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Review Article

# Hyaluronic Acid in Spinal Disorders: A Narrative Review of Hot Spots and Research Perspectives

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## Abstract

Hyaluronic acid (HA), a cell behavior modulator with anti-aging, anti-inflammatory, and immunomodulatory properties, is a member of the glycosaminoglycan family. In orthopedics, HA has been utilized for its chondroprotective, anti-inflammatory, immunomodulatory, and cushioning effects, owing to its extreme lubricity and hydrophilicity. HA has been investigated for various diagnostic and therapeutic applications in spinal diseases.

This narrative review aimed to clarify that HA may serve as a biomarker in spinal diseases and as a therapeutic agent in several applications, such as tissue engineering for intervertebral disc degeneration, management of spinal pain, prevention of postoperative epidural fibrosis, and minimally invasive treatment of vertebral compression fractures.

Although the efficacy of HA as a viable alternative or adjunct to existing therapies for various spinal conditions has been investigated, further experimental and clinical studies are required to explore regulatory considerations, refine clinical applications, and develop potential interdisciplinary management strategies before general recommendations can be established.

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## What's Known

- Hyaluronic acid is a cell behavior modulator with anti-inflammatory and immunomodulatory properties. It improves nourishment of the avascular regions of articular cartilage and reduces pain sensation by decreasing both nerve impulse frequency and nerve sensitivity.

## What's New

- Hyaluronic acid has various diagnostic and therapeutic applications in spinal diseases.
- Both intra-articular facet joint injection and interlaminar epidural injection, as well as selective nerve root block using hyaluronic acid, have been evaluated for the management of spinal pain.

## Introduction

*History*

Hyaluronic acid (HA) is an unbranched biopolysaccharide belonging to the glycosaminoglycan family. It was extracted from bovine vitreous humor by Karl Meyer and John Palmers in 1934. Its name is derived from the Greek word *hyalos* (meaning "glass"), reflecting its physical properties, and the "uronic acid". The first medical application of hyaluronan in humans was for vitreous replacement surgery in the 1950s.[1, 2] Subsequently, HA was adopted in orthopedics for its chondroprotective, anti-inflammatory, immunomodulatory, and cushioning properties. The clinical use of viscosupplementation started in Japan in 1987 and later in the United States in 1997.[3] Cross-linked HA has also been used in dermatology for wound healing and cosmetic applications due to its longevity, in cardiovascular surgery to reduce thrombus formation on grafts and stents, and in orthopedic and abdominal surgery to minimize postoperative adhesions.[4]

*Molecular Biology*

Hyaluronan may exist as an acid (hyaluronic acid) or a salt with physiologic PH, such as sodium hyaluronate. In the human body, HA is predominantly in the salt form (hyaluronate) and is found in high concentrations within the extracellular matrix of various tissues, including the lungs, kidneys, brain, soft connective tissues, muscles, and epithelial and neural tissues. It is notably abundant in areas subject to friction, such as the pericardium, pleura, joints, and tendons.

HA is categorized into two forms based on chain length: low molecular weight HA (LMWHA; <1000 kDa), which acts as a potent inducer of angiogenesis and inflammation, and high molecular weight HA (HMWHA; >2000 kDa), which exhibits immunosuppressive and anti-angiogenic activity. HA can be derived from human or animal sources, such as rooster combs, or produced via bacterial fermentation.

Hyaluronan solutions are extremely lubricious and hydrophilic, leading to their characterization as a “pseudo-plastic” substance. This property underpins its ability to reduce postoperative adhesion formation following orthopedic surgery.[1-3, 5]

Normal HA turnover occurs via the lymphatic system and lysosomal digestion. This turnover is extremely rapid; degradation can take place in a few minutes within the bloodstream or up to 70 days in the vitreous of the eye. Approximately 30% of HA degradation occurs in local tissues, while the remaining 70% enters the lymphatic drainage.[6]

*Therapeutic Applications of HA and Biological Function*

HA is a cell behavior modulator with anti-diabetic, anti-aging, anti-inflammatory, and immunomodulatory properties. Due to its chondroprotective and cushioning effects, HA improves nourishment in the avascular regions of articular cartilage and reduces pain sensation by decreasing both nerve impulse frequency and nerve sensitivity.[1, 7, 8]

Beyond its established use in inflammatory joint disease and tendinopathy, HA exhibits therapeutic effects in a range of conditions, including intervertebral disc disease, inflammatory skin disease, wound healing, inflammatory bowel disease, lung inflammation, inflammatory disease of the oral cavity, bladder inflammation, and renal and cardiac inflammation.[5] HA also has various diagnostic and therapeutic applications in spinal diseases. This narrative review aimed to synthesize the potential applications of HA as a viable alternative or adjunct to existing therapies for spinal disorders, examining the existing evidence and studies in this field.

