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REVISITING HYALURONIC ACID THERAPY IN ORTHOPEDICS: BETWEEN SCIENCE AND SKEPTICISM

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ABSTRACT

Introduction: Hyaluronic acid (HA) is a long, unbranched polysaccharide classified as a glycosaminoglycan. Since its isolation from the vitreous body of an ox in 1934 by Karl Meyer and John Palmer, HA has attracted considerable interest across medical disciplines. Naturally occurring HA possesses several favorable properties, including high water-binding capacity, biocompatibility, viscoelasticity, free radical scavenging, and unique rheological characteristics. It also exhibits anti-inflammatory, antiangiogenic, and immunosuppressive effects, contributing to its increasing popularity—especially in orthopedics. HA is present in high concentrations within synovial fluid, joint capsules, and cartilage, making it highly relevant in conditions involving joint degeneration or injury. Accordingly, HA-based therapies have found widespread application in treating osteoarthritis, rheumatoid arthritis, tendinopathies, and other soft tissue disorders.
Aim: The aim of this work is to evaluate the clinical relevance, efficacy, and safety of hyaluronic acid (HA) in the treatment of orthopedic conditions, particularly osteoarthritis, tendinopathies, and other soft tissue injuries. The objective is to clarify HA's therapeutic value, especially via intra-articular injection, amid ongoing debate regarding its clinical effectiveness compared to placebo and standard non-surgical treatments.
Materials and Methods: This review is based on an analysis of numerous studies, particularly randomized controlled trials (RCTs), that assessed the efficacy of HA in orthopedic applications. Emphasis was placed on comparing HA treatment outcomes—most notably intra-articular injections—with those of placebo and conventional non-operative therapies. Literature was reviewed from relevant medical databases and peer-reviewed sources.
Results: Evidence from multiple studies suggests that intra-articular HA injections can lead to improvements in pain and joint function compared to baseline or non-surgical treatments. However, many randomized controlled trials have shown no statistically significant advantage of HA over placebo. Despite this, patient-reported outcomes often indicate symptom relief and improved function following HA administration.
Conclusion: Due to conflicting data regarding its clinical utility, the use of HA in orthopedics remains a topic of ongoing debate. Nonetheless, HA's favorable safety profile and biological properties support its consideration in selected orthopedic cases. When used appropriately, HA injections may offer a viable non-surgical option for managing joint and soft tissue disorders.

KEYWORDS
Hyaluronic Acid, Intra-Articular Injections, Osteoarthritis, Tendinopathy, Orthopedics

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Introduction.

The first scientific reference to hyaluronic acid (HA) dates back to 1880 [1,2]. The term "hyaluronic" is derived from the Greek word *hyalos*, meaning "glass," referring to the compound's translucent, gel-like appearance. HA was first isolated in 1934 from the vitreous humor of bovine eyes by Karl Meyer and John Palmer [3]. Subsequent research revealed HA's ubiquitous presence in human and animal tissues, as well as in certain bacterial species, including *Streptococcus zooepidermicus* and *Escherichia coli* [4–6].

HA is a linear, high-molecular-weight polysaccharide with several advantageous biological and physicochemical properties. These include a high capacity for water retention [12], excellent biocompatibility [12], viscoelasticity [12], free radical scavenging, and specific rheological behavior [12]. Owing to its linear structure and modifiable functional groups, HA is highly adaptable for medical and pharmaceutical applications [10]. Consequently, HA-based formulations have been increasingly used across various medical specialties, including dermatology, ophthalmology, and notably, orthopedics.

Aim of the Work

The aim of this study is to evaluate the clinical applications, efficacy, and safety of hyaluronic acid (HA) in orthopedic practice. By reviewing relevant scientific literature, the work seeks to clarify the biological mechanisms of HA, its methods of administration, and its therapeutic potential in the treatment of osteoarthritis, tendinopathies, and other soft tissue injuries. This review also aims to address the ongoing debate regarding HA's clinical value and to provide evidence-based guidance for its use in orthopedic patients.

