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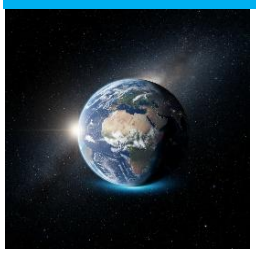

Quality in Sport. eISSN 2450-3118.

Journal Home Page
https://apcz.umk.pl/QS/index

KOŚĆ, Kacper, MUZYKA, Natalia, BUKWALD, Weronika, PANEK, Gabriela, ABRAMOWICZ, Amanda, RUMIN, Magdalena, PILIŃSKI, Remigiusz, GIERSZ, Jakub, PRUSEK, Adam and GOSZTYŁA, Dominika. Evaluation of the effectiveness of hyaluronic acid viscosupplementation in the treatment of knee osteoarthritis - a narrative review of the current literature. Quality in Sport. 2026;53:69889. eISSN 2450-3118. https://doi.org/10.12775/QS.2026.53.69889

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 l.p. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 16.03.2026. Revised: 30.03.2026. Accepted: 30.03.2026. Published: 31.03.2026.

Evaluation of the effectiveness of hyaluronic acid viscosupplementation in the treatment of knee osteoarthritis - a narrative review of the current literature

Authors: Kacper Kość[1], Natalia Muzyka[2], Weronika Bukwald[2], Gabriela Panek[3], Amanda Abramowicz[3], Magdalena Rumin[3], Remigiusz Piliński[3], Jakub Giersz[4], Adam Prusek[5], Dominika Gosztyła[6,7]

Kacper Kość[1] https://orcid.org/0009-0000-5344-8667
E-mail kacper.kosc34@gmail.com
[1] Kazimierz Pułaski University of Technology and Humanities, Radom, Poland

Natalia Muzyka[2] https://orcid.org/0009-0000-3164-216X
E-mail muzyka.natalia@gmail.com
[2] Military Institute of Medicine, Warsaw, Poland

Weronika Bukwald[2] https://orcid.org/0009-0001-5651-4815
E-mail weronikabukwald78@gmail.com
[2] Military Institute of Medicine, Warsaw, Poland

Gabriela Panek[3] https://orcid.org/0009-0004-3588-5336
E-mail gabriela.panek99@gmail.com
[3] Military Institute of Aviation Medicine, Warsaw, Poland

Amanda Abramowicz[3] https://orcid.org/0009-0004-6674-0594
E-mail amanda.abramowicz1@gmail.com
[3] Military Institute of Aviation Medicine, Warsaw, Poland

Magdalena Rumin[3] https://orcid.org/0009-0009-4281-8971
E-mail mada.rumin@gmail.com
[3] Military Institute of Aviation Medicine, Warsaw, Poland

Remigiusz Piliński[3] https://orcid.org/0009-0003-5543-7058
E-mail remigiusz.pilinski99@gmail.com
[3] Military Institute of Aviation Medicine, Warsaw, Poland

Jakub Giersz[4] https://orcid.org/0009-0002-6374-1730
E-mail gierszjakub@gmail.com
[4] 4th Military Clinical Hospital with Polyclinic, Wrocław, Poland

Adam Prusek[5] https://orcid.org/0009-0004-3343-2835
E-mail adam.prusek@o2.pl
[5] 5th Military Clinical Hospital with Polyclinic, Kraków, Poland

Dominika Gosztyła[6,7] https://orcid.org/0009-0007-9156-3499
E-mail dominika.gosztyla@o2.pl
[6] 10th Military Clinical Hospital with Polyclinic, Bydgoszcz, Poland
[7] Private Medical Practice, Bydgoszcz, Poland

Corresponding author
Kacper Kość
E-mail kacper.kosc34@gmail.com

Abstract
Background: Knee osteoarthritis (OA) is a leading cause of global disability. This narrative review systematically evaluates the effectiveness of intra-articular hyaluronic acid (IAHA) viscosupplementation. The analysis assesses clinical efficacy, durability, safety, biomechanical and biological mechanisms, patient prognostic factors, and advanced formulations (tribosupplementation).
Methods: A comprehensive literature search (PubMed/MEDLINE, Scopus, Google Scholar) up to 2026 was conducted, including systematic reviews, randomized controlled trials (RCTs), meta-analyses, and biomechanical studies. Clinical outcomes were primarily assessed using VAS and WOMAC scores.
Results: IAHA provides moderate, highly durable pain and functional improvements. While intra-articular corticosteroids offer superior short-term analgesia (up to 4 weeks), IAHA

demonstrates significantly greater sustained efficacy in the medium-to-long term (up to 6 months). Cross-linked HA enables effective single-injection regimens. Efficacy relies heavily on patient phenotype, with optimal results in non-obese patients having early-to-moderate OA (Kellgren-Lawrence grades I-III). IAHA benefits stem predominantly from long-term biological processes and viscoinduction rather than simple mechanical lubrication. Advanced fluid additives (e.g., bottle-brush polymers, hydrogels) represent a promising therapeutic future. **Conclusions**: IAHA is a highly effective and safe non-surgical OA treatment when guided by precision medicine and proper patient phenotyping. To maximize benefits and prevent dynamic joint overloading, HA injections must be strictly combined with targeted physical rehabilitation and gait retraining.

