; 2 groups (HA, CS)	Total: 442 - HA: 221 - CS: 221	Mean age: 61.9 ± 9.6 (HA), 61.5 ± 9.9 (CS); Gender: 51% female (HA), 47% female (CS)	HA: 60 mg/3 ml, single i.a. injection CS: Methylprednisolone acetate 40 mg/1 ml, single i.a. injection	Baseline, 6, 12, 18, and 26 weeks Open-Label Extension:	WOMAC pain, stiffness, physical function; OMERACT-OARSI; Get-up-and-go;	No serious AEs reported; most common AE: arthralgia (17.2% in HA), (3.2% in CS)	HA was not inferior to CS at 12 weeks. HA showed sustained benefits through 26

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
				KL grade II–III		28, 39, and 52 weeks	10-meter timed walk		weeks, and a second HA injection at week 26 resulted in further improvement. There was no increased sensitivity observed with the second injection.
4. Housman et al, 2014, USA, Canada, France, UK, Germany[36]	To compare the efficacy and safety of one or two HA injections versus a single CS injection for pain caused by KOA.	RCT, 3 groups (HA-1, HA-2, CS)	Total: 391 - HA-1: 130 - HA-2: 129 - CS: 132	Mean age: 60.6 ± 9.9 (HA-1), 62.0 ± 9.7 (HA-2), 60.1 ± 9.3 (CS); Gender: 39% male (HA-1), 29% male (HA-2), 31% male (CS) KL grade I–III	HA-1: 4 ml (HMW HA derivative), one i.a. injection; HA-2: 4 ml (HMW HA derivative), two i.a. injections, 2-week interval; CS: 1 ml (40 mg) methylprednisolone acetate, one i.a. injection	Baseline, 4, 8, 12, 16, 20, and 26 weeks	WOMAC pain, WOMAC A1 walking pain, PTGA, COGA, OMERACT-OARSI	No AEs reported; Similar incidences of arthralgia, stiffness, swelling, and effusion among the groups	All treatments significantly improved pain. HMW HA was well tolerated and effective but did not show superiority over CS.
5. Filardo et al, 2015, Italy[37]	To evaluate the benefits provided by PRP in treating knee joint degeneration compared to HA.	RCT, 2 groups (PRP, HA)	Total: 192 - PRP: 96 - HA: 96	Mean age: 53.3 ± 13.2 (PRP), 57.6 ± 11.8 (HA) Gender: 63.8% male (PRP), 58.4% male (HA) KL grade I–III	PRP group: 5 ml of leukocyte-rich PRP, three i.a. injections, 1-week interval); HA group: 2 ml of HMW HA (>1500 kDa), three i.a. injections, 1-week interval,	Baseline, 2, 6, and 12 months	IKDC, KOOS (Symptom, Pain, ADL, Sport, QoL), EQ-VAS, Tegner score, ROM, transpatellar circumference	Two severe events in HA group (pain, swelling); PRP: no major AEs, post-injection pain and swelling	PRP was as effective as HA in clinical improvement; however, the PRP group experienced more local reactions. Both HA and PRP improved symptoms and function with no significant difference

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
									between the groups.
6. Trueba Davalillo et al, 2015, Mexico[38]	To compare the clinical efficacy of HA versus CS in KOA over 12 months.	RCT, 2 groups (HA, CS)	Total: 200 - HA: 100 - CS: 100	Mean age: 62.7 ± 0.6 (HA), 62.8 ± 0.6 (CS) Gender: 60.8% female (HA), 58.2% female (CS) KL grade II–III	HA: 2.5 ml of 1% HA (900,000 Da), 5 i.a. injections weekly; CS: 1 ml (Betamethasone dipropionate 5 mg + Betamethasone sodium phosphate 2 mg), 2 i.a. injections on day 0 and week 4	Baseline, 3, 6, 9, and 12 months	VAS pain, WOMAC (total, pain, function, stiffness scores)	Pain, effusion and erythema at the injection site: 3.5%	CS were more effective in the short-term, while HA was superior in long-term efficacy for pain relief and improved function. Over 80% of patients in the HA group achieved MCII at 9-12 months, compared to less than 10% in the CS group.
7. Raeissadat et al, 2015, Iran[39]	To compare the long-term efficacy of PRP and HA injections in KOA.	RCT, 2 groups (PRP, HA)	Total: 160 - PRP: 87 - HA: 73	Mean age: 56.85 ± 9.13 (PRP), 61.13 ± 7.48 (HA) Gender: 89.6% female (PRP), 75.8% female (HA) KL grade I–IV	HA: 20 mg/2 ml of HMW HA (500,000–730,000 Da), 3 i.a. injections, 1-week interval; PRP: 4–6 ml of leukocyte-rich PRP, 2 i.a. injections, 4-week interval	Baseline, 4, 24, and 52 weeks	WOMAC (pain, stiffness, function, total), SF-36 (physical and mental health scores)	No AEs reported	HA injections resulted in a significant improvement in WOMAC pain scores and bodily pain at 12 months. However, PRP provided even greater improvement in pain reduction, stiffness, function, and quality of life. All groups showed improvement without any serious adverse events.

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
8. Cole et al, 2017, USA[40]	To compare the clinical and biological effects of PRP versus HA in patients with mild to moderate KOA.	RCT; 2 groups (PRP, HA)	Total: 99 (12 out of 111 lost to follow-up) - PRP: 49 - HA: 50	Mean age: 55.9 ± 10.4 (PRP), 56.8 ± 10.5 (HA) Gender: 42.9% female (PRP), 60% female (HA) KL grade I–III	HA: 2 ml of MHW cross-linked HA (6 MDa), 3 i.a. injections, weekly; PRP: 4 ml of leukocyte-poor PRP, 3 i.a. injections, weekly	Baseline, 2, 3, 6, 12, 24, and 52 weeks	VAS pain, WOMAC pain, IKDC score, Lysholm score, synovial IL-1β, TNF-α	No AEs reported	No difference in WOMAC pain scores was observed. However, PRP significantly improved IKDC and VAS scores at both 24 and 52 weeks. A trend towards reduced levels of IL-1β and TNF-α at 12 weeks with PRP treatment was noted.
9. Tammachote et al, 2016, Thailand[32]	To compare the efficacy of single-shot HA and CS injections in relieving pain and improving function in patients with KOA.	RCT; 2 groups (HA, CS)	Total: 99 - HA: 50 - CS: 49	Mean age: 61.0 (CS), 62.6 (HA) Gender: 73.5% female (CS), 86.0% female (HA) KL grade I–IV	HA: 6 ml of cross-linked HMW HA (6 MDa) (single i.a. injection); CS: 1 ml of 40 mg triamcinolone acetonide + 5 ml 1% lidocaine with epinephrine (single i.a. injection)	Baseline, 1–3 days, 1, and 2 weeks, 1, and 6 months	VAS pain, modified WOMAC, active knee range of motion (flexion, extension)	No serious AEs reported; One patient in the HA group experienced mild swelling and pain on day 2.	Both CS and HA showed similar improvements in pain, function, and ROM at 6 months. However, CS provided better pain control during the first week and exhibited better function after 2 weeks.
10. Montañez-Heredia et al, 2016, Spain[41]	To evaluate the efficacy of PRP versus HA in KOA.	RCT, 2 groups (PRP, HA)	Total: 53 - PRP: 27 - HA: 26	Mean age: 66.3 ± 8.3 (PRP), 61.5 ± 8.6 (HA) Gender: 55.6% female (PRP), 65.4% female (HA) KL grade I–III	HA: 25 mg/2.5 ml of HA, 3 i.a. injections, 2-week interval; PRP: autologous PRP prepared from 37.5 ml of whole blood, 3 i.a. injections, 2-week intervals	Baseline, 3, and 6 months	VAS, KOOS, EUROQoL	Pain at injection site (PRP: 9/27, HA: 4/26); Transient swelling: one patient in the PRP group.	Both PRP and HA reduced pain at 6 months. PRP improved VAS by at least 50% at 3 months. PRP was more effective in

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
									patients with KL grade II KOA. There were no significant differences between the two groups.
11. Askari et al, 2016, Iran[31]	To evaluate the therapeutic effect of HA compared with CS for KOA.	RCT, 2 groups (HA, CS)	Total: 140 - HA: 71 - CS: 69	Mean age: 57.0 ± 9.1 (CS): 58.5 ± 8.3 (HA) Gender: 17.4% male (CS); 12.7% male (HA) KL grade II–III	HA: 2 ml of HMW HA, single i.a. injection; CS: 40 mg of CS, single i.a. injection	Baseline, 1, 2, and 3 months	VAS, WOMAC, KOOS	No AEs reported	HA provided longer lasting pain relief than CS. Both treatments improved KOOS daily activities and physical function, but pain and stiffness did not show significant improvement in either group.
12. Duymus et al, 2017, Turkey [18]	To compare the efficacy of PRP, HA and ozone injections in patients with mild to moderate and moderate KOA.	RCT, 3 groups (PRP, HA, ozone)	Total: 102 - PRP: 33 - HA: 34 - Ozone: 35	Mean age: 60.4 ± 5.1 (PRP), 60.3 ± 9.1 (HA), 59.4 ± 5.7 (Ozone) Gender: 97.0% female (PRP), 97.1% (HA), 88.6% (Ozone) KL grade II–III	PRP: 3–4 m of PRP (from 14 ml blood), 2 i.a. injections, 1-month interval; HA: 40 mg/2 ml of HA (1.6 MDa), single i.a. injection; Ozone: 15 ml of ozone (30 µg/ml), 4 i.a. injections, weekly along with 2 ml of lidocaine	Baseline, 1, 3, 6, and 12 months	VAS pain, WOMAC (pain, stiffness, function, total)	No AEs reported	PRP was superior to HA and ozone at 12 months. Both HA and PRP were effective up to month 6, while ozone's effectiveness lasted only until month 3.
13. Siddharth et al, 2017, India[42]	To compare the effectiveness and safety of CS and HA injections for treating KOA.	RCT; 2 groups (HA, CS)	Total: 150 - HA: 75 - CS: 75	Mean age: 71.4 ± 1.4 (HA), 69.5 ± 1.7 (CS) Gender: 40% male (HA), 50.7% male (CS)	HA: single i.a. injection of HA (product and volume of injection not specified); CS: single i.a. injection of 80 mg	Baseline, 3, and 6 months	VAS pain, WOMAC score	No AEs reported	No significant difference in WOMAC and VAS scores were found at 6 months between HA

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
				KL grade: not specified	methylprednisolone				and CS. Males responded better to the treatment than females.
14. Louis et al, 2018, France[28]	To assess non-inferiority of a single PRP injection versus HA in patients with KOA and to determine the biological characteristics of PRP that may influence its efficacy.	RCT, 2 groups (PRP, HA)	Total: 54 (per-protocol analysis: 46) - PRP: 22 - HA: 24	Mean age: 53.2 ± 11.7 (PRP), 48.5 ± 11.5 (HA) Gender: 58.3% male (PRP), 45.8% male (HA) KL grade II	PRP: 3 ml of very pure PRP (2.4 ×10^6 platelets), single i.a. injection; HA: 60 mg/3 ml non-animal stabilized HA, single i.a. injection	Baseline, 1, 3, and 6 months	WOMAC, VAS, satisfaction, responder rate	No AEs related to treatment reported;	A single injection of very pure PRP is not inferior to HA for treating KOA. The PRP group showed a higher responder rate (73% *vs.* 46%), although it was not statistically significant. High doses of TGF-β1 and PDGF-AB were correlated with poorer outcomes.
15. Lisi et al, 2018, Italy[43]	To compare the efficacy of activated PRP versus HA in patients with KOA.	RCT, 2 groups (PRP, HA)	Total: 58 - PRP: 30 - HA: 28	Mean age: 56.2 ± 6.8 (PRP), 56.8 ± 7.4 (HA) Gender: 68.9% female (PRP), 68.2% female (HA) MRI grade II–III (Shahriaree classification)	PRP: autologous PRP + calcium gluconate, 3 i.a. injections, 4-week interval HA: 20 mg/2 ml of HMW HA,3 i.a. injections, 4-week interval	Baseline, 15 days, 6, and 12 months	MRI grading (primary), VAS, WOMAC, AKSS, Lysholm, Tegner, Lequesne, ROM	No AEs reported	Activated PRP significantly improved MRI grading (48.3% *vs.* 8%, $p < 0.003$), WOMAC ADL, AKSS, and Lequesne scores. PRP may delay progression of the condition and improve QoL.
16. Ahmad et al,	To compare the	RCT, 2	Total: 89	Mean age: 56.2	HA: 20 mg/2 ml of	Baseline,	VAS pain,	No AEs	HA improved all