Materials and Methods

A comprehensive literature review was conducted to evaluate the clinical applications, efficacy, and safety of hyaluronic acid (HA) in orthopedic practice. The search was performed using the PubMed database, focusing exclusively on English-language articles published within the past two decades. Keywords used in the search included "hyaluronic acid," "osteoarthritis," "tendinopathy," and "intra-articular injection." The inclusion criteria comprised randomized controlled trials (RCTs), systematic reviews, and meta-analyses that investigated the biological functions, mechanisms of action, and clinical outcomes associated with HA use in orthopedic contexts. Articles were selected based on their relevance to HA's therapeutic potential, methods of administration, and reported safety profiles in conditions such as osteoarthritis and soft tissue disorders. The collected data were synthesized to provide an evidence-based overview of HA's role in orthopedic treatment strategies.

Structure, Synthesis and Degradation of Hyaluronic Acid

Hyaluronic acid (HA) is a long, unbranched polysaccharide composed of disaccharide units consisting of D-glucuronic acid and N-acetyl-D-glucosamine, alternately linked by β-(1-3) glycosidic bonds [7]. It is classified as a glycosaminoglycan (GAG); however, unlike other compounds in this group, it does not contain sulfate groups.

Unlike other glycosaminoglycans, hyaluronic acid is not synthesized in the Golgi apparatus. In the human body, its synthesis is catalyzed by hyaluronan synthase (HAS)—a membrane-bound enzyme located on the inner (cytoplasmic) surface of the cell membrane. Three isoforms of HAS exist, which differ in tissue-specific expression, metabolic activity, and the molecular weight of the HA they produce: HAS1, HAS2, and

HAS3. HAS1 exhibits the lowest enzymatic activity, producing HA of molecular weight similar to the moderately active HAS2 (ranging from 2×10^5 Da to 2×10^6 Da), whereas HAS3 is the most active isoform and is responsible for producing the smallest HA molecules (up to 2×10^5 Da) [8,9]. Based on the molecular size and thus chain length, HA can be categorized into small, medium, and large polymers. The first two types have pro-inflammatory properties, promoting processes like angiogenesis and heat shock protein release. In contrast, large polymers act mainly as immunosuppressants and inhibit angiogenesis [11].

Hyaluronic acid degradation occurs both enzymatically and chemically. The key enzymes involved in its breakdown include: HYAL1 – a lysosomal enzyme that hydrolyzes intracellular HA into tetrasaccharides; HYAL2 – responsible for breaking down high-molecular-weight HA into fragments smaller than 20 kDa [12]; and PH-20, found in sperm, which degrades the HA layer surrounding the oocyte.

Mechanisms of Action

It has been proven that HA inhibits chondrocyte apoptosis and promotes their proliferation. These effects are mediated by various mechanisms, many of which result from HA binding to the CD44 receptor (a cell surface adhesion protein). One mechanism includes the suppression of IL-1β gene expression, which leads to decreased activity of matrix metalloproteinases (MMPs) -1, -2, -3, -9, and -13 [21, 22, 23]. HA binding to CD44 also inhibits the production of nitric oxide (NO) [23, 24] and prostaglandin E2 [23, 25] in the synovial membrane, and reduces the activity of ADAMTS enzymes (a disintegrin and metalloproteinase with thrombospondin motifs) [23, 26]. Another mechanism through which HA protects cartilage is its interaction with the RHAMM receptor (Receptor for Hyaluronan-Mediated Motility) [17, 22, 23]. Additionally, many studies highlight HA's ability to reduce friction and absorb shocks, owing to its viscoelastic properties and capacity to bind large amounts of water [18, 23].

Clinical Applications in Orthopedics

Distribution and Physiological Role

The body of an average 70 kg person contains approximately 15 g of HA. It is found in the highest concentrations in the skin, synovial fluid, vitreous body, umbilical cord, and other areas exposed to mechanical stress [12]. High HA content in synovial fluid, joint capsules, and articular cartilage is due to the high susceptibility of these tissues to degeneration and injury. Therefore, HA-based products are widely used in orthopedics—mainly in the treatment of osteoarthritis, rheumatoid arthritis, tendinopathies, and other soft tissue injuries [13,14,15].