1. Introduction

Osteoarthritis (OA) is a chronic, progressive, and multifactorial degenerative disorder of the musculoskeletal system that represents one of the leading causes of global disability [1, 2]. The condition is fundamentally conditioned by a disturbance of tissue homeostasis within the joint environment, resulting from a persistent and pathological imbalance between anabolic repair processes and catabolic degradation [3, 4]. While historically characterized as a simple "wear and tear" disease isolated to the articular cartilage, contemporary understanding defines osteoarthritis as an active disease process involving all tissues forming the synovial joint organ [3].

This encompasses the articular cartilage, the subchondral bone layer, the joint capsule, the ligaments, and the synovial membrane, ultimately resulting in irreversible structural and functional changes [3].

The etiology of osteoarthritis most often involves a highly complex interaction of genetic predispositions, mechanical stressors, and metabolic factors [2, 3]. The initiating physiological moment typically involves microscopic or macroscopic damage to the articular cartilage, leading to a critical loss of its shock-absorbing properties and a profound disturbance of its protective function across the articulating surfaces. In a compensatory biomechanical mechanism secondary to the damage of joint structures, there is a development of degenerative-productive changes, which are clinically observed as marginal osteophytosis (bone spur formation), alongside the sclerotization and densification of the subchondral bone layer [3, 5]. The described mechanical mechanism is subsequently amplified by a localized inflammatory cascade [4]. The release of pro-inflammatory cytokines, matrix metalloproteinases (MMPs), and other catabolic enzymes accelerates tissue destruction, transitioning the joint from a state of mechanical failure to one of chronic biochemical degradation [4].

The clinical picture of knee osteoarthritis (gonarthrosis) is dominated by joint pain of a mechanical nature - often presenting as start-up pain and exertional pain - which typically worsens during physical activity and subsides at rest [1]. Accompanying symptoms include severe morning stiffness, a progressively limited range of motion, the presence of crepitus during flexion and extension, visible deformation of joint contours, and a secondary weakness of the periarticular musculature resulting from pain-induced disuse [1]. The epidemiological burden of this condition is immense. The global prevalence of osteoarthritis has surged by an estimated 132.2% since 1990, currently affecting more than 7.6% of the global population [6]. In the adult population specifically, the prevalence is estimated at 10% to 15%, demonstrating a strong, positive correlation with advancing age [2]. Radiological features of the disease are found in over 80% of patients older than 75 years, and the condition shows a distinct epidemiological predilection for the female sex [2, 6]. The leading risk factors, alongside advanced age, include excessive body weight (a primary biomechanical driver particularly relevant in the etiology of gonarthrosis), a history of musculoskeletal injuries, and chronic biomechanical overload of the weight-bearing joints [1, 2, 3].

To understand the therapeutic interventions utilized in osteoarthritis, one must understand the native anatomy of the joint and the role of its endogenous lubricants. Hyaline cartilage is a highly specialized, hydrated, avascular, aneural, and alymphatic connective tissue that provides a smooth, nearly frictionless surface for joint articulation while supporting compressive loads [7, 8]. The extracellular matrix (ECM) of healthy cartilage is composed primarily of water, anionic proteoglycans (comprising glycosaminoglycans like chondroitin sulfate and keratan sulfate bound to a core protein), and a highly organized fibrous type II collagen network [7].

Cartilage Zone	Volume Percentage	Structural and Compositional Characteristics	Primary Function
Superficial (Tangential) Zone	10% - 20% [7]	Highest water concentration (~80%) [7]. Collagen fibrils (primarily type II and IX) packed tightly and aligned parallel to the articular surface [7]. Contains a high density of flattened chondrocytes [7].	Protects deeper layers from shear stresses and is responsible for most of the tensile properties of cartilage [7].
Middle (Transitional) Zone	40% - 60% [7]	Thicker collagen fibrils organized obliquely [7]. Contains spherical chondrocytes distributed at low density [7]. High content of proteoglycans [7].	Serves as the first line of resistance to compressive forces; provides an anatomic and functional bridge between zones [7].
Deep Zone	~ 30% [7]	Lowest water concentration (~65%) and highest proteoglycan content [7]. Largest diameter collagen fibrils arranged perpendicularly (radial disposition) to the joint line [7]. Chondrocytes in columnar orientation [7].	Provides the greatest resistance to compressive forces; collagen fibrils anchor the tissue to the underlying calcified cartilage and subchondral bone [7,8].

Hyaluronic acid (HA), structurally known as hyaluronan, is a biopolymer naturally occurring in the human body that plays an indispensable role in maintaining the biomechanical integrity of this system [9, 10]. Chemically, HA is a non-sulfated glycosaminoglycan (GAG) characterized by a highly conserved, unbranched macromolecular structure that completely lacks species specificity, rendering it highly biocompatible [9, 10]. This compound exhibits outstanding hygroscopic properties, possessing the ability to bind water in amounts up to 1000 times its own volume [11]. Under physiological conditions, it predominantly occurs in the form of a sodium salt (sodium hyaluronate) [9]. While the largest reservoir of hyaluronic acid in the body is the skin (accounting for approximately 50% of total body HA), its physiological role in the musculoskeletal system is absolutely critical [10, 11].