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
2018, Egypt[11]	efficacy of PRP and HA in patients with primary KOA and to determine whether clinical outcomes are associated with structural changes in ultrasonography.	groups (PRP, HA)	- PRP: 45 - HA: 44	± 6.8 (PRP), 56.8 ± 7.4 (HA) Gender: 68.9% female (PRP), 68.2% female (HA) KL grade I–III	HMW HA, 3 i.a. injections, 2-week interval; PRP: 4 ml of PRP (prepared from 8 ml of peripheral blood, single centrifugation, not leucocyte-free), 3 i.a. injections, 2-week interval	3, and 6 months	IKDC score, Ultrasound: synovial vascularity, synovial hypertrophy, and effusion	reported	clinical and ultrasonography outcomes measured at 3 and 6 months. However, PRP was significantly more effective in reducing pain, synovial hypertrophy, vascularity, and effusion, as well as improving IKDC scores compared to HA.
17. Di Martino et al, 2019, Italy[44]	To compare the long-term clinical outcomes provided by PRP or HA in treating KOA.	RCT, 2 groups (PRP, HA)	Total: 192 - PRP: 96 - HA: 96	Mean age: 52.7 ± 13.2 (PRP), 57.5 ± 11.7 (HA) Gender: 62.4% male (PRP), 57.3% male (HA) KL grade I–III	PRP: 5 ml of leukocyte-rich PRP, 3 i.a. injections, 1-week interval; HA: 30 mg/2 ml of HMW HA (>1500 KDa), 3 i.a. injections, 1-week interval	Baseline, 2, 6, 12, and 24 months	IKDC, EQ-VAS, Tegner	Two patients discontinued treatment in the PRP group due to AEs	Both PRP and HA improved symptoms with no significant difference in scores or effect duration. The PRP group had a lower reintervention rate at 24 months (22.6% vs 37.1%, p = 0.036).
18. Huang et al, 2019, China[45]	To compare the efficacy of PRP, HA, and CS in the treatment of early KOA.	RCT; 3 groups (PRP, HA, CS)	Total: 120 - PRP: 40 - HA: 40 - CS: 40	Mean age: 54.8 ± 1.1 (HA), 54.3 ± 1.4 (CS), 54.5 ± 1.2 (PRP) Gender: 47.5% male (HA), 52.5% male (CS), 62.5% male (PRP)	HA: 2 ml of HA (500–730 kDa), 3 i.a. injections, 1-week interval; CS: 1 ml of corticosteroid, single i.a. injection; PRP: 4 ml of LP-PRP (prepared from 8 ml	Baseline, 3, 6, 9, and 12-months	WOMAC, VAS	No infections or fever reported; Mild pain, nausea, and dizziness occurred in HA (1.7%), CS (2.5%), and	HA injection resulted in a significant improvement in pain and function, which was sustained for up to 12 months. PRP

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
				KL grade I–II	of peripheral blood, single centrifugation, leucocyte-poor), 3 i.a. injections, 3-week interval			PRP (4.2%)	showed superior long-term outcomes compared to HA and CS.
19. Buendía-López et al, 2019, Spain[46]	To evaluate the safety and clinical efficacy of a single leukocyte-poor PRP injection compared with a single HA injection and daily NSAID in patients with KOA and to assess radiographic and MRI progression at 52 weeks.	RCT, 3 groups (PRP, HA, NSAID)	Total: 98 - PRP: 33 - HA: 32 - NSAID: 33	Mean age: 56.2 ± 6.8 (PRP), 56.8 ± 7.4 (HA) Gender: 68.9% female (PRP), 68.2% female (HA) KL grade I–III	HA: 60 mg/2 ml of HMW HA, single i.a. injection; PRP: 5 ml of LP-PRP (prepared from 60 ml of peripheral blood, double centrifugation), activated with 1 ml calcium chloride, single i.a. injection; NSAID: oral etoricoxib 60 mg/day + omeprazole 20 mg/day for 52 weeks	Baseline, 6, and 12 months	WOMAC (pain, stiffness, physical function), VAS, MRI, X-ray	Two AEs in the HA group (pain and post-injection swelling); No AEs reported in the PRP or NSAID groups.	LP-PRP showed significant improvement in pain, stiffness, and physical function at 6 and 12 months compared to HA and NSAID. No differences in KL grade or cartilage thickness on MRI were observed.
20. Lin et al, 2019, Taiwan[14]	To compare the efficacy of PRP and HA with saline (NS) in KOA.	RCT; 3 groups (PRP, HA, NS)	Total: 87 - PRP: 31 - HA: 29 - NS: 27	Mean age: 61.17 ± 13.08 (PRP), 62.53 ± 9.9 (HA), 62.23 ± 11.71 (NS) Gender: 70.97% female (PRP), 65.52% female (HA), 62.96% female (NS) Ahlbäck stage I–III	PRP: 2 ml of leukocyte-poor PRP, 3 weekly i.a. injections; HA: 20 mg/2 ml of HA (>2,500 kDa), 3 weekly i.a. injections; NS: 2 ml of normal saline, 3 weekly i.a. injections	Baseline, 1, 2, 6, and 12 months	WOMAC, IKDC	No serious AEs, transient injection-site pain resolved spontaneously	PRP provided sustained improvement in WOMAC and IKDC scores at all follow-up points. PRP was found to be statistically and clinically superior to HA and NS. HA showed no significant difference compared to NS after 1 month. PRP was the

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
									only treatment that achieved MCID at all timepoints.
21. Kesiktas et al, 2020, Turkey[16]	To compare the efficacy of peptides with HA and PRP in patients with KOA.	RCT, 3 groups (peptides, HA, PRP)	Total: 54 - peptides: 18 - HA: 18 - PRP: 18	Mean age: 59.7 ± 6.8 (peptides), 52.7 ± 8.3 (PRP), 55.1 ± 10.3 (HA) Gender: 77.8% female (peptides), 88.9% female (PRP), 77.8% female (HA) KL grade II–IV	Peptides: 2 ml of peptides 1.5%, single i.a. injection; HA: 2 ml of linear macromolecular HA (1.7–2.1 MDa), single i.a. injection; PRP: 2-3 ml of PRP containing buffy coat (prepared from 17–18 ml blood), single i.a. injection	Baseline, 1 week, 1, and 3 months	VAS (rest, movement), WOMAC (pain, stiffness, function, total), HAQ, Lequesne Index	No AEs reported	HA, peptides, and PRP improved pain and function. The peptide group showed significantly better WOMAC pain and VAS-resting pain at 3 months compared to the other groups. There was no difference in other outcomes among the groups.
22. Bahrami et al, 2020, Iran[9]	To compare the effects of cross-linked HMW HA versus linear LMW HA on pain and functional improvement in patients with KOA.	RCT, 2 groups: (HMW HA, LMW HA)	Total: 90 - HMW HA: 44 - LMW HA: 46	Median age: 56 (41–66) (HMW-HA), 59.5 (45–70) (LMW-HA). Gender: 71.8% female (HMW-HA), 75% female (LMW-HA) KL grade II–III	HMW HA: 60 mg/3 ml of cross-linked HA, single i.a. injection; LMW HA: 20 mg/2 ml of linear LMW HA (500–730 kDa), 3 weekly i.a. injections	Baseline, 2, and 6 months	WOMAC, Lequesne, VAS	No systemic AEs reported; Minor events: injection pain, stiffness, and swelling	A single i.a. cross-linked HMW HA injection was found to be as effective as three weekly i.a. LMW HA injections over 6 months in improving pain and function. Only WOMAC stiffness at 2 months favored LMW HA ($p = 0.021$).
23. Park et al,	To compare the	RCT, 2	Total:	Mean age:	PRP: 3 ml of	Baseline, 6	IKDC, VAS	No serious	The PRP

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
2021, Republic of Korea[47]	efficacy of PRP versus HA in KOA and to assess the association between PRP composition and clinical efficacy.	groups (PRP, HA)	110 - PRP: 55 - HA: 55	60.6 ± 8.2 (PRP), 62.3 ± 9.6 (HA) Gender: 29.1% male (PRP), 14.5% male (HA) KL grade I–III	leukocyte-rich PRP, single i.a. injection; HA: 30 mg/3 ml of HA (>10,000 kDa), single i.a. injection	weeks, 3, and 6 months	pain, WOMAC, Patient Global Assessment, SMC patellofemoral score	AEs reported; Mild to moderate AEs occurred in both groups	treatment showed a significantly greater improvement in IKDC scores after 6 months. A higher percentage of patients achieved scores above the MCID for VAS after 6 months with high levels of PDGF-BB and PDGF-AB observed in responders.
24. Raeissadat et al, 2021, Iran[25]	To compare the short- and long-term efficacy of HA, PRP, PRGF, and ozone in patients with KOA.	RCT, 4 groups (HA, PRP, PRGF, Ozone)	Total: 200 - PRP: 52 - PRGF: 51 - HA: 49 - Ozone: 48	Mean age: 56.09 ± 6.0 (PRP), 56.07 ± 6.3 (PRGF), 57.91 ± 6.7 (HA), 57.60 ± 6.1 (Ozone) Gender: 75.0% female (PRP), 72.5% female (PRGF), 75.5% female (HA), 75.0% female (Ozone) KL grade II–III	HA: 20 mg/2 ml of HMW HA, 3 i.a. injections; 1-week interval; PRP: 4 ml of PRP (prepared from 35 ml of peripheral blood, double centrifugation, not leucocyte-free), 2 i.a. injections, 3-week interval; PRGF: 2 ml of PRGF, 2 i.a. injections, 3-week interval; Ozone: 10 ml	Baseline, 2, 6, and 12 months	VAS, WOMAC (pain, stiffness, function), Lequesne index (pain, walk, ADL, total)	No serious AEs reported; Minor post-injection pain was more common in the PRP and PRGF groups.	Treatment with HA resulted in a modest reduction in pain compared to baseline. Ozone showed superior short-term efficacy. After 6 months, HA, PRP, and PRGF were superior to ozone. At 12 months, only PRP and PRGF maintained significant clinical benefits and were superior to both HA and ozone.

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
					of ozone-oxygen (30 μg/ml), 3 i.a. injections, 1-week interval				
25. Bansal et al, 2021, India[12]	To standardize the ideal PRP dosage and assess the subjective, structural and physiological efficacy of PRP in KOA.	RCT; 2 groups (PRP, HA)	Total: 150 - PRP: 75 - HA: 75	Mean age: 64.4 (PRP), 65.8 (HA) Gender: 60.9% male (PRP), 61.8% male (HA) KL grade II–III	HA: 4 ml of HMW HA (22 mg/ml), single i.a. injection; PRP: 8 ml of PRP (10 billion platelets), inactivated, leukocyte-free, single i.a. injection	Baseline, 1, 3, 6, 9, and 12-months	WOMAC, IKDC, 6MWD, X-ray (JSW), MRI (cartilage thickness), IL-6, IL-8, TNF-α	Mild transient AEs (pain, stiffness, synovitis), no permanent adverse events	PRP injection significantly improved WOMAC, IKDC and 6MWD scores for up to 12 months and showed better maintenance of JSW and cartilage thickness compared to HA. PRP was also more effective than HA in reducing pain and cytokines.
26. Arliani et al, 2021, Brazil[13]	To compare the effects of i.a. infiltration of PRP versus HA in patients with primary KOA.	RCT; 2 groups (HA, PRP)	Total: 29 - HA: 15 - PRP:14	Mean age: 62.78 ± 6.10 (PRP); 63.40 ± 4.99 (HA) Gender: 78.6% female (PRP); 86.7% female (HA) KL grade II–III	HA: 48 mg/6 ml of cross-linked HA (6 MDa), single i.a. injection; PRP: 5 ml of PRP, 3 i.a. injections, 1-week interval	WOMAC: baseline, 1, 3, and 6 months VAS: 2, and 4 months	WOMAC (pain, function), VAS pain score	No serious AEs or allergic reactions reported	Both HA and PRP improved pain and function temporarily. There was no significant difference between the two groups during the follow-up period.
27. Wang et al, 2022, Taiwan[23]	To compare the efficacy of PRP	RCT, 2 groups	Total: 110	Mean age: 61.87 ± 5.46	PRP: 4 ml of PRP, leukocyte-poor,	Baseline, 1, 3, and 6	WOMAC: pain, stiffness,	Mild joint swelling in 4	Both PRP and HA improved

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
	versus novel crosslinked HA for early-stage KOA.	(PRP, HA)	- PRP: 54 - HA: 56	(PRP), 63.00 ± 5.33 (HA) Gender: 77.8% female (PRP), 71.4% female (HA) KL grade I–II	single i.a. injection; HA: 60 mg/3 ml of cross-linked HA, single i.a. injection	months	function, total	patients of the HA group but resolved in 1-3 days	WOMAC scores at 6 months, with no significant difference between the two groups. However, PRP showed faster improvement within the first 1-3 months.
28. Khan et al, 2023, Pakistan[33]	To evaluate the effectiveness of HA and CS in the management of KOA.	RCT; 2 groups (HA, CS)	Total: 88 - HA: 44 - CS: 44	Mean age: 58.08 ± 7.89 Gender: 31.8% male KL grade II–III	HA: 48 mg/6 ml of HA + 1 ml of 2% lignocaine, single i.a. injection; CS: 40 mg/1 ml of triamcinolone acetonide + 1 ml of 2% lignocaine, single i.a. injection.	Baseline, 2, 6 weeks, and 3 months	VAS pain score; WOMAC score	No AEs reported	CS showed rapid but temporary effects, while HA showed slow yet sustained improvement. By the second week, CS was more effective but by the sixth week and the third month, HA showed better improvement than CS.
29. Tschopp et al, 2023, Switzerland*[15]	To compare the clinical outcomes of CS, HA, or PRP with a placebo in patients with mild to moderate KOA.	RCT, 4 groups (placebo, CS, HA, PRP)	Total: 120 - CS: 30 - HA: 30 - PRP: 30 - Placebo: 30	Mean age: 60.0 (PRP), 64.0 (HA) Gender: 42.9% female (PRP), 37.5% female (HA) KL grade I–III	Placebo: 1 ml of contrast agent (single i.a. injection); CS: 40 mg/1 ml of triamcinolone (single i.a. injection); HA: 6 ml of HA (single i.a. injection); PRP: 3 ml of PRP (prepared from 15 ml of blood,	Baseline, 1 week, 3, 6, 9, 12, 15, 18, 21, and 24 months	NRS, WOMAC (pain, stiffness, physical function), Tegner Activity Scale, ROM, thigh circumference	Two patients in the CS group: 05 AEs including facial redness, palpitations, joint effusion, nausea, vomiting	HA injection showed small reductions in pain compared to baseline, with no statistically or clinically significant superiority over placebo. Overall, there