Administration Methods

1. Oral Administration

Over the years, numerous studies have been conducted to determine the optimal administration route for HA products. In 2008, Lajos Balogh et al. published research evaluating the absorption, distribution, and excretion of a single oral dose of HA in rats and dogs [27]. They used HA labeled with the metastable isotope of technetium-99 (99mTc) to assess its absorption in connective tissue. Histopathological analysis and scintigraphy of animal tissues confirmed that a small amount of orally administered HA can reach peripheral tissues such as joints, bones, and skin, where it exhibits localized effects. It is assumed that HA is similarly distributed in humans, although this lacks definitive scientific confirmation [27].

Toshiyuki Tashiro and colleagues conducted a clinical study where patients with osteoarthritis (Kellgren-Lawrence grade 2 and 3), under 70 years of age, received 200 mg/day of oral HA for 12 months. The therapy, combined with quadriceps-strengthening exercises, proved effective [28].

However, many studies suggest that oral HA therapy is less effective compared to intra-articular administration. In 2016, M. Ricci et al. conducted a study on 60 patients with early-stage osteoarthritis. They were randomized into two groups: the first received three weekly intra-articular injections of 1.6% HA solution; the second received 300 mg of oral HA daily for 20 days, followed by 150 mg daily for another 20 days. Results showed better therapeutic outcomes in the injection group [29]. While oral HA reaches joints, current evidence does not support its superiority over intra-articular injections [28,29].

2. Intra-articular Administration

Intra-articular HA injection—also known as viscosupplementation (VS)—is commonly used to improve the biomechanical properties of joints and tendons. The first clinical study on its efficacy and safety for osteoarthritis was conducted in the 1970s [19].

Osteoarthritis

Osteoarthritis is the most common inflammatory joint disease, particularly in those over 60. It is defined as a condition caused by biological or mechanical disturbances that disrupt joint homeostasis—due to an imbalance between the synthesis and degradation of chondrocytes, extracellular matrix, and subchondral bone. It leads to progressive cartilage degradation, osteophyte formation, subchondral sclerosis, and synovial membrane changes [12,31]. It also alters the rheological properties of synovial fluid, reducing its ability to absorb shocks and minimize friction. The disease affects both intra-articular and periarticular structures (muscles, tendons, ligaments) [32]. Clinically, it presents with effusions, joint deformities, axis deviations, and pain, leading to functional limitations and decreased quality of life [20].

A key factor in osteoarthritis pathogenesis is HA depolymerization, increasing the ratio of small to large HA molecules. Therefore, intra-articular HA supplementation appears logical.

In 2012, Sascha Colen et al. reviewed the effects of intra-articular HA in various joints (e.g., MTP-1, ankle, hip, SIJ, facet joints, CMC-1, shoulder, TMJ) [33]. While short-term outcomes (<12 months) showed improvement in pain and function scores, no superiority was found compared to control groups, corticosteroid injections, or other treatments. Due to variability in products, dosing, and populations, clear recommendations could not be made.

In 2020, De Lucia et al. reviewed 370 interventions involving HA and corticosteroid injections in various joints. Again, improvements were noted from baseline, but no clear advantage over corticosteroids was observed [34].

In 2022, TV Pereira et al. published a meta-analysis of 24 placebo-controlled RCTs on knee osteoarthritis, involving 8997 patients. Results showed a small but statistically significant improvement in pain and function scores from baseline, but no clinically relevant difference versus placebo. Adverse event rates were higher in the HA group [15,33–36].

In summary, while intra-articular HA appears effective versus baseline and non-operative therapies, most studies do not show a clear advantage over placebo, resulting in ongoing debate about its clinical value [37–39].

Use in Tendinopathies and Soft Tissue Injuries

The term *tendinopathy* describes a spectrum of changes in damaged or diseased tendons that result in pain, impaired function, and reduced tensile strength. Overuse-related pathologies most commonly affect the rotator cuff tendons, proximal extensor tendons of the forearm, patellar ligament, gluteal tendons, and Achilles tendon. These injuries often occur during high-load or repetitive activities, such as sports or even playing musical instruments. The pathogenesis is complex and includes inflammation, collagen fiber degradation, increased angiogenesis, changes in ECM composition, and enhanced apoptosis. Treatment includes physical therapy, pharmacotherapy, and surgery, but the effectiveness of these methods remains unclear [40,41].