In the synovial joint, hyaluronic acid is the leading non-protein component of the synovial fluid [12]. It determines the fluid's non-Newtonian, viscoelastic properties, conditioning the optimal lubrication of articular surfaces and providing essential shock absorption under fluctuating mechanical loads [12, 13]. With the natural aging of the body, a physiological and progressive decline in the endogenous synthesis and tissue concentration of hyaluronic acid is observed [11]. Clinically, this metabolic decline manifests as the progressive loss of connective tissue elasticity and the degeneration of joint structures. In the pathomechanism of knee osteoarthritis, a profound and significant decrease in both the concentration and the molecular weight of endogenous hyaluronic acid is observed within the synovial fluid [9, 12, 13]. This biochemical depletion results directly in the deterioration of the rheological parameters of the synovia specifically, a precipitous decrease in its viscosity and elasticity - and the consequent loss of its chondroprotective potential [12, 13].

Viscosupplementation has thus emerged as a targeted method of symptomatic and structure-modifying treatment for osteoarthritis, consisting of the direct, intra-articular injection of exogenous hyaluronic acid preparations [14]. The theoretical foundations of viscosupplementation - defined as the therapeutic substitution of pathological synovial fluid using an elastoviscous exogenous HA solution - were formulated following the pioneering isolation of HA from the vitreous humor of a bovine eye in 1934 by K. Meyer and J. Palmer [15, 16]. Following successful applications in veterinary medicine, where intra-articular injections in race horses with post-traumatic osteoarthritis resulted in objective clinical improvements, the first documented *in vivo* clinical trials involving humans occurred in the early 1970s [16]. A major pharmaceutical breakthrough was recorded in 1987 with the authorization of the first commercial HA preparations on the Japanese and Italian markets, initially utilizing extraction from animal material (rooster combs). By 1997, the US Food and Drug Administration (FDA) issued authorizations for HA preparations in the therapy of knee osteoarthritis, catalyzing widespread global clinical adoption [14].

Modern technological evolution has largely replaced animal tissue extraction with bacterial biofermentation processes, virtually eliminating the risk of zoonotic allergic reactions [14]. Furthermore, structural modifications, such as molecular cross-linking, have significantly extended the intra-articular retention time of the preparations, enabling a reduction in the frequency of therapeutic injections required to achieve clinical efficacy [14]. The therapeutic effect of viscosupplementation rests on a highly complex, bidirectional mechanism of action [14]. The biomechanical (rheological) component involves the exogenous HA creating an insulating, protective layer on the articular surfaces, directly reducing mechanically derived nociception and inhibiting the progression of cartilage abrasion via lubrication [12, 14]. The biological-metabolic component involves the stimulation of synoviocytes to increase the synthesis of endogenous, high-molecular-weight hyaluronic acid - a phenomenon termed viscoinduction [14]. Moreover, HA binding to specific cellular receptors, notably the cluster determinant 44 (CD44) and the receptor for hyaluronate-mediated motility (RHAMM), exerts profound immunomodulatory and anti-inflammatory effects by modulating cell proliferation and inhibiting the activity of proteolytic enzymes responsible for the degradation of the cartilaginous extracellular matrix [12].

2. Aim of the study

The primary objective of this study is to systematically evaluate and synthesize the effectiveness of intra-articular hyaluronic acid viscosupplementation in the comprehensive management of knee osteoarthritis. This analysis seeks to consolidate the vast and occasionally conflicting current evidence landscape regarding the clinical efficacy, functional outcomes, safety profiles, and long-term durability of HA therapies. Furthermore, this review aims to critically examine the biomechanical and tribological impacts of HA on joint friction, fluid-film lubrication, and gait kinematics. It will delineate the influence of specific patient prognostic factors - such as age, sex, body mass index, and radiographic disease severity - on therapeutic responsiveness. Additionally, the study aims to explore the vanguard of osteoarthritis therapy by reviewing advanced formulations, including stimuli-responsive hydrogels, liposomal carriers, bottle-brush polymers, and advanced matrix enhancers. Finally, the analysis will scrutinize the methodological and economic rationales underpinning the divergent recommendations present across contemporary international clinical practice guidelines, providing a cohesive framework for clinical decision-making.

3. Material and methods

To achieve a rigorous and comprehensive evaluation of the subject, an exhaustive narrative synthesis of contemporary literature was conducted. The literature search was performed utilizing major scientific databases, including PubMed/MEDLINE, Scopus, and Google Scholar, to identify relevant studies published up to the year 2026. The search strategy

incorporated specific keywords and Medical Subject Headings (MeSH) terms, such as "knee osteoarthritis", "viscosupplementation", "hyaluronic acid", "rheology", "tribology", and "clinical practice guidelines". The analyzed literature encompasses recent systematic reviews, umbrella reviews, randomized controlled trials (RCTs), network meta-analyses, and fundamental *in vitro* and *ex vivo* biomechanical investigations.

To establish highly robust estimates of treatment effect sizes without conducting a primary mathematical meta-analysis, data extraction prioritized large-scale, previously published systematic reviews and meta-analyses. Through the narrative evaluation of these aggregated clinical data - encompassing numerous RCTs and thousands of patients across the selected meta-analyses - patient-reported outcome measures (PROMs) were assessed. These primarily included the Visual Analog Scale (VAS) for pain and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

Furthermore, the longitudinal efficacy of viscosupplementation was evaluated by synthesizing existing comparative evidence across predefined short-term (2–6 weeks), medium-term (12–16 weeks), and long-term (17 weeks to 12 months) intervals, particularly against intra-articular corticosteroids and saline placebo controls. To evaluate the fundamental mechanical and physiological mechanisms of action, data from advanced tribological and biomechanical studies - including dynamic pin-on-plate tribometer studies, passive pendulum human cadaveric tests, atomic force microscopy, and *in vivo* kinematic gait analyses - were integrated into this review. Finally, the synthesis examined the methodological criteria and health-economic rationales underpinning current clinical practice guidelines from major global authoritative bodies, including the American Academy of Orthopaedic Surgeons (AAOS), the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), and the Osteoarthritis Research Society International (OARSI).