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
					leukocyte-poor), single i.a. injection				was no evidence that HA, PRP, or CS injections had superior short- or long-term effects compared to placebo.
30. Tschopp et al, 2024, Switzerland**[48]	To detect and compare knee cartilage changes after CS, HA, or PRP treatment to placebo using quantitative and morphological MRI parameters in patients with mild to moderate KOA.	RCT, 4 groups (CS, HA, PRP, placebo)	Total: 120 - CS: 30 - HA: 30 - PRP: 30 - Placebo: 30	Median age: 60.0 (54.0–68.0) KL grade I–III	Placebo: 1 ml of contrast agent, single i.a. injection; CS: 40 mg/1 ml of triamcinolone, single i.a. injection; HA: 6 ml of HA, single i.a. injection; PRP: 3 ml of PRP (prepared from 15 ml of blood, leukocyte-poor), single i.a. injection	Baseline, 3, and 12 months	*Quantitative* MRI, Outerbridge grade, bone marrow edema, subchondral cysts, osteophytes	No AEs reported	PRP improved cartilage quality in the medial femoral compartment at 12 months compared to CS and placebo. There were no group differences in morphological MRI outcomes and no significant effect was found with HA.
31. Ghorbani et al, 2024, Iran[26]	To compare the short-term therapeutic effects HA and PRP in patients with KOA.	RCT, 2 groups (HA, PRP)	Total: 90 - PRP: 45 - HA: 45	Mean age: 60.24 ± 1.97 (PRP), 61.90 ± 2.06 (HA) Gender: 63.4% female (PRP), 59.1% female (HA) KL grade I–III	PRP: 5 ml of PRP, 3 i.a. injections, 1-month intervals; HA: 20 mg/2 ml of HA, 3 i.a. injections, 1-week intervals	Baseline, 3 months	WOMAC: pain, stiffness, physical function, total	No AEs reported	The PRP group experienced a significantly greater reduction in pain, stiffness, and improvement in physical function compared to the HA group at 3 months post-injection, regardless of KL

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
									grade.
32. Partan et al, 2024, Indonesia[27]	To evaluate the efficacy of PRP compared to HA and correlation with PDGF-BB.	RCT, 2 groups (PRP, HA)	Total: 30 - HA: 15 - PRP: 15	Mean age: 54.3 ± 9.1 (PRP), 55.5 ± 6.2 (HA) Gender: 93% female (PRP), 93% female (HA) KL grade II–III	HA: 20 mg/2 ml of HMW HA, 3 i.a. injections, 2-week interval PRP: 4 ml of PRP (prepared from 8 ml of blood, not leucocyte-free), 3 i.a. injections, 2-week interval	Baseline, 12 weeks	VAS, WOMAC, PDGF-BB concentration	No serious AEs reported; minimal side effects (mild pain, effusion)	PRP showed a greater reduction in VAS (from 5 to 1) and WOMAC (from 79 to 20) compared to HA (VAS from 5 to 2; WOMAC from 55 to 21). PRP also increased PDGF-BB levels which had a strong negative correlation with pain and function scores.
33. Küçükakkaş et al, 2022, Turkey[34]	To evaluate the effects of HA and PRP injections on femoral cartilage thickness in chronic KOA and compare their efficacy.	RCT; 2 groups: HA and PRP	Total: 40 - HA: 20 - PRP: 20	Mean age: 57.5 ± 10.6 (PRP), 57.0 ± 10.1 (HA) Gender: 80.0% female (PRP), 70.0% female (HA) KL grade II–III	HA: 48 mg of HA 2% (3 MDa), single i.a. injection; PRP: 5 ml of PRP, single i.a. injection	Baseline, 1, and 6 months	VAS-rest, VAS-movement, WOMAC, femoral cartilage thickness (medial, lateral, mean)	No serious AEs reported	HA increased femoral cartilage thickness at 1 and 6 months, while PRP did not. Both HA and PRP were effective in improving pain, stiffness, and function with no superiority between the two treatments.

*, ** Two papers share the same trial but analyze different outcomes: one focuses on clinical effects, the other on cartilage MRI.

Units and Data Presentation: Continuous variables (e.g., age, outcome scores) are presented as mean ± standard deviation (SD) where available. Categorical variables (e.g., sex distribution, Kellgren-Lawrence grade) are reported as percentage or ordinal scales. Intervention details, including intra-articular injection regimens, doses, frequencies, and molecular weight (e.g., high molecular weight hyaluronic acid), are described based on the authors' original reporting. Outcome measures such as VAS, WOMAC, KOOS, and OMERACT-OARSI responder criteria are cited as used in the original studies.

Abbreviations: ADL, activities of daily living; AEs, adverse events; CS, corticosteroid; COGA, clinician overall global assessment; EQ-VAS, EuroQol visual analogue scale; HA, hyaluronic acid; HAQ, health assessment questionnaire; HMW, high molecular weight; i.a., intra-articular; IKDC, International Knee Documentation Committee; IL, interleukin; JSW, joint space width; KL, Kellgren-Lawrence; KOA, knee osteoarthritis; KOOS, Knee Injury and Osteoarthritis Outcome Score; LP-PRP, leukocyte-poor platelet-rich plasma; LMW, low molecular weight; MCID, minimal clinically important difference; MCII, minimal clinically important improvement; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; NS, normal saline; NRS, numeric rating scale; OARSI, Osteoarthritis Research Soci-

ety International; OMERACT, Outcome Measures in Rheumatology; PDGF, platelet-derived growth factor; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma; PTGA, patient global assessment; QoL, quality of life; RCT, randomized controlled trial; ROM, range of motion; SF-36, 36-Item Short Form Health Survey; SMC, standardized mean change; TGF-β, transforming growth factor-beta; TIMP-1, tissue inhibitor of metalloproteinase-1; TNF-α, tumor necrosis factor-alpha; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

pain reduction on the VAS scale at 4–6 months, outperforming lower-weight products. Colen et al[29] reported that the benefits of HA became apparent only after several weeks, suggesting a delayed-onset response rather than immediate relief.

Several RCTs support these findings. Arliani et al[13] found that both HA and PRP led to temporary pain relief and improved function for up to 6 months, with no significant difference between the two groups. Ahmad et al[11] observed that intra-articular HA resulted in significant pain and function improvements after 6 months, indicating sustained effectiveness in the midterm. Leighton et al[35] showed that cross-linked HMW HA injection provided lasting clinical benefits for KOA from week 12 to 26. Although both HA and CS showed similar pain relief at week 12, HA maintained or enhanced its effects over time, while CS efficacy declined. By week 26, HA demonstrated significantly better outcomes in pain reduction, joint function, and stiffness, with a favorable safety profile and no serious adverse events.[35]

These outcomes align with HA's delayed-onset biological actions, including CD44 receptor interaction, modulation of inflammatory cytokines, and restoration of synovial fluid rheology. Together, they suggest that HA achieves optimal therapeutic efficacy in the mid-term phase, especially in patients with mild-to-moderate KOA. This evidence supports the clinical preference for HA in patients seeking symptomatic relief beyond the acute phase, warranting further evaluation of its long-term utility.

LONG-TERM EFFICACY OF HA BEYOND A 6-MONTH PERIOD

Long-term data suggest that HA can provide sustained symptom relief beyond 6 months, although the magnitude of benefit remains modest. This sustained effect appears to be more prominent with high-quality formulations or repeated injection protocols. While early improvements may be limited, some studies report gradual, cumulative benefits over time.[24,37-40,43,44,46]

Supporting this, several RCTs provide corroborating evidence. In a 52-week RCT, Buendía-López et al[46] found that a single injection of HMW HA resulted in limited short- to medium-term improvements in WOMAC and VAS scores, but no sustained benefit at 12 months.

By contrast, the AMELIA trial, a 40-month randomized, placebo-controlled study, demonstrated that repeated intra-articular HA injections significantly improved KOA symptoms compared to placebo (80.5% *vs*. 65.8% responders, $p = 0.004$). Clinical benefits increased over successive cycles and persisted up to one year after the final injection, indicating a sustained carry-over effect. HA was well tolerated, with a safety profile comparable to placebo, supporting its role in long-term symptomatic management of KOA.[24]

Similarly, in a five-year double-blind RCT, Di Martino et al[44] evaluated the long-term clinical outcomes of intra-articular HA injections in patients with KOA. HA treatment led to significant improvements in knee function and symptoms up to 24 months post-injection, with the International Knee Documentation Committee (IKDC) score rising from 50.3 ± 13.2 at baseline to 62.1 ± 20.8. However, at final follow-up (mean 64.3 months), the clinical benefit had diminished, with IKDC scores returning close to baseline (55.7 ± 18.8, not significant). The median duration of patient-reported symptom relief was approximately 9 months.[44]

Overall, these findings indicate that the long-term efficacy of HA may depend on the injection regimen and patient selection. The delayed but progressive biological mechanisms— such as synovial restoration, anti-inflammatory signaling, and cartilage protection—likely contribute to sustained effects. Accordingly, repeated administration or synergistic combinations may optimize long-term outcomes. Significantly, HA continues to demonstrate durable clinical utility beyond the short and mid-term, especially when tailored to formulation and patient phenotype.

COMPARATIVE EFFICACY OF HIGH- VERSUS LOW-MOLECULAR-WEIGHT HA

The clinical efficacy of intra-articular HA has been shown to vary across different formulations, with molecular weight emerging as a crucial factor that influences treatment outcomes. This section aims to summarize the current evidence comparing HMW and uhMW HA with LMW formulations, focusing on symptom relief, longevity, and direct comparisons from clinical trials.

HMW and uhMW HA have been found to offer better pain relief and functional improvement compared to LMW formulations. Several systematic reviews and meta-analyses have shown that not all HA products yield equivalent clinical benefit, with molecular weight being a key distinguishing factor. In a comprehensive network meta-analysis of 137 RCTs, Bannuru et al[51] identified HMW HA as one of the most effective non-surgical treatments for KOA, ranking it higher than LMW HA and various oral interventions. Similarly, in a systematic review of 68 studies, Altman et al[50] reported that HMW HA led to greater improvements in pain, often exceeding the MCID. These results collectively confirm that molecular size is a clinical factor in determining the efficacy of HA treatment.

HMW and uhMW HA are also associated with longer-lasting symptom relief and a reduced need for repeat injections. The durability of treatment effect is particularly important in chronic conditions such as KOA, where frequent interventions may pose practical and economic challenges. In a network meta-analysis of 64 RCTs, Phillips et al[52] showed that HMW HA was the only intra-articular treatment to consistently exceed the MCID for both pain and function at 3 months, whereas LMW HA did not. These findings suggest that HMW HA may provide more durable symptomatic relief, which could potentially translate into reduced reinjection requirements. These sustained benefits are believed to be due to superior viscoelastic properties, longer intra-articular residence time, and enhanced interaction with CD44 receptors on chondrocytes and synoviocytes. These biological mechanisms result in improved joint biomechanics and delayed symptom recurrence, supporting the preferential use of HMW formulations in long-term

management. Supporting this, a 40-month RCT by Navarro-Sarabia et al[24] demonstrated that repeated cycles of HA (900 kDa) led to cumulative improvements in pain and function, with responder rates exceeding 80% by the fourth cycle, reinforcing the importance of durability in HA therapy.

Direct head-to-head RCTs provide additional support for the clinical superiority of uhHMW over LMW HA. In a study by Huang et al,[53] a head-to-head RCT compared PRP combined with either LMW or uhMW HA. The results showed that the uhMW HA group had better outcomes in terms of pain and WOMAC scores especially in patients with more severe symptoms, underscoring the enhanced efficacy of higher molecular weight formulations.

Overall, these recent findings from head-to-head RCTs further validate the clinical rationale for prioritizing HMW or uhMW HA in the management of mild-to-moderate KOA.

COMBINATION THERAPY

HA AND PRP

The combination of HA and PRP offers superior pain relief and functional improvement compared to monotherapies. Several RCTs have demonstrated that HA and PRP yield greater clinical benefits than either agent alone. The HA and PRP combination therapy for KOA is presented in Table 2.

In a double-blind RCT, Lanna et al[54] reported that patients receiving HA and PRP showed significantly greater reductions in VAS at all time points up to 12 months compared to those receiving HA alone (with p-values ranging from 0.011 to <0.0001). Additionally, HA and PRP outperformed PRP alone in WOMAC physical activity scores at early time points (1-3 months). Ciapini et al[56] also found that HA and PRP achieved superior improvements in both VAS and WOMAC scores at 6 months compared to HA or PRP monotherapy, with statistically significant pain reduction ($p < 0.005$). In a large-scale trial involving 360 patients, Yu et al[19] observed that the HA and PRP group had the greatest reduction in total WOMAC score over 52 weeks (mean reduction: 23.7 points), significantly outperforming HA alone (10.9) and PRP alone (15.8) ($p < 0.0001$). These findings are further supported by a meta-analysis conducted by Du et al,[62] which confirmed the clinical superiority of the PRP and HA combination over PRP monotherapy across multiple outcome measures, including pain and function scores.