In 2021, Francesco Oliva et al. published a study on HA use in tendinopathy and its effects on tendon physiology. They found that HA exerts beneficial effects both at injury sites and on the tendon sheath, reducing inflammation and promoting healing through the activation of epitenon and endotenon cells. A review of HA injections in tendinopathies of the rotator cuff, patellar, Achilles, and forearm extensor tendons revealed that HA can reduce pain and speed recovery. However, due to insufficient data, the conclusions remain tentative.

Moin Khan et al., in 2022, published the results of a meta-analysis of randomized clinical trials evaluating the use of hyaluronic acid (HA) in the treatment of soft tissue injuries, including rotator cuff tendinopathy, proximal extensor tendon insertions of the forearm, patellar ligament, and Achilles tendon. The effects of HA injections were compared with routinely used therapies such as physiotherapy, platelet-rich plasma (PRP), extracorporeal shockwave therapy (ESWT), nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids (CS), lidocaine, and placebo.

The majority of the data pertained to patients with rotator cuff injuries. The analysis revealed that the pain reduction effect of HA, assessed using the Visual Analog Scale (VAS), exceeded the minimal important difference (MID) when compared to placebo. No significant differences were observed between HA and corticosteroid or PRP injections. However, a better safety profile was demonstrated for HA injections, which may justify their use in patients whose pain is poorly controlled with analgesics and physiotherapy [13].

In summary, the results of the cited studies indicate potentially beneficial effects of HA injections in the treatment of tendinopathies and other soft tissue injuries. However, further evidence is needed to confirm the safety and efficacy of this therapy in comparison to routinely used treatment modalities [13, 40, 41].

Discussion

The evidence synthesized in this review underscores the complex and somewhat controversial role of hyaluronic acid (HA) in orthopedic treatment. While in vitro and mechanistic studies provide a strong foundation for HA's biological efficacy—highlighting its interactions with receptors such as CD44 and RHAMM [17, 21, 22, 23, 24], as well as its modulation of inflammatory mediators—clinical translation remains inconsistent. In osteoarthritis management, the small but statistically significant improvements observed in meta-analyses raise questions about clinical relevance, especially when compared to placebo or corticosteroids. These findings suggest that HA may function more effectively as part of a multimodal therapeutic strategy rather than as a stand-alone solution. In tendinopathies, emerging evidence shows promise, particularly in reducing pain and promoting tissue repair, but the heterogeneity of methodologies, limited sample sizes, and variation in outcome measures hamper definitive conclusions. Furthermore, the differences in efficacy between oral and intra-articular administration call for better understanding of HA's pharmacokinetics and bioavailability in human tissues. Importantly, HA's favorable safety profile continues to position it as a viable option for patients who are contraindicated for other treatments. Moving forward, the orthopedic community must prioritize standardized protocols and high-quality clinical trials to determine how and when HA can be used most effectively, with attention to molecular weight, dosing regimens, and patient-specific factors.

Conclusions

Both in vitro and in vivo studies have demonstrated that hyaluronic acid exhibits anti-inflammatory, wound-healing, anti-angiogenic, and immunosuppressive properties. For this reason, its use in clinical practice—particularly in orthopedics—has become increasingly common in recent years. Although the efficacy of HA in the treatment of osteoarthritis, tendinopathies, and other soft tissue injuries remains a matter of debate—mainly due to the lack of a clear therapeutic effect over placebo—many studies support its effectiveness in improving pain and function when compared to patients' baseline status or to outcomes following other standard non-operative treatments.

When administered intra-articularly under aseptic conditions, HA is associated with a relatively low risk of adverse events. Nevertheless, the issue of recommending HA for osteoarthritis or tendinopathy treatment remains inconclusive. The decision to implement this type of therapy should be made on an individual basis and in consultation with the patient.

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