4. Results and Discussion

4.1 Temporal Clinical Efficacy and Therapeutic Trajectories

(Note: In the following analysis, negative standardized mean differences (SMD) denote a reduction in pain, favoring the assessed intervention). The clinical efficacy of intra-articular hyaluronic acid (IAHA) in the treatment of knee osteoarthritis has been exhaustively quantified through standardized patient-reported outcome measures [17, 18]. The primary clinical utility of IAHA lies in its capacity to provide moderate, yet highly durable, pain relief and functional restoration, effectively delaying the necessity for surgical intervention [18]. When analyzing pain reduction timelines, meta-analytical data reveal a distinct and highly critical temporal divergence between the mechanisms and efficacy of IAHA versus intra-articular corticosteroids (IACS) [18].

Corticosteroids operate through potent, rapid anti-inflammatory mechanisms. By suppressing pro-inflammatory cytokines, prostaglandins, and matrix metalloproteinases within the synovial joint environment, IACS effectively reduces synovial inflammation and nociceptive signaling [19]. Consequently, corticosteroids demonstrate vastly superior short-term pain relief [18]. Pooled standardized mean differences (SMD) indicate a moderate reduction in pain for IACS compared to control interventions at 1 to 2 weeks (SMD -0.48; 95% CI -0.70 to -0.27) and a small to moderate effect at 4 to 6 weeks (SMD -0.41; 95% CI -0.61 to -0.21) [19]. However, the analgesic efficacy progressively diminishes beyond this initial post-injection window, showing only a small effect at 13 weeks (SMD -0.22; 95% CI -0.44 to 0.00) and no evidence of an effect at 26 weeks (SMD -0.07; 95% CI -0.25 to 0.11) [19]. Similarly, functional improvements are small to moderate at 1 to 2 weeks (SMD -0.43; 95% CI -0.72 to -0.14) and 4 to 6 weeks (SMD -0.36; 95% CI -0.63 to -0.09), with no evidence of an effect on function at 13 weeks (SMD -0.13; 95% CI -0.37 to 0.10) or at 26 weeks (SMD 0.06; 95% CI -0.16 to 0.28) [19]. Furthermore, within this analysis, there was no evidence of an effect of corticosteroids on

joint space narrowing compared to control interventions (SMD -0.02; 95% CI -0.49 to 0.46) [19].

Conversely, hyaluronic acid injections exhibit a delayed onset of action but provide significant therapeutic benefit over a moderate treatment duration [18]. During the first few weeks post-injection, the analgesic effect of HA is often modest [18]. Some patients, particularly those with advanced joint degeneration or highly active synovitis, may even report a transient worsening of symptoms due to the mechanical volume of the injection or a mild immune-mediated post-injection flare. However, network meta-analysis evaluating outcomes at a 3-month (12-week) follow-up demonstrates that IAHA provides a statistically significant reduction in pain compared to intra-articular placebo, yielding an SMD of -0.34 (95% CI -0.42 to -0.26) [20].

In direct, head-to-head meta-analyses comparing HA to CS, a distinct therapeutic trajectory is observed [18]. While IACS outperforms HA at the 2-week mark (SMD -0.39; 95% CI -0.65 to -0.12), the two approaches demonstrate equal efficacy by week 4 (SMD -0.01; 95% CI -0.23 to 0.21) [18]. Beyond this point, however, hyaluronic acid demonstrates significantly superior pain reduction at 12 weeks (SMD -0.35; 95% CI -0.66 to -0.03) and maintains this superiority through the 26-week (6-month) interval (SMD -0.39; 95% CI -0.59 to -0.18) [18].

Follow-up Interval	**Corticosteroids (IACS)**	**Hyaluronic Acid (IAHA)**	**Primary Clinical Indicator**
Short-term (1 - 4 weeks)	Peak efficacy. Rapid, moderate pain reduction (SMD -0.48 at 1-2 weeks; SMD -0.41 at 4-6 weeks) [19].	Modest early efficacy. Delayed onset. Potential for transient flare (due to volume or immune response) [18].	IACS outperforms IAHA at 2 weeks, but both approaches demonstrate equal efficacy by week 4 [18].
Medium-term (12 - 13 weeks)	Diminishing efficacy. Only a small effect on pain (SMD -0.22) and no evidence of effect on function (SMD -0.13) at 13 weeks [19].	Significant pain reduction. Statistically significant SMD vs placebo (-0.34) [20] and vs IACS (-0.35) at 12 weeks [18].	IAHA demonstrates significantly superior pain reduction compared to IACS [18].
Long-term (26 weeks / 6 months)	Loss of efficacy. No evidence of an effect on pain (SMD -0.07) or function [19]. No evidence of effect on joint space narrowing [19].	Sustained efficacy. Maintains significant superiority in pain reduction through 6 months (SMD -0.39) [18].	IAHA provides durable, sustained therapeutic benefit, whereas IACS effects return to baseline [18,19].