HA and PRP show potential benefits for structural improvements and diseasemodifying effects. In addition to providing relief from symptoms, recent evidence suggests that HA and PRP may have a positive impact on structural outcomes in KOA. A study by Zhang et al[58] utilized MRI-based WORMS scoring and found that at 12 months, HA and PRP significantly reduced bone marrow edema, a benefit not observed in the HA only group. While overall symptom scores were similar between the two groups, the structural changes seen may indicate a disease-modifying effect. Wu et al[21] also emphasized the synergistic biological mechanisms of HA and PRP: HA improves the rheological environment, while PRP promotes chondrogenesis. Together, they work to reduce inflammation through CD44 and TGF-βII signaling pathways, ultimately contributing to the protection and regeneration of cartilage.

HA and PRP may prolong therapeutic effects and decrease the frequency of reinjections. Some studies suggest that this combination therapy provides longer-lasting benefits.[54,55,58] In a 12-month study, Lanna et al[54] reported sustained improvements in VAS and WOMAC scores for the HA and PRP group compared to the HA-only group, demonstrating better durability throughout the study period. Zhang et al[58] further noted that while HA provided better shortterm relief, the HA and PRP group exhibited progressive structural and symptomatic improvements over time, indicating additive benefits with repeated cycles. According to a meta-analysis by Zhang et al[63] which included 9 RCTs the combination of PRP and HA in the treatment of KOA resulted in slight improvements in pain and joint function compared to PRP alone. However, these improvements did not reach the threshold for clinical significance. Notably, the combination therapy significantly reduced the incidence of adverse events, and may be a preferred option for patients prioritizing minimizing side effects, despite its modest symptomatic benefits. Although long-term data are still limited, the combination appears promising for reducing the need for frequent intra-articular injections. However, findings are not entirely consistent. In a double-blind RCT, Fossati et al[57] found no significant differences in WOMAC, VAS, KOOS, or IKDC scores at 6 or 12 months among patients treated with HA and PRP, HA alone, or PRP alone. Subgroup analyses based on age, BMI, or KOA grade did not show superior outcomes for the combination therapy. These results suggest that the potential benefits of HA and PRP may depend on patient selection, protocol standardization, and the specific formulation used.

HA AND CS

The combination of HA and CS provides synergistic effects, offering both rapid symptom relief and longer-term functional improvement. CS exhibit fast-acting anti-inflammatory effects, typically within days, while HA takes longer time to demonstrate its viscoelastic and chondroprotective benefits.[64] The complementary pharmacodynamics of these agents make their combination clinically appealing for KOA. The combination therapy of HA and CS for KOA is presented in Table 2.

In a double-blind RCT, Wang et al[61] found that HA and CS resulted in greater pain reduction at 1 and 3 months compared to HA monotherapy. By 6 months, the effect of CS diminished, while HA maintained its efficacy, making the combination comparable to HA alone. Similarly, Campos et al[60] reported that the combination of CS and HA led to greater improvements in

Lysholm and Knee Society Score (KSS) scores at one month in patients with Kellgren– Lawrence grade IV KOA, reflecting the rapid-onset effect of CS. However, these ben-

Table 2. Combination Therapy for KOA: HA with PRP and HA with CS

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
1. Lana et al, 2016, Brazil[54]	To evaluate the clinical effects of HA and PRP as monotherapy and in combination for mild to moderate KOA.	RCT, 3 groups (HA, PRP, HA + PRP)	Total: 105 - HA: 36 - PRP: 36 - HA + PRP: 33	Mean age: 60.0 ± 6.6 (HA), 60.9 ± 7.0 (PRP), 62.0 ± 6.1 (HA + PRP) Gender: 91.7% female (HA), 80.6% female (PRP), 81.8% female (HA + PRP) KL grade I–III	HA: 20 mg/2 ml of non-cross-linked HMW HA (2.4–3.6 MDa), 3 i.a. injections, 2-week interval; PRP: 5 ml of WBC-rich PRP, 3 i.a. injections, 2-week interval; HA + PRP: sequential injections of HA (20 mg/2 ml) then PRP (5 ml), same schedule	Baseline, 1, 3, 6, and 12 months	WOMAC (pain, stiffness, PA), VAS pain, CRP	Mild swelling in knee (3–5 days post-injection), no major AEs	HA in combination with PRP showed greater improvements in VAS and WOMAC PA compared to HA alone at all timepoints. PRP was superior to HA alone in pain and PA at 1 year, while HA + PRP was superior to PRP in PA at 30 and 90 days.
2. Yu et al, 2018, China[19]	To evaluate the efficacy and safety of PRP, HA, and their combination in patients with KOA.	RCT, 4 groups (PRP, HA, PRP + HA, placebo)	Total: 360 - PRP: 104 - HA: 88 - PRP + HA: 96 - Placebo: 72	Mean age: 46.2 ± 8.6 (PRP), 51.5 ± 9.3 (HA), 46.5 ± 7.5 (PRP + HA), 56.2 ± 8.4 (placebo) Gender: 51.9% female (PRP), 45.5% female (HA), 47.9% female (PRP + HA), 41.7% female (placebo)	PRP: 8 ml, weekly i.a. injection; HA: 0.2 mg of HA, weekly i.a. injection; PRP + HA (8 ml + 0.2 mg), weekly i.a. injection; Placebo: normal saline, weekly i.a. injection	Baseline, double-blind trial phase (4 weeks), double-blind extension phase (52 weeks)	WOMAC (pain, stiffness, physical function, total score), serum cytokines (e.g., IL-1β, IL-6, IL-10, VEGF, TNF-α, IL-17A, PD-ECGF, RANKL)	Hypertension, proteinuria, constipation, diarrhea, rash, vomiting, fatigue, hypertriglyceridemia, edema peripheral; Most common: hypertension, proteinuria	The combination of PRP and HA significantly improved pain, physical function, stiffness, and WOMAC scores more than PRP or HA alone. Additionally, combination therapy reduced inflammatory markers (IL-1β, IL-6,

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
									TNF-α, IL-17A, RANKL) and increased anti-inflammatory/ angiogenic markers (IL-10, VEGF, PD-ECGF).
3. Sun et al, 2021, Taiwan[55]	To investigate the efficacy and safety of combining cross-linked HA with a PRP versus PRP alone in patients with KOA.	RCT, 2 groups (PRP, HA + PRP)	Total: 85 - PRP: 42 - HA + PRP: 43	Mean age: 58.4 ± 8.1 (PRP), 60.6 ± 8.4 (HA + PRP) Gender: 56.4% female (PRP), 46.2% female (HA + PRP) KL grade II	PRP: 3 ml of PRP, single i.a. injection; HA + PRP: 3 ml of cross-linked HA, single i.a. injection, followed by 3 ml of PRP, sequential i.a. injections	Baseline, 1, 3, and 6 months	VAS pain, WOMAC (pain, stiffness, function), Lequesne index, SLS, rescue analgesics, patient satisfaction	Mild to moderate knee swelling and pain in 11.9% (PRP) and 13.9% (HA + PRP); resolved without treatment; no serious AEs	Both regimens were effective and safe over 6 months. PRP alone showed greater improvement in VAS pain and WOMAC scores at 1 month. Cross-linked HA plus PRP showed significantly greater reduction in VAS pain reduction at 6 months, indicating long-term benefits in moderate KOA.
4. Wu et al, 2022, Taiwan[21]	To assess the efficacy of PRP injection prior to HA compared to PRP alone in KOA on symptoms, balance, and risk of falls.	RCT, 2 groups (PRP + HA, PRP + NS)	Total: 45 - PRP + HA: 22 - PRP + NS: 23	Mean age: 62.2 ± 1.5 (PRP + HA), 61.3 ± 1.4 (PRP + NS) Gender: 81.8% female (PRP + HA), 78.3% female (PRP + NS)	PRP + HA: single i.a. injection of leukocyte-poor PRP, followed by single i.a. injection of HA (60 mg/3 ml of 2% cross-linked HA); PRP + NS: single	Baseline, 1, 3, 6, and 12 months	WOMAC (pain, stiffness, function, total), static balance (OSI, APSI, MLSI), risk of falls (Biodex	No side effects observed	PRP + HA significantly improved WOMAC pain, stiffness, and total scores, as well as static balance, compared to

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
				Ahlback stage I–III	i.a. injection of normal saline (3 ml) one week after PRP injection		Balance System)		PRP alone. There was no significant difference in WOMAC function or risk of falls between the two groups.
5. Huang et al, 2022, Taiwan[53]	To compare the efficacy of PRP combined with different types of HA in patients with KOA.	RCT, 2 groups (PRP + linear LMW HA, PRP + cross-linked HA)	Total: 99 - PRP + linear LMW HA: 50 - PRP + cross-linked HA: 49	Mean age: 61.9 ± 8.8 (linear LMW HA), 61.0 ± 8.1 (cross-linked HA) Gender: 64.6% female (linear LMW HA), 63.8% female (cross-linked HA) KL grade II	PRP + linear LMW HA: single i.a. injection of HA (25 mg/2.5 ml, avian-derived, 900 kDa), followed by single i.a. injection of PRP (3 ml); PRP + cross-linked HA: single i.a. injection of HA (60 mg/3 ml, fermentation -derived, >15 million Da), followed by single i.a. PRP (3 ml)	Baseline, 1, 3, and 6 months	VAS (pain), WOMAC (pain, stiffness, function, total), Lequesne index, single-leg stance (SLS), patient satisfaction, rescue analgesic use	Mild AEs: transient knee pain/swelling (12.0% linear LMW HA, 14.3% cross-linked HA); all resolved within 2 days; no serious AEs reported	Both groups demonstrated significant improvements in pain and function over a 6-month period. The PRP + linear LMW HA group showed better Lequesne index at 1 month and improved WOMAC-stiffness at 6 months. The PRP + cross-linked HA group showed superior SLS scores at 1, 3, and 6 months. There were no serious AEs, and both groups reported high patient satisfaction.
6. Ciapini et al, 2023,	To evaluate and compare the effectiveness of a	RCT, 3 groups	Total: 60	Median age: 60.2 (39–80),	HA: 40mg/2 ml of HA (1550 kDa),	Baseline, 3, and 6	VAS (pain), WOMAC	No adverse symptoms or signs	The PRP + HA group showed

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
Italy[56]	combination of PRP and HA with its two components administered alone in patients with grade II-III KOA.	(PRP + HA, HA, PRP)	- PRP + HA: 20 - HA: 20 - PRP: 20	Gender: 50% females per group KL grade II–III	monthly i.a. injection × 3 doses; PRP: 4 ml of PRP (prepared from 8 ml of blood), monthly i.a. injection × 3 doses; PRP + HA: 2 ml of HA + 4 ml of PRP, monthly i.a. injection × 3 doses	months	(function)	attributable to the received treatments reported	greatest improvements in VAS and WOMAC scores at 6 months. It was the only group that demonstrated continuous improvement from baseline to 3 and 6 months. The HA group showed initial improvement, but no further benefit was seen at 6 months. The PRP group showed a short-term benefit that was maintained at 6 months.
7. Fossati et al, 2024, Italy[57]	To evaluate the efficacy of combining PRP and HA in treating mild to moderate KOA, in comparison to using PRP or HA alone.	RCT, 3 groups (PRP + HA, PRP, HA)	Total: 173 - PRP + HA: 58 - PRP: 58 - HA: 57	Mean age: 60.8 ± 11.6 (PRP + HA), 59.7 ± 11.1 (PRP), 61.3 ± 11.4 (HA) Gender: 62.1% female (overall) KL grade: I–III	PRP + HA: 3 i.a. injections of homogeneous solution, 2-week interval; PRP: 3 i.a. injections; HA: 40 mg/2 ml of non-cross-linked HA, 3 i.a. injections	Baseline, 3, 6, and 12 months	WOMAC, KOOS, IKDC, VAS, Tegner activity score Paracetamol/ NSAID use recorded	Mild pain/swelling: (34.5% in PRP + HA, 32.8% in PRP, 43.9% in HA), not statistical significance (p = 0.49); No serious AEs reported	All treatments (PRP + HA, PRP, HA) significantly improved pain and function. There were no statistically significant differences among the groups at 6 or 12 months in WOMAC, KOOS, IKDC,

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
									VAS, or Tegner scores. Combination therapy was found to be safe, but not superior to the others.
8. Zhang et al, 2025, Singapore[58]	To compare the efficacy of HA + PRP versus HA alone for KOA using clinical outcomes and MRI structural analysis.	RCT, 2 groups (HA + PRP, HA)	Total: 58 - HA + PRP: 29 - HA: 29	Mean age: 57.7 ± 8.0 (HA + PRP), 56.7 ± 8.1 (HA) Gender: 44.8% female (both groups) KL grade: II–III	HA + PRP: 3 ml of leukocyte-poor PRP + 20 mg/2 ml of non-crosslinked HA (1550 kDa), 2 i.a. injections, 2–4 weeks apart; HA: 20 mg/2 ml of non-crosslinked HA (1000–2900 kDa), 2 i.a. injections, 2–4 weeks apart	Baseline, 1, 3, 6, and 12 months	VAS (pain), WOMAC (total, pain, stiffness, difficulty), EQ-5D-5L, MRI-based WORMS (total score, bone marrow edema, synovitis)	No serious AEs reported; Mild and transient pain/swelling at injection site with no significant difference between groups	Both HA + PRP and HA reduced pain and improved function at 12 months. HA showed greater pain reduction at 1 and 6 months. Additionally, HA + PRP significantly reduced bone marrow edema on MRI at 12 months, indicating potential structural benefits. However, clinical superiority over HA alone was not established.
9. Petrella et al, 2015, Canada, Europe, Curaçao[59]	To evaluate the safety and initial performance of HA, HA + CS, and cross-linked HA in patients with KOA.	RCT, 3 groups (HA, HA + CS, cross-linked HA)	Total: 98 - HA: 32 - HA + CS: 34 - Cross-linked HA: 32	Mean age: 59 ± 12 (HA), 61 ± 11 (HA + CS), 59 ± 12 (cross-linked HA) Gender: 62.5% female (HA), 58.8% female	HA: 6 ml of linear HA, single i.a. injection; HA + CS: 6 ml of linear HA + 10 mg triamcinolone acetonide, single i.a. injection;	Baseline, 2, 6, 13, and 26 weeks	WOMAC (pain, stiffness, function); OMERACT-OARSI, responder rate	AEs in ≥ 5%: arthralgia (HA + CS 21%), headache (12%), muscle spasm (9%). 3 AEs related to treatment in HA + CS group; no treatment-related serious AEs	HA + CS showed faster and greater pain relief at 2 weeks (-12.4 mm *vs.* HA, $p = 0.04$), with all groups

Authors, year, region	Aim of study	Study design, No. of groups	Sample size	Population Characteristics	Interventions and Comparators	Evaluated timepoints	Outcome parameters	Adverse events	Key findings
				(HA + CS), 50% female (cross-linked HA) KL grade II–III	Cross-linked HA: 6 ml of cross-linked HA, single i.a. injection				showing improvement. HA + CS had fewer treatment-related AEs.
10. Campos et al, 2017, Brazil[60]	To evaluate the short-term effects of visco-supplementation in patients with severe KOA.	RCT, 3 groups (CS, HA, CS + HA)	Total: 143 - CS: 51 - HA: 46 - CS + HA: 46	Gender: 73.3% female (overall) KL grade IV	CS: 20 mg/1 ml of triamcinolone hexacetonide, single i.a. injection; HA: 6 ml of HA, single i.a. injection; CS + HA: 1 ml of CS + 6 ml of HA, single i.a. injection	Baseline, 1, 3, and 6 months	Lysholm score, KSS (functional and total)	No severe AEs reported	All groups showed functional improvement at 1-3 months, but the effects declined by 6 months. There were no significant differences between the HA and CS groups.
11. Wang et al, 2018, China[61]	To investigate whether the co-injection of HA and CS is superior to HA alone in the treatment of KOA.	RCT, 2 groups (HA, HA + CS)	Total: 120 - HA: 60 - HA + CS: 60	Mean age: 62.5 ± 6.6 (HA), 63.6 ± 6.2 (HA + CS) Gender: 73.3% female (HA), 76.7% female (HA + CS) KL grade II–IV	HA: 4 ml of HMW HA, single i.a. injection; HA + CS: 4 ml of HMW HA + 3 ml of compound betamethasone solution, single i.a. injection	Baseline, 1 week, 1, 3, and 6 months	VAS pain; WOMAC score (pain, stiffness, function); knee flexion ROM	No severe AEs reported	HA + CS resulted in faster pain relief and improved function from 1 week to 3 months; however, there was no significant difference at 6 months. HA alone also showed improvement in symptoms. Co-injection did not demonstrate superior long-term outcomes.

Units and Data Presentation: Continuous variables are presented as mean ± standard deviation. Age is reported in years, and gender as a percentage per group. Sample size is shown as total and per group. KOA severity is classified using KL grade or Ahlbäck stage, where applicable. HA, PRP, and CS doses are reported in ml or mg, with molecular weight specified if available. Follow-up duration is presented in weeks or months. Outcomes include VAS, WOMAC, Lequesne index, KOOS, IKDC, EQ-5D-5L, Lysholm score, KSS, ROM, and MRI-based WORMS. Adverse events are described by type and frequency or rate.

Abbreviations: IA, intra-articular; HA, hyaluronic acid; PRP, platelet-rich plasma; KOA, knee osteoarthritis; RCT, randomized controlled trial; KL, Kellgren–Lawrence; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; PA, physical activity; CRP, C-reactive protein; IL, interleukin; VEGF, vascular endothelial growth factor; TNF-α, tumor necrosis factor alpha; PD-ECGF, platelet-derived endothelial cell growth factor; RANKL, receptor activator of nuclear factor kappa-B ligand; SLS, single-leg stance; NS, normal saline; OSI, overall stability index; APSI, anterior–posterior stability index; MLSI, medial–lateral stability index; KOOS, Knee injury and Osteoarthritis Outcome Score; IKDC, International Knee Documentation Committee; Tegner, Tegner activity score; EQ-5D-5L, EuroQol 5 Dimensions 5 Levels; MRI, magnetic resonance imaging; WORMS, Whole-Organ Magnetic Resonance Imaging Score; HMW, high molecular weight; LMW, low molecular weight; AEs, adverse events; CS, corticosteroid; i.a., intra-articular; KSS, Knee Society Score; N/A, not available; OMERACT-OARSI, Outcome Measures in Rheumatology – Osteoarthritis Research Society International; ROM, range of motion.

efits diminished over time, and by 6 months, no significant differences were found between treatment groups.

Co-formulated intra-articular injections that combine HA and CS may enhance early symptom relief and improve treatment adherence through single-dose administration. Fixeddose formulations that deliver both agents simultaneously provide logistical advantages and may optimize short-term efficacy, particularly for patients seeking rapid pain control. In a RCT, Petrella et al[59] assessed a novel injectable formulation containing cross-linked HA and triamcinolone acetonide. This injectable combination led to significantly greater VAS pain reduction at 2 weeks (-35.6 mm *vs*. -23.3 mm, $p = 0.04$), with benefits sustained through 26 weeks, compared to HA alone and a standard HMW HA comparator. These findings support the therapeutic rationale for combining anti-inflammatory and viscoelastic components into a single preparation to achieve early efficacy without compromising durability.

MULTIFUNCTIONAL HA COMBINATIONS: BEYOND VISCOSUPPLEMENTATION

Combining HA with biologically active agents enhances symptomatic relief and functional outcomes in KOA more effectively than HA alone. While HA provides viscoelastic support and modest anti-inflammatory effects, pairing it with agents like fibrinogen, peptides, PDRN, and neuromodulators may amplify therapeutic efficacy through complementary mechanisms. These strategies aim not only to improve lubrication but also to modulate the joint microenvironment, reduce oxidative stress, and stimulate tissue regeneration.

For instance, in a randomized trial, Kandel et al[65] showed that HA conjugated with fibrinogen significantly improved pain (measured by VAS), function (WOMAC), and IKDC scores at 6 months compared to baseline, likely due to better retention and enhanced extracellular matrix stability. Similarly, Kesiktas et al[16] found that a peptide-enriched HA formulation containing oligopeptides resulted in greater reductions in WOMAC pain scores than both PRP and HA monotherapy at 3 months ($p < 0.05$), indicating that peptide-mediated modulation of inflammatory cytokines may boost HA efficacy. Furthermore, Yoon et al[66] reported that HA combined with PDRN outperformed HA alone in all categories of the KSS at 6 months, demonstrating potential regenerative synergy without compromising safety.

These findings collectively support the development of next-generation HA formulations that integrate mechanical support with molecular or cellular-level interventions, especially for patients with moderate KOA who are seeking both pain relief and functional recovery. The details are presented in Table 3, which covers emerging intra-articular combinations in KOA treatment, and Table 4, which provides an overview of meta-analyses on HA monotherapy and combination strategies in managing KOA.

REVIEW AND INSIGHTS

Intra-articular HA remains a crucial option for managing symptoms of KOA, especially for patients with mild to moderate disease who do not respond to oral medications or are unwilling to undergo surgery. This review of current literature provides valuable insights into the effectiveness of HA, both as a standalone treatment and when used in combination with other intra-articular agents.

Meta-analyses and high-quality RCTs consistently demonstrate that HA monotherapy results in statistically significant, albeit modest, improvements in pain and function compared to placebo or CS.[15,17,29,31,33,42,48,71] These benefits are particularly notable when using high or ultra-high molecular weight formulations, which may offer improved viscoelasticity, longer synovial residence time, and a higher likelihood of achieving MCID thresholds.[22,50-52] However, the variability in patient response underscores the importance of careful patient selection. Evidence suggests that HA is most effective in early-stage KOA (Kellgren–Lawrence I-II), with reduced efficacy in more advanced stages. Molecular weight is also an important factor in patient selection. HMW HA has demonstrated more consistent and clinically meaningful improvements in pain and function, making it suitable for patients with moderate-to-severe symptoms or those who require longer-lasting relief before considering surgery. In contrast, LMW HA may be more appropriate for individuals with earlier-stage disease or for those who place greater emphasis on cost, although the clinical benefits are generally less pronounced and repeat treatment may be required sooner.[52]

Additionally, differences in HA formulations appear to impact treatment outcomes. While early studies did not consistently demonstrate the superiority of one formulation over another,[29] more recent meta-analyses suggest that factors such as molecular weight, crosslinking, and injection protocols (single *vs*. multi-dose) can significantly influence clinical results.[22,24,50,74] These findings support a more tailored approach to HA product selection in clinical practice.

Combination therapies are increasingly recognized for their potential to improve outcomes by targeting different pathological pathways. Among these, the combination of HA and PRP is the most well-supported, with numerous RCTs and meta-analyses indicating superior pain relief and functional outcomes compared to monotherapy.[53,55,58,62,63,75,77,78] HA combined with CS also shows short-term benefits, particularly for managing symptomatic flares, although these effects tend to diminish after 12 weeks.[30,59-61,72] Additionally, newer combinations such as HA with fibrinogen, HA with botulinum toxin type A, and HA analogues such as polynucleotides (PN) and PDRN have demonstrated promising preliminary results. However, many of these strategies remain investigational, with limited long-term data and significant variability in study design, agent composition, and injection protocols.

It is essential to recognize the limitations within the current evidence base. Many trials are hindered by small sample sizes, short follow-up periods, and a lack of direct com-

Table 3. Emerging intra-articular combinations in KOA treatment

Authors, year, region	Study design; No. of groups	Sample Size/ Groups	Main Patient Characteristics	Interventions and Comparators	Evaluated timepoints	Results	Adverse events	Quality of study	Proposed mechanism of action
1. Ertürk et al, 2016, Turkey[67]	RCT, 2 groups - Group 1: HA - Group 2: HA + lidocaine–CS (PALCI)	Total: 70 - Group 1: 35 - Group 2: 35	Mean age: 61.4 ± 8.4 (HA), 62.7 ± 7.8 (HA + lidocaine-CS) Gender: 74.3% female (HA), 77.1% female (HA + lidocaine-CS) KL grade II–IV	Group 1: 25 mg/2.5 ml of HA, weekly i.a. injection × 5 weeks; Group 2: same HA regimen + single periarticular injection of 6.43 mg betamethasone dipropionate + 2.63 mg betamethasone sodium phosphate + 20 mg lidocaine HCl to tender medial soft tissue area	Baseline, 1, 3, 6, 12, 26, and 52 weeks	There was significant improvement in VAS, WOMAC, and HSS scores in Group 2 during the first 3 weeks. However, there was no difference at 6-52 weeks.	Minor AEs in 6/35 (17%): pain, bleeding, ecchymosis at injection site (resolved) in Group 2; Minor AEs in 2 patients: local swelling, pain	RCT, Level I, single-blind, moderate sample size	Corticosteroids reduce inflammation by inhibiting phospholipase A2. Lidocaine provides local analgesia, while HA provides viscosity and chondroprotection.
2. Turajane et al, 2017, Thailand[68]	RCT, 3 groups - Group 1: HA + AAPBSC + PRP + hG-CSF + MCS - Group 2: HA + AAPBSC + PRP + MCS - Group 3: HA	Total: 60 - Group 1: 20 - Group 2: 20 - Group 3: 20	Mean age: 54.9 ± 6.1 (group 1), 55.4 ± 2.3 (group 2), 54.7 ± 3.5 (group 3) Gender: group 1: 50% female, group 2: 85% female, group 3: 70% female KL grade II–III	Group 1: MCS, i.a. AAPBSC + PRP + hG-CSF + HA, i.a. once weekly × 3 weeks; Group 2: MCS, i.a. AAPBSC + PRP + HA, i.a. weekly × 3 weeks; Group 3: HA i.a. weekly × 3 weeks	Baseline, 1, 6, and 12 months	Significant improvements were observed in WOMAC scores, with Group 1 showing the highest improvement followed by Group 2 and then Group 3. Group 1 demonstrated a faster onset of improvement and a greater magnitude of	No notable AEs reported	RCT, moderate sample size, single center	AAPBSC and PRP may stimulate cartilage regeneration through paracrine effects, such as TGF-β, VEGF, and IGF-1. hG-CSF may enhance MSC recruitment, differentiation, and anti-inflammatory effects.