4.2 The Shift Toward Single-Injection Regimens: Outcomes of Cross-Linked Hyaluronic Acid

The shift toward high-molecular-weight and cross-linked HA formulations has been driven by the need to maximize the intra-articular residence time and extend the therapeutic window of a single injection. Cross-linking the biopolymer network significantly reduces its susceptibility to enzymatic degradation by hyaluronidases, thereby allowing for single-injection regimens [21]. The efficacy and real-world durability of single-injection, highly cross-linked high-molecular-weight hyaluronic acid have been rigorously demonstrated in landmark multicenter trials [21]. In a pivotal prospective, double-blind, randomized controlled trial involving 253 patients with symptomatic knee osteoarthritis, a single 6-mL intra-articular injection of cross-linked HA provided statistically significant and clinically meaningful improvements over a 26-week follow-up period [21].

Patients receiving the single-injection cross-linked HA demonstrated a statistically significantly superior reduction in WOMAC A (pain) scores compared to placebo, with an estimated change from baseline over 26 weeks of -0.84 versus -0.69 (estimated treatment difference of -0.15; p=0.047) [21]. Furthermore, secondary measures such as pain while walking (WOMAC A1) showed significant improvements, with 64% of HA-treated patients classified as responders at 26 weeks compared to 50% in the placebo group (p=0.028) [21]. The clinical gains regarding pain reduction achieved within the first month were remarkably stable through the end of the 6-month observation period without degradation of effect [21]. These outcomes underscore that advanced cross-linking technologies enable primary reductions in nociception to translate into sustained, long-term clinical benefits, simultaneously eliminating the risks of repeated joint punctures required by traditional multi-dose regimens [21].

4.3 Prognostic Phenotyping and Demographic Influences

The high degree of heterogeneity frequently observed in generalized clinical trial outcomes for IAHA therapies can be largely explained by patient-specific prognostic factors. Observational registries and clinical cohort studies provide critical insights into the necessity of patient phenotyping for optimizing viscosupplementation outcomes in weight-bearing joints, including both the knee and the hip [22, 23, 24]. Radiographic severity is arguably the most robust predictor of IAHA efficacy across varying joint pathologies [22, 23, 24]. Narrative reviews and clinical data demonstrate that patients with early to moderate knee osteoarthritis (conventionally measured as Kellgren-Lawrence grades I, II, and early III) achieve the most significant and durable improvements in pain and function following HA injection. In these early stages, sufficient viable articular cartilage and functional synoviocytes remain within the joint capsule to adequately respond to the properties of the exogenous HA [23]. Conversely, patients with advanced, bone-on-bone knee osteoarthritis (KL grade IV) frequently fail to respond to treatment, often rendering IAHA merely a temporary palliative bridge therapy to delay surgical arthroplasty [23]. Similar structural limitations are observed in hip osteoarthritis, where advanced baseline radiological severity - specifically Kellgren-Lawrence grade 3 and severe joint space narrowing - is significantly associated with a poor clinical response to viscosupplementation [24].

Demographic variables and systemic factors also exert a profound influence on treatment trajectories. Body Mass Index (BMI) acts as a substantial, independent negative predictor of functional outcome [22, 23]. Excess adiposity increases the biomechanical shear and compressive loads across the joints during the gait cycle, while systemic adipose tissue acts as an endocrine organ, contributing to low-grade, chronic systemic inflammation via adipokines [22]. Clinical studies have clearly demonstrated an inverse relationship between obesity and the efficacy of viscosupplementation. Obese patients (defined as BMI $\geq$30 kg/m^2) experience diminished peak efficacy and are significantly less likely to be classified as OMERACT-OARSI responders compared to non-obese individuals. Crucially, post-hoc analyses of prospective trials reveal that the combination of obesity and severe structural radiological degradation (e.g., OARSI grade 3) yields the lowest therapeutic response rates. This underscores the absolute necessity of integrating structured weight management protocols into the viscosupplementation treatment algorithm to maximize therapeutic outcomes [22].

4.4 Biomechanical and Tribological Performance Models

The therapeutic premise of viscosupplementation relies heavily on the physical alteration of the joint's tribological environment. Healthy hyaline cartilage provides a nearly frictionless surface for joint articulation, achieving coefficients of friction as low as 0.001. This is accomplished through a sophisticated interplay of fluid-film lubrication and boundary lubrication, dictated by the macroscopic loads and velocities applied to the joint. This dynamic is classically modeled by the Stribeck curve, which delineates the coefficient of friction based on the Hersey number

(a dimensionless number derived by multiplying sliding velocity by lubricant viscosity, divided by the load).

In high-load, low-speed scenarios (e.g., initiating movement from a standing position), the Hersey number is low, and the joint relies entirely on boundary lubrication. In this mode, articulating surfaces are separated only by a microscopically thin film, and macromolecules like proteoglycan 4 (PRG4/lubricin), hyaluronic acid (HA), and surface-active phospholipids (SAPL) protect the surfaces from mechanical asperity contact [25, 26]. During high-speed, low-load scenarios (e.g., the swing phase of human gait), fluid-film lubrication dominates; the coefficient of friction is lowered as the interposed lubricating fluid (synovial fluid) drives the articulating surfaces apart via elastohydrodynamic lubrication, governed largely by the viscosity of the HA.