Authors, year, region	Study design; No. of groups	Sample Size/ Groups	Main Patient Characteristics	Interventions and Comparators	Evaluated timepoints	Results	Adverse events	Quality of study	Proposed mechanism of action
						improvement.			
3. Seihee Yoon et al, 2019, Korea[66]	RCT, 2 groups - HA + PDRN - HA	Total: 30 - HA + PDRN: 15 - HA: 15 (14 completed)	Mean age: 65.33 ± 4.78 (HA + PDRN), 64.86 ± 4.45 (HA) Gender: 53.3% female (HA + PDRN), 57.1% female (HA) KL grade II–III	HA: 3 weekly i.a. injections of HA; HA + PDRN: 3 weekly i.a. injections of HA and PDRN	Baseline, 1, 3, and 6 months	There was a significant improvement in VAS, WOMAC (excluding stiffness), and KSS (all domains) in the HA + PDRN group compared to the HA group at 6 months ($p < 0.05$).	No AEs, ADRs, or complications reported	RCT, moderate sample size, single center	PDRN may enhance the anti-inflammatory effect of HA by upregulating IL-10, inhibiting pro-inflammatory cytokines, and promoting extracellular matrix stabilization
4. Kesiktas et al, 2020, Turkey[16]	RCT, 3 groups - HA+ peptides - HA - PRP	Total: 54 - Group 1: 18 - Group 2: 18 - Group 3: 18	Mean age: 59.7 ± 6.8 (group 1), 55.1 ± 10.3 (group 2), 52.7 ± 8.3 (group 3) Gender: 77.8% female (Group 1 & 2), 88.9% female (Group 3) KL grade II–IV	Group 1: HA 1.5% + peptides, single i.a. injection; Group 2: HA (linear HA 1.7-2.1 MDa), single i.a. injection; Group 3: PRP, single i.a. injection	Baseline, 1 week, 1, and 3 months	There was a significant improvement in VAS (rest and movement), WOMAC, HAQ, and Lequesne Index in all groups. The peptide group showed significantly better WOMAC pain and VAS rest pain at 3 months compared to the HA or PRP ($p < 0.05$).	No AEs reported	RCT, small sample size, single center	Peptides modulate cytokine release, reduce inflammation, and prevent cartilage degeneration. HA provides viscosupplementation. PRP delivers growth factors such as TGF-β, VEGF, and IGF-1.
5. Kandel et al, 2020, Israel[65]	RCT, 4 groups - HA	Total: 67 - HA+PDF: 21 - HA+	Mean age: 67.26 ± 7 Gender:	HA+PDF: 4 ml of HA + pooled PDF, i.a.	Baseline, 1, 3, 4, and 6 months	VAS scores were significantly	AEs: not stratified by group due to	RCT, moderate sample size,	Fibrinogen is hypothesized to enhance the intra-

Authors, year, region	Study design; No. of groups	Sample Size/ Groups	Main Patient Characteristics	Interventions and Comparators	Evaluated timepoints	Results	Adverse events	Quality of study	Proposed mechanism of action
	+pooled PDF - HA + autologous PDF - Placebo → HA + PDF - Placebo → HA + autologous PDF	autologous PDF: 18 - Placebo → HA + PDF: 10 - Placebo → HA+autologous PDF: 10	74.24% female overall KL grade II–IV	injections at baseline and 3 months; HA+ autologous PDF: 4 ml of HA + autologous PDF, i.a. injection at baseline and 3 months; Placebo (0.9% NaCl) at baseline → HA + pooled PDF at 3 months; Placebo (0.9% NaCl) at baseline → HA + autologous PDF at 3 months		lower in the groups receiving treatment compared to placebo at 3 months ($p < 0.002$); WOMAC and IKDC showed improvement at baseline, but were not significantly different from placebo. These improvements were; sustained for up to 6 months.	blinding; Total: 34 AEs (52.9% mild, 38.2% moderate, 8.8% severe); 41.2% possibly treatment-related; no serious AEs reported.	multicenter, interim analysis	articular retention of hyaluronic acid, stabilize the extracellular matrix, and potentially provide a scaffold that supports tissue repair processes.
6. Bettonville et al, 2021, Belgium[69]	RCT, 4 groups - Group 1: HA + clonidine+ plasma - Group 2: HA + clonidine +plasma - Group 3: HA + clonidine +plasma - Group 4: cross-linked HMW HA (48 mg/6	Total: 164 - Group 1: 41 - Group 2: 41 - Group 3: 41 - Group 4: 41	Mean age: 64.2 ± 8.0 (group 1), 61.7 ± 7.0 (group 2), 62.9 ± 7.2 (group 3), 61.8 ± 7.7 (group 4) Gender: 75.6% female (group 1), 58.5% female (group 2), 65.9% female (group 3), 73.2% female (group 4). KL grade: II–III	Group 1: 20 mg/2 ml of HA + 100 µg clonidine + plasma protein solution (2 ml), single i.a. injection; Group 2: 20 mg/2 ml of HA + 200 µg clonidine + plasma protein solution (2 ml), single i.a. injection; Group 3: 20 mg/2 ml of HA	Baseline, 2 weeks, 3, and 6 months	Intra-articular injections of HA, clonidine, and plasma for the treatment of KOA were not superior to HA alone. However, *post-hoc* analyses on pooled data from all formulations of HA, clonidine, and plasma	Total AEs: 292 events in 116/164 patients (70.7%); Treatment-related AEs: group 1: 3/41 (7.3%), group 2: 8/41 (19.5%), group 3: 12/41 (29.3%), group 4: 11/41 (26.8%); Most common treatment-	Phase II/III, double-blind, multicenter RCT	HA and plasma proteins form a clotting gel through the coagulation cascade. This gel creates a 3D matrix that mimics synovial fluid, providing lubrication and protection for cartilage. Clonidine provides short-term analgesia.

Authors, year, region	Study design; No. of groups	Sample Size/ Groups	Main Patient Characteristics	Interventions and Comparators	Evaluated timepoints	Results	Adverse events	Quality of study	Proposed mechanism of action
	mL)			+ 200 µg clonidine + plasma protein solution (4 ml), single i.a. injection; Group 4: 48 mg/6 ml of cross-linked HMW HA, single i.a. injection		showed statistically significant larger improvements in WOMAC pain subscale scores than HA alone at 3 and 6 months.	related AEs: arthralgia, injection site pain, procedural hypotension. Serious AEs: 11 events in 8 patients (4.9%) across all groups		
7. Hegde et al, 2024, India[70]	RCT, 2 groups - Botulinum toxin type A + HA - PRP + HA	Total: 54 - Botulinum toxin + HA: 27 - PRP + HA:27	Mean age: 68.4 ± 7.64 (botulinum toxin + HA), 60.22 ± 8.52 (PRP + HA) Gender: 85.2% female (botulinum toxin + HA), 74.1% female (PRP + HA) KL grade III–IV	Botulinum toxin + HA: 100 units of Botulinum A + 60 mg of cross-linked HA, bilateral i.a. injection once; PRP + HA: 4 ml of PRP + 60 mg cross-linked HA, bilateral i.a. injection once	Baseline, 2, 4, 12, and 24 weeks	There was a significant reduction in NRS and WOMAC scores in both groups. However, the PRP + HA group showed greater improvement ($p < 0.001$).	No AEs in Botulinum A + HA group reported; 2 cases of increased pain in PRP + HA group (7.4%)	RCT, small sample size, single center	Botulinum toxin A inhibits acetylcholine release, reduces substance P, CGRP, and proinflammatory cytokines, and modulates pain centrally and peripherally. PRP promotes tissue repair, and modulates inflammation, and improves cartilage regeneration.

Units and Data Presentation: Continuous variables are expressed as mean ± standard deviation (SD). Categorical variables are presented as number (n) and percentage (%). Outcome measures include Visual Analog Scale (VAS) for pain, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Lequesne Index, Knee Society Score (KSS), International Knee Documentation Committee (IKDC) score, Health Assessment Questionnaire (HAQ), Hospital for Special Surgery (HSS) score, Numerical Rating Scale (NRS), and the 12-Item Short Form Survey (SF-12), as reported in individual studies. Kellgren–Lawrence (KL) grading was used to classify radiographic severity of osteoarthritis. Adverse events (AEs) are reported as total number and/or percentage per group, with further classification by severity when available. Follow-up durations and evaluation timepoints are presented in weeks or months as specified by the original authors.

Abbreviations: AE, adverse event; AAPBSC, autologous activated peripheral blood stem cells; ADR, adverse drug reaction; CGRP, calcitonin gene-related peptide; HA, hyaluronic acid; HAQ, Health Assessment Questionnaire; HMW, high molecular weight; HSS, Hospital for Special Surgery; hG-CSF, human granulocyte colony-stimulating factor; i.a., intra-articular; IKDC, International Knee Documentation Committee; IL-10, interleukin-10; KL, Kellgren–Lawrence; KSS, Knee Society Score; MCS, Microdrilling Mesenchymal Cell Stimulation; MW, molecular weight; N/A, not available; NRS, Numerical Rating Scale; PALCI, periarticular lidocaine-corticosteroid injection; PDF: plasma-derived fibrinogen; PDRN, polydeoxyribonucleotide; PRP, platelet-rich plasma; RCT, randomized controlled trial; SF-12, 12-Item Short Form Survey; TNFα, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; VAS, Visual Analog Scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

Table 4. Overview of meta-analyses on HA monotherapy and combination strategies in managing KOA

Author, year	Aim of study	Study design; No. of groups	Databases searched	Inclusion Criteria	Outcomes	Statistical Methods	Risk of Bias	Conclusion
1. Colen et al, 2012[29]	Evaluate the effectiveness of HA compared to a placebo in treating KOA, and compare the efficacy of various HA products.	Systematic review and meta-analysis (MOOSE guideline); Total sample size: not explicitly reported (e.g., 1180 patients from 18 RCTs comparing HA *vs* placebo); Groups: - HA: i.a. injections with various molecular weights, volumes, and dosing regimens; - Comparators: placebo (saline), other HA products, CS, PT Comparison: HA vs placebo; HA *vs* CS; HA *vs* PT or others	Medline, Cochrane systematic reviews, Cochrane clinical trial register, Embase (up to June 2011)	All RCTs evaluating i.a. injections of HA in KOA, regardless of severity, and all types/routes of HA	VAS for pain (primarily), WOMAC, KOOS, etc.	Random/ fixed-effects model, SMD, I^2 for heterogeneity, and subgroup analysis by product	Some studies were industry-sponsored, with high heterogeneity (I^2 = 92%). Potential publication bias was acknowledged.	HA showed modest efficacy compared to the placebo at 3 months, with no HA product clearly superior. The placebo effect was substantial, making the clinical significance of a ~10 mm difference on the VAS debatable.
2. Bannuru et al, 2015[51]	To compare the effectiveness of pharmacologic interventions for KOA in improving pain.	Network meta-analysis (PRISMA guidelines); Number of studies: 137 RCTs (39,556 participants); Sample size: 39,556 patients (total);	Medline, Embase, Cochrane library (up to August 2013)	All RCTs evaluating pharmacological treatments for KOA with a follow-up of at least 12 weeks	WOMAC pain (0–100)	Bayesian hierarchical random-effects model; SUCRA; SMD	Most trials were at low-to-moderate risk of bias (Modified Cochrane risk of bias).	HA and NSAIDs were the most effective treatments for KOA, while acetaminophen showed minimal effectiveness in comparison. The differences in effectiveness among the active treatments were small.

Author, year	Aim of study	Study design; No. of groups	Databases searched	Inclusion Criteria	Outcomes	Statistical Methods	Risk of Bias	Conclusion
		Interventions: acetaminophen, NSAIDs (e.g., diclofenac, ibuprofen, naproxen, celecoxib), i.a. HA, CS; Comparison: all interventions *vs* each other and *vs* placebo						
3. Wang et al, 2015[30]	Evaluate the therapeutic effect of HA versus CS for KOA.	Meta-analysis (no registered protocol); Number of studies: 7 RCTs Sample size: total n = 583 (HA: 298; CS: 285); Interventions: HA (various products and regimens, 1–5 i.a. injections); Comparison: CS (various agents, mostly single i.a. injection)	Pubmed, Embase, Cochrane central register of controlled trials, hand-search	All RCTs comparing HA versus CS with a follow-up of at least 3 months	VAS, Lequesne index, KSS, max flexion, AEs	Fixed/ random-effects model, inverse variance method, heterogeneity (I^2), sensitivity analysis	Most trials had a Jadad score of 3 or higher, indicating high overall quality. However, blinding varied among trials.	HA and CS were equally effective in the short term, but HA showed greater effectiveness at 3 to 6 months. AEs were similar for both treatments.
4. Trojian et al, 2016[71]	Evaluate the clinical efficacy of HA and CS compared to a placebo using the OMERACT-OARSI responder criteria.	Network meta-analysis (not registered); Number of studies: 11 RCTs; Sample size: Total n ≈ 3,691 (range per study: ~30–588); Interventions:	Medline, Embase, Cochrane central; grey literature; manual reference check	All RCTs in patients with KOA compared HA and CS versus placebo or each other. The outcomes included OMERACT-OARSI response or WOMAC scores at 8-26 weeks post-injection.	OMERACT-OARSI responder rate, WOMAC pain, stiffness, function	Random-effects meta-analysis and network meta-analysis, SMD, Egger test, heterogeneity (I^2), "netmeta" in R used for NMA	Most studies were assessed as having low risk of bias using the Cochrane Risk of Bias tool. However, there were some concerns related to blinding and incomplete data.	HA recommended for KOA (KL II-III) in individuals over 60 years old was found to be more effective than CS and placebo in OMERACT-OARSI response. CS was not found to be better than placebo.