Rigorous *in vitro* mechanical testing confirms that synovial fluid constituents play a critical role in reducing mechanical friction [26]. Biomechanical evaluations utilizing bovine cartilage models have demonstrated that HA and PRG4 contribute independently to lowering the boundary friction coefficient in a dose-dependent manner [26]. Furthermore, advanced nanotribological investigations using atomic force microscopy (AFM) coupled with targeted enzymatic digestion (utilizing trypsin, hyaluronidase, and phospholipase-C) have elegantly elucidated the specific boundary-lubricant layers of articular cartilage [25]. These highly controlled experimental conditions confirm that the enzymatic depletion of HA or superficial zone proteins significantly impairs the joint's tribological properties, highlighting HA's critical role as an effective boundary layer lubricant capable of substituting for depleted endogenous molecules under static testing conditions [25, 26].

However, the tribological reality *in vivo* under dynamic load is highly complex. A rigorous study utilizing twelve human cadaveric knee joints (categorized into mild and moderate OA based on the MRI Osteoarthritis Knee Score - MOAKS) examined friction using a passive pendulum setup to simulate realistic, gait-like loading conditions [27]. Contrary to pure *in vitro* cartilage explant models, this investigation found that HA supplementation did not lead to an immediate, dramatic decrease in overall macroscopic knee joint friction in the whole-joint cadaveric model [27]. While extracted cartilage and meniscus samples tested in a dynamic pin-on-plate tribometer showed localized tribological responses, the macroscopic whole-joint damping properties remained largely unchanged immediately following HA injection [27]. These findings carry profound clinical implications: they imply that the clinical success of IAHA is not exclusively due to an immediate mechanical reduction in gross joint friction upon injection [27]. Instead, this evidence strongly supports the hypothesis that the dominant long-term therapeutic mechanisms of HA are biological rather than purely mechanical. The true clinical efficacy of HA likely stems from viscoinduction (the biological stimulation of endogenous HA synthesis by synoviocytes over weeks to months), the restoration of the anti-inflammatory milieu via receptor binding, and the gradual re-establishment of interstitial fluid pressurization within the cartilage matrix, rather than acting solely as an inert mechanical grease.

4.5 Functional Restoration and Gait Kinematics

Clinically, these complex biomechanical and biological adjustments manifest as measurable improvements in human gait. Chronic knee pain inevitably leads to the emergence of compensatory, pain-avoidance gait patterns designed to minimize joint load, typically characterized by slow walking speeds, shortened step lengths, and altered joint kinematics [28]. Unfortunately, these adaptations often persist even after pain subsides, leading to secondary musculoskeletal issues in adjacent joints.

Kinematic analyses utilizing advanced motion capture systems demonstrate that patients treated with IAHA experience a significant restitution of normal gait parameters. Following IAHA therapy, recent systematic reviews confirm statistically significant improvements in spatiotemporal variables, including walking speed, step length, stride length, and step cadence

[28]. These parameters show marked improvement as the viscoelastic and biological properties of the joint are transiently restored, allowing patients to achieve functional mobility that more closely resembles healthy populations [28].

Crucially, however, kinetic evaluations of the knee adduction moment (KAM) - a critical metric associated with medial compartment loading - reveal a clinical paradox [28, 29]. An elevated KAM directly correlates with the accelerated progression of medial compartment osteoarthritis. Biomechanical studies investigating joint loads during walking demonstrate that as nociception decreases following effective intra-articular therapies, patients walk with increased velocity and mechanical confidence [29]. Consequently, this increased walking speed inadvertently increases or maintains the peak KAM, meaning the medial compartment remains subjected to high dynamic loads despite the absence of pain [29].

Therefore, the protective effect of HA is predominantly biological and tribological, rather than directly unloading the joint's kinetic axis. These biomechanical realities underscore a fundamental clinical directive: IAHA should not be utilized as an isolated mechanical cure [30]. Comprehensive reviews of conservative osteoarthritis management highlight that combining HA injections with targeted physical rehabilitation, gait retraining, and muscle-strengthening exercises is absolutely essential [30]. This multimodal approach maximizes the benefits of HA by ensuring that the biochemical reduction in nociception is safely translated into functionally optimized, long-term joint loading without accelerating structural wear [30].

4.6 The Evolution of Tribosupplementation: Advanced Fluid Additives

The limitations of standard linear hyaluronic acid - namely, its susceptibility to rapid enzymatic degradation by hyaluronidases and reactive oxygen species (ROS) clearance - have driven the development of "tribosupplementation" [31]. This approach involves the engineering of highly advanced, non-HA or modified-HA lubricants designed to address specific tribological and biological deficits within the osteoarthritic joint [31].

To emulate the boundary lubrication provided by native cartilage proteins, researchers have developed linear and bottle-brush fluid additives [31]. For example, semi-synthetic brush-like polymers composed of a hyaluronic acid backbone grafted with poly(acryloylamino-2-methyl-1-propanesulfone) (HA/PA) or poly(2-methacryloyloxyethyl phosphorylcholine) (HA/PM) have been successfully synthesized [31]. These brush-like polymers provide extreme hydration lubrication. *In vivo* models of OA demonstrated that these biomimetic polymers mitigated disease and regenerated cartilage significantly better than standard HA or saline [31]. Recombinant human PRG4 (rhPRG4/Lubricin) is another major advancement. Full-length rhPRG4, as well as truncated versions (LUB:1), function as pure boundary lubricants, significantly reducing the coefficient of friction and decreasing urinary levels of CTX-II (a biomarker of cartilage degradation) in animal models [31].