Author, year	Aim of study	Study design; No. of groups	Databases searched	Inclusion Criteria	Outcomes	Statistical Methods	Risk of Bias	Conclusion
		i.a. injections of HA (various products and molecular weights, 1–5 injections); Comparison: HA versus CS and placebo						
5. Altman et al, 2016[50]	Determine the differences in efficacy and safety regarding the intrinsic properties of different HA treatments for KOA.	Meta-analysis (not registered), adapted from PRISMA; Number of studies: 68 RCTs using only single i.a. HA; Sample size: n = 5354 (total across all groups); - HMW HA group: n = 2094 - MMW HA group: n = 621 - LMW HA group: n = 2639 Interventions: single i.a. HA injection (various products); Comparison: placebo (saline), subgroup comparison by molecular weight and production method	Medline, Embase, Pubmed (search date: May 21, 2014)	RCTs on HA for KOA, reporting pain (measured by WOMAC or other scales), published after 1995, in English.	Pain (WOMAC, VAS), AEs (flare-up, effusion), trial discontinuation	Pooled effect sizes (Hedges' g), CI; P-values, subgroup analysis by molecular weigh and source	The quality of the studies was heterogeneous. There were incomplete safety data reported in some RCTs.	The efficacy of HA products varied in their properties. HMW HA and Bio-HA provided better efficacy and safety profiles.
6. Jevsevar	Evaluate the effectiveness of	Network meta-analysis;	Pubmed, Embase,	RCTs in English on KOA with a	VAS pain and WOMAC	Bayesian NMA,	Most of the studies were of	Naproxen was the most effective for pain and

Author, year	Aim of study	Study design; No. of groups	Databases searched	Inclusion Criteria	Outcomes	Statistical Methods	Risk of Bias	Conclusion
et al, 2018[10]	NSAIDs, acetaminophen, CS, PRP, and HA compared to placebo in KOA.	Number of studies: 56 RCTs; Total sample size: not explicitly stated; Interventions: i.a. CS, i.a. PRP, i.a. HA, NSAIDs (ibuprofen, naproxen, diclofenac, celecoxib), acetaminophen; Comparison: oral placebo, i.a. placebo, head-to-head	Cochrane central (last search Oct 7, 2015)	minimum of 30 patients per group and a follow-up of at least 28 days. The studies included human participants with at least 80% of individuals diagnosed with KOA.	function, both converted to MCID units	random-effects model, MCID unit conversion, posterior distribution over 200,000 iterations, OpenBUGS	high quality with a I^2 value of 0% in over 90% of studies. Publication bias was unlikely based on the funnel plots.	function, while i.a. CS and PRP were effective for pain relief. HA (i.a.) was not superior to i.a. placebo. Acetaminophen was the least effective.
7. Zhang et al, 2018[49]	Evaluate the effectiveness of PRP compared to HA in treating KOA.	Meta-analysis (PRISMA guideline); Number of studies: 13 studies (10 RCTs, 3 prospective); Sample size: PRP: n = 788; HA: n = 736; Interventions: i.a. PRP (1-3 injections, 3-8 ml), i.a. HA (various molecular weights, 1-3 injections); Comparison: PRP *vs* HA	Pubmed, Embase, Science-direct, Cochrane library (up to Sep 2017)	RCTs or prospective trials compared PRP with HA in KOA.	WOMAC, VAS, IKDC, EQ-VAS	RevMan 5.1, random-effects model, MD, 95% CI, heterogeneity (I^2), subgroup analysis by timepoints	Quality was assessed using the Cochrane RoB tool. Some trials were found to have unclear or high risk in the performance and/or selective reporting domains.	PRP was more effective than HA for pain relief at 6 and 12 months as assessed by WOMAC. However, PRP was not superior to HA in VAS scores.
8. Smith et al,	Evaluate the effectiveness	Systematic review and	Medline, Embase,	RCTs included KOA patients	WOMAC pain, WOMAC total,	Random-effects model,	Three out of eight trials were	Combining CS with HA demonstrated greater

Author, year	Aim of study	Study design; No. of groups	Databases searched	Inclusion Criteria	Outcomes	Statistical Methods	Risk of Bias	Conclusion
2019[72]	and safety of combining CS and HA versus using HA alone in patients with KOA.	meta-analysis (PRISMA guideline); Number of studies: 8 RCTs; Total sample size: 751; Interventions: CS + HA (various regimens and preparations); Comparison: HA alone	Cochrane library (to June 23, 2017)	receiving i.a. CS + HA versus i.a. HA alone with a follow-up of at least 4 weeks and pain outcome assessment.	OMERACT-OARSI responder rate, AEs	SMD and OR, I^2 for heterogeneity, sensitivity analysis excluding industry-funded studies	considered to be of high quality. Randomization and blinding varied among the trials, with some trials receiving industry funds.	effectiveness than HA alone for pain reduction at key timepoints. However, functional improvements were not significant. There was no increase in AEs.
9. Vincent et al, 2019[73]	Evaluate the effectiveness of a single i.a. HA injection versus a placebo for KOA.	Meta-analysis (not registered), adapted from PRISMA; Number of studies: 28 studies (20 RCTs, 8 observational) using only single i.a. HA; Sample size: n = 3,360 (HA), n = 769 (placebo); Total = 4,129; Interventions: single i.a. HA injection (various products); Comparison: i.a. placebo (saline), matching KL profiles across arms	Pubmed, Google, Google scholar, references in meta-analyses (until Apr 2018)	Clinical studies on KOA of any design involved a single i.a. HA injection. WOMAC scores were recorded at baseline and follow-up in patients with a known profile including age, BMI, and KL grade.	Pain (WOMAC A)	Effect size (Cohen's d) with 95% CI, inverse variance pooling, funnel plots, χ^2 for KL-matching	Most studies had a moderate risk of bias with outliers being excluded. KL-profile matching was employed to reduce bias, and Publication bias was found to be low based on funnel plots.	A single i.a. HA injection provided statistically and clinically significant pain relief compared to a placebo in KOA. The effect size at month 6 exceeded MCID.
10. Chevalier et al,	Estimate the short- and long-term efficacy	Systematic review and Bayesian	Medline, Embase, Cochrane	All RCTs evaluated the efficacy and safety of i.a. CS and	Pain (1, 3, and 6 months), AEs (overall,	Bayesian NMA using SMD and OR,	All RCTs were generally at low risk of bias with	At 6 months, HA was shown to be more effective than CS. Both treatments

Author, year	Aim of study	Study design; No. of groups	Databases searched	Inclusion Criteria	Outcomes	Statistical Methods	Risk of Bias	Conclusion
2020[74]	and safety of i.a. HA versus CS in KOA.	network meta-analysis; Number of studies: 42 RCTs; Sample size: Total n = 8,047; Interventions: i.a. HA (single or 3 injections); Comparison: i.a. CS, placebo, or other HA formulations	central, conference abstracts (2016–2018), hand search	HA in adults with KOA.	treatment-related, serious AEs)	random-effects model, Gemtc in R	some domains showing unclear or high risk of selection and/or performance bias.	were well tolerated with no statistically significant difference in safety.
11. Phillips et al, 2020[52]	Evaluate the effectiveness and safety of i.a. therapies for primary KOA using network meta-analysis.	Network meta-analysis (frequentist model, PRISMA guideline); Number of RCTs: 64 Total sample size: 9,710 Interventions: - HA (various molecular weights) - PRP - CS (standard-release) - CS (extended-release) Comparison: all interventions compared to saline using indirect comparisons through NMA	Medline, Embase, Cochrane central (search date: Nov 12, 2018)	All RCTs in adults with KOA compared HMW/ LMW HA, PRP, CS (standard or extended-release) versus saline, with assessment of pain, function and AEs at 3 ± 1 months.	VAS pain, KOOS, WOMAC function, AEs	Frequentist NMA, SMD and RR, p score ranking, heterogeneity via I^2 and Cochran's Q	Some studies were found to have a high risk of bias, particularly in terms of allocation concealment, as assessed using the Cochrane Risk of Bias tool.	The HMW HA treatment consistently showed benefits. Extended-release CS likely outperformed the standard treatment. The effects of PRP were uncertain. All treatments resulted in only minor AEs.
12. Zhao et al, 2020[75]	Evaluate the effectiveness and safety of	Systematic review and meta-analysis	Pubmed, Cochrane library,	RCTs and cohort studies compared the treatment of	VAS (1, 3, and 6 months), WOMAC	Random/ fixed- effects meta-analysis,	Five RCTs were assessed using the Cochrane	HA combined with PRP improved pain and function more effective than PRP

Author, year	Aim of study	Study design; No. of groups	Databases searched	Inclusion Criteria	Outcomes	Statistical Methods	Risk of Bias	Conclusion
	i.a. HA plus PRP versus PRP or HA alone in KOA.	(PRISMA guidelines); Number of studies: 5 RCTs, 2 cohort studies; Total sample size: 941 Interventions: HA + PRP (autologous PRP, 2-8 ml/ session; 3-9 weekly session); Comparison: PRP alone or HA alone	Embase, CNKI (to Dec 2019)	KOA using a combination of HA and PRP versus PRP or HA alone.	function and total scores (at 12 months), Lequesne Index (at 6 months), AEs	I^2, Egger's/ Begg's tests for publication bias	RoB tool, while two cohort studies were rated as having a NOS of 9, indicating low risk of bias. Overall, the studies were of good quality.	alone, while maintaining similar safety profiles. There was evidence supporting the use of this combination in the treatment of KOA.
13. Han et al, 2021[8]	Evaluate the clinical effects of HA, CS, PRP, and MSCs versus placebo in KOA.	Network meta-analysis (PRISMA-NMA guideline); Total sample size: 5554 (43 RCTs) Groups: - HA: n = 1305 (1–5 i.a. injections; various molecular weights); - CS: n = 1271 - Single i.a. PRP: n = 496 - Multiple i.a. PRP: n = 622 - MSC (adipose-derived): n = 193 - Placebo: n = 1667 Comparison: all	Medline, Embase, Cochrane library, Scopus, Web of science (to June 30, 2019)	RCTs on KOA reported two or more of the following interventions: HA, CS, PRP, MSC, and placebo. The trials assessed pain and function outcomes, as well as adverse events lasting at least 4 weeks.	Pain (WOMAC, VAS), Function (WOMAC, IKDC, KOOS), AEs, SAEs	Random-effects NMA, SUCRA, I^2 for heterogeneity, SMD for continuous outcomes, OR for AEs, funnel plots for bias	Quality was assessed by the Detsky score, with most trials scoring 15 out of 20 or higher. Publication bias was found to be low, as indicated by symmetrical funnel plots.	CS was the most effective treatment for managing pain and improving function. HA was better than a placebo with fewer AEs. Both MSC and PRP were less effective in comparison. However, the differences in effectiveness were small and not clinically meaningful.

Author, year	Aim of study	Study design; No. of groups	Databases searched	Inclusion Criteria	Outcomes	Statistical Methods	Risk of Bias	Conclusion
		interventions compared with each other and with a placebo (in the 6-arm network study)						
14. Anil et al, 2021[76]	Evaluate the effectiveness of HA, PRP, CS, MSC, SVF, etc., in treating KOA.	Network meta-analysis (PRISMA guidelines); Number of RCTs: 79 Total sample size: 8,761 Interventions: - HA (various molecular weights) - PRP (leukocyte-rich or poor); - CS; - MSC; - SVF (stromal vascular fraction); Comparison: each intervention compared to the others and saline placebo	Medline, Embase, Cochrane library (to Feb 2020)	RCTs compared i.a. injections in patients with KOA with outcomes including VAS and WOMAC scores.	VAS, WOMAC	Frequentist NMA, random effects, SMD for continuous, OR for dichotomous, P-score for ranking	Most studies had a Jadad score of 3 or higher indicating low risk and high quality Level I RCTs.	SVF was the most effective overall in improving pain and function. HMW HA + CS and PRP were also effective at certain timepoints. Ozone was found to be less effective than the placebo.
15. Zhang et al, 2022[63]	Evaluate the effectiveness and safety of PRP in combination with HA versus PRP alone in KOA.	Systematic review and metaanalysis; Number of RCTs: 9 Total sample size: 1,118 Groups: - PRP + HA (i.a. injection);	Pubmed, Embase, Cochrane library, CNKI (to Jan 15, 2022)	RCTs or cohort studies on KOA compared PRP in combination with HA versus PRP alone with at least one outcome measure (such as VAS, WOMAC, KOOS, IKDC,	Pain (VAS), Function (WOMAC, KOOS, IKDC, Lequesne), AEs	RevMan 5.3, MD and RR with 95% CI, Fixed/random effects, MCID used for clinical significance	The Cochrane tool was used for RCTs and the NOS was used for cohort studies. Most studies were found to have a low risk of bias, with a mean NOS	PRP in combination with HA was not superior to PRP alone in improving pain and function. Additionally, it showed a safer profile with fewer AEs.

Author, year	Aim of study	Study design; No. of groups	Databases searched	Inclusion Criteria	Outcomes	Statistical Methods	Risk of Bias	Conclusion
		- PRP alone; Comparison: PRP + HA *vs* PRP		Lequesne, AEs).			score of 8.25.	
16. Bensa et al, 2024[64]	To quantify and compare the clinical effectiveness of CS versus HA and PRP in KOA.	Systematic review and metaanalysis; Total sample size: 3348 (35 RCTs) Groups: - CS: n = 1553 (various molecules, 1-5 i.a. injections); - HA: n = 1325 (various formulations); - PRP: n = 470 (autologous, mostly single or 3 i.a. injections) Comparison: CS *vs* HA; CS *vs* PRP	Pubmed, Cochrane, Web of science (search date: July 20, 2023)	RCTs compared CS versus HA or CS versus PRP in patients with KOA.	VAS pain, WOMAC, KSS, KOOS, SF-36, others	Random-effects model, MD, CI, I^2, MetaXL for Excel	The RoB 2.0 tool was used to assess the quality of studies. Out of the total 35 studies reviewed, 14 were classified as low risk, 18 had some concerns, and 3 were deemed high risk.	CS offered short-term benefits as HA and PRP, with PRP showing superiority at longer follow-ups both statistically and clinically.
17. Gupta et al, 2025[77]	Evaluate the mid- to long-term effectiveness of HA, CS, PRP, and their combinations in KOA.	Network meta-analysis (PRISMA guideline); Total sample size: 5089; Groups: - HA: n = 1797; - CS: n = 400; - PRP: n = 1499 - HA + CS: n = 51; - HA + PRP: n = 243; Comparison: all interventions compared with	Pubmed, Embase, Scopus, Cochrane (to Oct 20, 2024	RCTs compared HA, CS, and PRP either alone or in combination in patients with KOA, with a minimum follow-up rate of 80% for at least 12 months.	Pain (VAS, WOMAC), Function (WOMAC, IKDC)	Bayesian random-effects NMA, SUCRA, node-splitting, residual deviance, Egger's test	The risk of bias was as follows: low at 67.5%, moderate at 32.4%, and high at 10.8% as determined by the Cochrane tool.	HA in combination with PRP showed the best long-term efficacy. PRP alone was also effective, while CS was the least effective in the long term.

Author, year	Aim of study	Study design; No. of groups	Databases searched	Inclusion Criteria	Outcomes	Statistical Methods	Risk of Bias	Conclusion
		each other and with a placebo						
18. Liu et al, 2025[78]	Evaluate the efficacy and safety of PRP + HA versus PRP alone in KOA.	Meta-analysis (PRISMA guidelines); Total sample size: 1,384; Number of RCTs: 16; Groups: - PRP + HA (various doses and timing; i.a. injection); - PRP alone; Comparison: PRP + HA *vs* PRP	Pubmed, Embase, Cochrane library (to July 2024)	RCTs compared PRP in combination with HA versus PRP alone, reporting outcomes such as VAS, WOMAC, Lequesne, and AEs in KOA patients.	VAS, WOMAC, Lequesne, AEs	RevMan 5.3.5, SMD, MD for continuous outcomes, OR for AEs; I^2, funnel plots	Most trials were at low risk, with some uncertainly in allocation concealment and outcome blinding as determined by the Cochrane RoB tool.	The combination of HA with PRP was more effective than PRP alone in providing long-term pain relief, improving function, and ensuring safety. The treatment sequence (PRP followed by HA) resulted in better outcomes.
19. Du et al, 2025[62]	Evaluate the clinical effectiveness and safety of PRP + HA versus PRP monotherapy in patients with KOA.	Systematic review and meta-analysis (PRISMA guidelines); Total sample size: 1,023; Number of RCTs: 11; Groups: - PRP + HA: i.a. injections with various protocols; - PRP alone Comparison: PRP + HA *vs* PRP	Pubmed, Embase, Scopus, Cochrane library (to July 31, 2024)	RCTs on KOA were conducted in patients aged 18 years and older. The reported outcomes included the WOMAC, VAS, Lequesne index, IKDC, and AEs.	WOMAC, VAS, Lequesne, IKDC, AEs	RevMan 5.4, MD/RR with 95% CI, heterogeneity (I^2), P values, funnel plot, Egger's test	The Cochrane RoB2 tool identified 8 studies at low risk, 2 at moderate risk, and 1 at high risk.	PRP combined with HA was found to be more effective and safer than PRP alone for KOA.
20. Migliorini et al, 2025[22]	Compare the effectiveness of HA injections with different molecular weights for	Bayesian network meta-analysis (PRISMA guideline); Number of	Pubmed, Web of science, Google scholar, Embase (up	RCTs in patients with KOA using specific molecular weights of HA showed Level I evidence, with the	Pain (VAS)	Bayesian random effects model, Wald test for consistency, statistics	Most studies showed a low to moderate risk with good baseline comparability as	UHMW and HMW HA reduced pain better than LMW/MMW. The best effect was observed at 4-6 months..

Author, year	Aim of study	Study design; No. of groups	Databases searched	Inclusion Criteria	Outcomes	Statistical Methods	Risk of Bias	Conclusion
	KOA.	studies: 66 RCTs; Sample size: Total n = 9,822; Interventions: HA injections (various molecular weights); Comparison: active control (e.g., PRP, steroids, MSCs) and placebo (saline)	to Nov 2024)	VAS as outcome measured.		using ANOVA, STATA, and SPSS	determined by the RoB2 tool. However, some studies were unblinded.	

Units and Data Presentation: All values are reported as they appear in the original articles. Continuous outcomes (e.g., VAS, WOMAC, IKDC scores) are presented as mean ± standard deviation (SD) or mean difference (MD) with 95% confidence intervals (CIs), as appropriate. Categorical outcomes such as adverse events (AEs) and responder rates are given as counts or percentages, and effect sizes are shown as odds ratios (ORs) or risk ratios (RRs) with 95% CIs. Standardized mean differences (SMDs) are used for pooled effect estimates when applicable. Heterogeneity is indicated using the I^2 statistic. Timepoints of assessment and follow-up durations are extracted as outlined in each study.

Abbreviations: AEs, adverse events; ACS, autologous conditioned serum; Bio-HA, biotechnologically produced hyaluronic acid; BoNTA, botulinum toxin type A; CI, confidence interval; CNKI, China National Knowledge Infrastructure; CS, corticosteroid(s); EQ-VAS, EuroQol Visual Analog Scale; HA, hyaluronic acid; HMW, high molecular weight; i.a., intra-articular; IKDC, International Knee Documentation Committee; KOA, knee osteoarthritis; KL, Kellgren–Lawrence; KSS, Knee Society Score; LMW, low molecular weight; MMW, medium molecular weight; MCID, minimal clinically important difference; MD, mean difference; MSCs, mesenchymal stem cells; NMA, network meta-analysis; NOS, Newcastle–Ottawa Scale; NSAIDs, non-steroidal anti-inflammatory drugs; OMERACT, Outcome Measures in Rheumatology; OARSI, Osteoarthritis Research Society International; OR, odds ratio; PRGF, plasma rich in growth factors; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRP, platelet-rich plasma; PROSPERO, International Prospective Register of Systematic Reviews; PT, physical therapy; RCT, randomized controlled trial; RR, risk ratio; RoB, risk of bias; SAEs, serious adverse events; SF-36, 36-Item Short Form Survey; SMD, standardized mean difference; SUCRA, surface under the cumulative ranking curve; SVF, stromal vascular fraction; UHMW, ultra-high molecular weight; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

parisons. Furthermore, there has been limited investigation into long-term structural changes, imaging outcomes, and cost-effectiveness - all critical factors in chronic disease management. Future studies should focus on standardized outcome reporting, longer follow-up durations, and stratification by disease severity to enhance personalized treatment algorithms.

Overall, HA is a clinically relevant and well-tolerated option for patients with KOA, especially within a framework of individualized, multimodal management. Ongoing research into formulation optimization and synergistic combinations is likely to enhance its therapeutic utility. Until more robust data are available, clinical decisions should consider patient phenotype, disease stage, and therapeutic goals when selecting HA-based interventions.

The findings of this review have significant implications for clinical decision-making and individualized treatment planning in KOA. As the disease burden increases among aging populations, particularly in areas with limited access to surgical options, intra-articular therapies like HA are becoming essential in bridging the gap between conservative and surgical care.[8]

First, the clinical effectiveness of HA as a standalone treatment is well established, particularly in patients with early to moderate-stage KOA who prefer non-systemic interventions with a favorable safety profile.[73,78] It is crucial for clinicians to understand that not all HA products are the same; factors such as molecular weight, crosslinking, and injection frequency can affect both efficacy and duration of benefit.[50] Customizing product selection based on patient characteristics, such as age, activity level, comorbidities, and radiographic severity, can improve therapeutic outcomes and enhance patient satisfaction.

Secondly, there is increasing evidence supporting the effectiveness of combination therapies, especially when HA is combined with PRP or CS. For instance, combining HA with PRP may be advantageous for younger, active patients with early cartilage degeneration who are seeking regenerative stimulation.[19,58,78] On the other hand, pairing HA with CS could offer rapid symptom relief for patients experiencing acute inflammatory flares or those who cannot use biologics.[76] These approaches enable clinicians to tailor intra-articular treatment plans based on individual clinical presentations and therapeutic objectives.

Emerging combinations of HA including those with fibrinogen, botulinum toxin type A, human plasma protein solutions, PDRN, and peripheral blood stem cells are still under investigation and have not yet been established for routine clinical practice. Preliminary evidence, such as observational data from non-randomized cohorts like the study by Conrozier et al,[79] which assessed cross-linked HA with mannitol, suggests these combinations may be promising for selected patients with persistent symptoms or those seeking biologically based interventions with limited systemic exposure. In RCTs, several combinations have demonstrated encouraging results. For instance, Kandel et al[65] reported that HA combined with fibrinogen improved VAS pain scores compared to placebo at 3 months, potentially due to enhanced intra-articular retention and matrix stabilization. Similarly, Seihee Yoon et al[66] showed that HA plus PDRN yielded superior improvements in WOMAC and KSS scores over

HA alone, supporting the anti-inflammatory and chondroprotective properties of PDRN. Hegde et al[70] compared HA combined with either PRP or botulinum toxin A and found that both combinations improved outcomes, though PRP appeared more effective overall; this supports the hypothesis that these agents may reduce nociceptive signaling and promote cartilage repair. Turajane et al[68] observed significantly better WOMAC outcomes and higher avoidance of total knee arthroplasty in patients receiving HA with PBSCs (with or without growth factors), suggesting regenerative potential. Meanwhile, Bettonville et al[69] explored a formulation of HA with plasma protein and clonidine, which did not outperform HA alone in the primary endpoint but showed clinical benefit in pooled analyses. Other pharmacological agents such as periarticular corticosteroid-lidocaine and peptide-enriched HA have also been investigated, with transient but meaningful pain relief observed.[16,67] As higher-quality randomized trials and long-term safety data become available, these innovative approaches could broaden the therapeutic options for KOA.

Moreover, the excellent tolerability and low systemic risk associated with HA-based interventions make them particularly attractive in populations where the use of NSAIDs or opioids is limited due to polypharmacy, cardiovascular risk, or gastrointestinal intolerance.[50] These qualities also enhance the role of HA in shared decision-making, as patients increasingly prefer non-pharmacologic, locally administered, and disease-modifying options.

In summary, HA-based therapies, whether used alone or in combination, provide a flexible, personalized, and evidence-supported approach to improving pain, function, and quality of life for individuals with KOA. Their significance is especially notable in multidisciplinary care models that emphasize symptom control, mobility preservation, and patient engagement in long-term management.

CONCLUSIONS

HA continues to play a crucial role in the non-surgical treatment of KOA. It offers a safe and locally acting option that can be used at various stages of the disease. Clinical studies have demonstrated that HA monotherapy is particularly effective in the early to moderate stages of KOA. Higher efficacy has been observed with HMW formulations and multi-injection protocols. There is a growing trend of combining HA with other intra-articular agents. Among these combinations, intra-articular HA and PRP have shown the most consistent synergistic effects on pain and function. Additionally, combining HA with CS provides short-term symptom relief, especially during acute flares. New combinations with fibrinogen, polynucleotides, and botulinum toxin A show promise, but differences in trial design, patient selection, and product characteristics hinder direct comparisons. Future randomized trials with standardized methods and long-term outcomes are necessary. Personalizing HA-based 501 strategies based on disease

stage, comorbidities, and patient expectations will be crucial for 502 optimizing care.

LIST OF ABBREVIATIONS

CS: Corticosteroid
HA: Hyaluronic acid
HMW: High-molecular-weight
IL-1β: Interleukin-1 beta
IKDC: International Knee Documentation Committee
KOA: Knee osteoarthritis
KSS: Knee Society Score
LMW: Low-molecular-weight
MCID: Minimal clinically important difference
MMP: Matrix metalloproteinase
PBSC: Peripheral blood stem cell
PDRN: Polydeoxyribonucleotide
PRP: Platelet-rich plasma
RCT: Randomized controlled trial
SANRA: Scale for the Assessment of Narrative Review Articles
uhMW: Ultra-high-molecular-weight
VAS: Visual analog scale
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

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Not applicable.

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KXC conducted the literature review, drafted the manuscript, and coordinated data organization.

HNAT provided supervision and contributed to the interpretation of findings.

MHT critically revised the manuscript, provided major intellectual input and gave final approval.

All authors read and approved the final manuscript

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ARTIFICIAL INTELLIGENCE USE

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