Hydrogels and particle-based fluid additives represent a shift toward multifunctional therapeutics that combine lubrication with extended drug delivery [32]. Advanced formulations, such as composite HA hydrogels and chitosan-based supramolecular hydrogels, offer tuneable viscoelasticity while remaining highly resistant to enzymatic degradation [32]. Crucially, through the utilization of dynamic covalent bonds, these advanced hydrogels possess the ability to self-heal after mechanical perturbation through a needle or dynamic joint loading [32].

Particle additives and microgels function distinctly by responding intelligently to the joint microenvironment. For instance, advanced hydrogel microspheres (such as those based on methacrylated HA or gelatin) coated with lubricious liposomes act as "biological ball bearings" that reduce friction at sliding interfaces via a rolling mechanism [31, 33]. As the microspheres wear down under joint loading, they expose new liposomes, forming self-renewing hydration layers that provide continuous, long-term lubrication [31]. When these sophisticated nanocarrier systems are loaded with agents like rapamycin to promote cellular autophagy, these particles drastically alleviate joint wear, promote macrophage polarization toward an anti-

inflammatory phenotype, and reduce structural degradation *in vivo* [32, 33]. Similarly, advanced micro-particles utilizing mussel-inspired dopamine adhesive coatings (polydopamine - PDA) can anchor superhydrophilic polymers like sulfobetaine methacrylate (SBMA) to provide a massive hydration layer while simultaneously scavenging ROS [31, 33]. When utilized as carriers for Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as diclofenac, these micro-particles simultaneously provide extreme boundary lubrication and localized anti-inflammatory drug release [33]. This mechanism effectively downregulates catabolic enzymes within the joint without the severe systemic gastrointestinal or cardiovascular side effects typical of chronic oral NSAID therapy [32, 33].

4.7 Matrix Enhancers in Tribosupplementation

While fluid additives remain suspended within the synovial fluid, matrix enhancers are designed to actively bind directly to the articular cartilage surface, localizing the tribosupplement exactly where the tissue is most damaged [34]. These constructs typically comprise two domains: a cartilage-reactive binding domain and a lubricious domain [34].

To achieve improved superficial zone localization, researchers have generated an aldehyde-modified version of PRG4 (PRG4-CHO) [34, 35]. This enhancer utilizes the aldehyde modification to covalently bind to the cartilage surface, resulting in a twofold increase in PRG4 retention on the tissue compared to unmodified PRG4, without sacrificing its boundary lubrication capabilities [34, 35].

Another innovative approach is the PGA-PMOXA-HBA polymer, composed of poly(2-methyl-2-oxazoline) (PMOXA) brushes grafted onto a poly(glutamic acid) (PGA) backbone [31, 34]. These polymers preferentially chemisorb onto degraded tissue via Schiff-base reactions between the aldehyde-bearing hydroxybenzaldehyde (HBA) functions and the exposed amines of the damaged cartilage [31]. This mechanism effectively targets the osteoarthritic lesions and restores their coefficient of friction to healthy baselines while acting as a biopassive barrier against further enzymatic degradation [31].

Furthermore, HABpep (and complex derivatives like HABPep-PEG-ColBPep) constructs utilize specific peptide sequences to bind both type II collagen and hyaluronic acid simultaneously [31, 34]. This effectively concentrates whatever endogenous or exogenously administered HA remains in the osteoarthritic joint directly at the cartilage surface [31]. *In vivo* fluorescence tracking demonstrated that this targeted surface modification increased local HA retention by 12-fold, extending joint residency time from a mere 6 hours to an impressive 72 hours post-injection [31]. These matrix enhancers represent a paradigm shift from treating the fluid to actively resurfacing the damaged tissue [34].

4.8 Divergence in International Clinical Practice Guidelines

Despite the voluminous literature demonstrating the efficacy, safety, and tribological logic of IAHA, profound inconsistencies exist among the clinical practice guidelines (CPGs) published by major international medical societies [23, 36, 37]. This polarization directly impacts global insurance reimbursement, clinical care pathways, and equitable patient access to care.

The divergence stems not from a lack of clinical data, but from varying interpretations of meta-analyses and the fact that different studies use different thresholds for determining a clinically significant difference [36]. On one side of the spectrum, the American Academy of Orthopaedic Surgeons (AAOS) advises against the routine use of IAHA for knee osteoarthritis [36]. The AAOS rationale notes that much of the literature surrounding viscosupplementation carries a significant degree of publication bias [36]. Furthermore, when aggregating massive meta-analyses that mistakenly pool all severities of OA (including end-stage KL Grade IV where HA mechanically fails), the overall aggregate SMD predictably fails to show significant differences compared to saline [23, 38]. The AAOS also heavily weighs the prominent placebo effect inherent in any intra-articular injection and cite the higher costs of certain cross-linked HA

preparations as unjustified by the statistically modest aggregate benefit over placebo across the general population [36, 38].

Conversely, the updated guidelines from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the Osteoarthritis Research Society International (OARSI) view the data through a phenotype-specific lens and recommend IAHA based on patient-specific scenarios [37]. ESCEO positions IAHA as a stage 2 treatment, particularly recommended when oral NSAIDs are contraindicated or when patients remain symptomatic despite NSAID use [37]. OARSI provides a conditional recommendation for IAHA, explicitly recognizing that its use should depend on patients' comorbidity profiles [37]. Correctly phenotyped subgroups (e.g., non-obese patients with lower radiographic severity like KL grades I-III) experience significant clinical benefit that may safely delay the need for total joint replacement [23].

To reconcile these international disparities, future clinical trials and systematic reviews must abandon generalized, "all-comers" methodologies [23]. Standardizing biomarker-driven patient selection, rigorously stratifying data by radiographic disease stage, and adopting precision-medicine approaches will be essential to harmonizing global guidelines and ensuring that patients who will genuinely benefit from viscosupplementation receive appropriate access [23, 39, 40].

4.9 Study Limitations

While this review provides a comprehensive overview of the current literature regarding intra-articular hyaluronic acid viscosupplementation, several limitations must be acknowledged. Primarily, as a narrative review rather than a systematic review or primary mathematical meta-analysis, the literature selection process may be subject to inherent selection bias. The analysis heavily relies on previously published systematic reviews and network meta-analyses, which themselves encompass heterogeneous randomized controlled trials with varying methodologies, patient populations, and cross-linked HA formulations. Consequently, directly comparing effect sizes across different time points involves synthesizing data from studies with diverse follow-up protocols and control groups. Furthermore, the rapid evolution of tribosupplementation and advanced biomaterials means that while this review captures recent vanguard therapies, it may not encompass every ongoing or unpublished clinical trial in this rapidly expanding field. Despite these limitations, the synthesized data accurately reflects the prevailing clinical consensus and current trajectory of osteoarthritis management.

5. Conclusion

The comprehensive review of the current literature supports the conclusion that intra-articular hyaluronic acid (IAHA) viscosupplementation is a highly effective, durable, and safe non-surgical intervention for the management of knee osteoarthritis, provided it is utilized within a carefully phenotyped patient population. By addressing the fundamental loss of synovial fluid viscoelasticity, the primary therapeutic value of IAHA lies not in acting as a simple mechanical lubricant, but rather in biologically engaging viscoinductive and anti-inflammatory pathways to decelerate extracellular matrix degradation.

Comparative analyses demonstrate a distinct temporal efficacy trajectory: while intra-articular corticosteroids offer superior rapid analgesia for short-term relief, hyaluronic acid provides significantly greater, sustained improvements in pain reduction and functional mobility over the medium to long term (up to 6 months) [17, 18, 19]. Furthermore, advancements in high-molecular-weight and cross-linked HA formulations have successfully enabled single-injection regimens, which maximize intra-articular residence time and provide clinically meaningful relief while eliminating the risks associated with repeated joint punctures [21].

However, the clinical success of IAHA is not strictly due to an immediate mechanical reduction in gross joint friction, but rather stems from profound biological mechanisms and gradual functional restoration [27]. Because pain relief following IAHA therapy can inadvertently lead

to increased walking speeds and elevated dynamic joint loads (such as the knee adduction moment), viscosupplementation must not be utilized as an isolated treatment. Combining HA injections with targeted physical rehabilitation and gait retraining is absolutely essential to translate biochemical nociception reduction into safe, long-term joint loading [29, 30].

The pronounced divergence in international clinical guidelines highlights the critical necessity of abandoning generalized, "all-comers" treatment algorithms in favor of precision medicine [23, 36, 38, 39, 40]. The efficacy of IAHA is exquisitely sensitive to patient-specific prognostic variables; optimal functional outcomes are achieved in non-obese patients with early to moderate osteoarthritis (Kellgren-Lawrence grades I-III), whereas it remains largely a palliative bridging therapy in end-stage, bone-on-bone disease [22, 23].

Ultimately, the future of osteoarthritis management lies in the evolution toward advanced tribosupplementation. The continued development of multifunctional therapeutics - including stimuli-responsive hydrogels, bottle-brush polymers, liposomal carriers, and matrix enhancers - will allow clinicians to actively resurface damaged tissue and provide targeted drug delivery [31, 32, 34]. When integrated with rigorous patient phenotyping and multimodal rehabilitation, modern viscosupplementation remains a vital cornerstone of joint preservation that effectively delays the need for total joint replacement.

Key words

knee osteoarthritis, viscosupplementation, hyaluronic acid, tribosupplementation, narrative review, precision medicine.

Disclosure:

Authors' Contributions:

Conceptualization: Kacper Kość, Natalia Muzyka, Gabriela Panek;

Methodology: Jakub Giersz, Adam Prusek, Remigiusz Piliński;

Check: Amanda Abramowicz, Magdalena Rumin, Dominika Gosztyła, Weronika Bukwald;

Formal analysis: Kacper Kość

Investigation: Adam Prusek, Natalia Muzyka, Dominika Gosztyła;

Resources: Kacper Kość, Jakub Giersz, Weronika Bukwald;

Data curation: Amanda Abramowicz, Gabriela Panek;

Writing – rough preparation: Kacper Kość, Remigiusz Piliński, Jakub Giersz;

Writing – review and editing: Natalia Muzyka, Weronika Bukwald, Dominika Gosztyła, Amanda Abramowicz, Magdalena Rumin, Adam Prusek, Gabriela Panek;

Visualization: Natalia Muzyka, Gabriela Panek;

Supervision: Kacper Kość;

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

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conflicts of Interest: The authors declare no conflict of interest.

Artificial intelligence disclosure:

In preparing this work, the authors used Gemini 3.1 Pro for the purpose of assistance with language editing and structural refinement. After using this tool, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

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