Intervertebral disc degeneration and facet joint osteoarthritis (OA) are among the most common causes of chronic low back pain.[9] The pathophysiology of facet OA, the only synovial joint in the spine, involves a distinct inflammatory process that differs from generalized spinal OA and degeneration. Specific biomarkers, such as HA and collagen type II, may help differentiate between phenotypes of spinal OA and thereby improve clinical insight for targeted interventions.[10]

Elevated cerebrospinal fluid levels of HA may indicate a more severe clinical presentation in neuromyelitis optica and multiple sclerosis.[11]

Hosogane and colleagues evaluated the serum level of cartilage metabolites, such as HA, keratan sulfate, cartilage oligomeric matrix protein (COMP), collagen type II cleavage, and procollagen type II C-propeptide, as a biomarker for predicting the development and progression of degenerative lumbar scoliosis (DLS). They found no significant differences in HA or COMP levels between patients with a Cobb angle >10° and the control group. However, higher levels of type II collagen biomarkers were detected in the DLS group. Therefore, they concluded that type II collagen was a main component of facet joint cartilage and nucleus pulposus (NP), and its increased turnover might be associated with the development and progression of DLS.[12]

Intervertebral disc degeneration and annulus fibrosus (AF) tears can result in NP herniation, causing compression of the spinal cord or nerve roots, leading to pain and neurological deficit. Currently, the standard surgical procedure for disc prolapse unresponsive to conservative management or causing neurological deficits is discectomy with partial nucleotomy. However, this approach leaves the annulus fibrosus (AF) defect unrepaired, which leads to NP re-herniation in 5-15% of patients. Furthermore, the damaged AF can lead to biomechanical imbalance of the injured disc, loss of disc height, and NP hydration, and accelerated degeneration over approximately 6 weeks.[13, 14] The resultant loss of disc height can induce further nerve compression and radicular pain in the short or long term after surgery. Thus, annular closure devices have been designed to prevent acute disc re-herniation after discectomy. However, they do not stimulate tissue healing and may not prevent long-term degeneration.[14, 15]

HA, a cell behavior modulator with anti-inflammatory, anti-apoptotic, and analgesic effects, serves as a suitable reservoir for growth factors and a microenvironment for cell

delivery to annular defects through hydrogel scaffolds. As an osmotically active molecule, its function relies on key properties, such as shock absorption, lubrication, and interaction with the CD44 receptor.[16]

Ethical considerations impose significant limitations on human studies evaluating the efficacy and safety of new tissue engineering approaches for intervertebral disc degeneration (IVDD). Consequently, numerous animal studies investigated the *in vivo* and *in vitro* effects of HA on AF tear repair and NP hydration for intervertebral disc (IVD) regeneration.[13] HA can enhance mitophagy and protect mitochondrial function in NP cells, thereby protecting them from oxidative stress. This mechanism represents a potential therapeutic strategy for managing IVDD. [17]

Wei and colleagues employed an AF tissue engineering strategy using a composite hydrogel of polyacrylamide, dopamine, and triple cross-linked oxidized HA modified with collagen mimetic peptide and transforming growth factor beta 1 (TGF-β1) to facilitate AF repair. This mechanically tough material demonstrated strong self-healing capability and bio-adhesiveness. This hydrogel showed a significant reparative effect on AF defects *in vivo* in a rat tail model.[13]

In another study, layered biomimetic micro/nanofibrous scaffolds composed of HA and collagen type I were used to promote AF repair after discectomy. The sustained release of basic fibroblast growth factor (bFGF) from these scaffolds promoted AF cell proliferation, thereby stimulating AF tissue regeneration *in vivo*.[18]

Although various injectable hydrogels have been introduced to repair AF defects after discectomy in animal models, none have proven capable of restoring NP hydration in degenerated intervertebral discs, a factor crucial for maintaining NP mechanical function. Therefore, a combined approach involving modified HA injection into the NP space, followed by a high-density collagen injection into the AF defect, was evaluated using an *in vivo* sheep lumbar spine model. This method better preserves IVD morphology and mechanical properties after discectomy compared to isolated AF repair, NP repair, or discectomy alone.[14] However, the risk of implant herniation under spinal loading must be considered.[19]

HA could also be incorporated into hybrid biosynthetic scaffolds, which have demonstrated significant effectiveness in human spinal fusion procedures.[20]

The safety and efficacy of HA injections for managing spinal pain have been evaluated in a limited number of studies. Techniques assessed include intra-articular facet joint injection, interlaminar epidural injection, and selective nerve root block (SNRB) with HA.[21-24]

Facet joint arthropathy is a leading cause of low back pain, accounting for 21-41% of cases. Conservative management includes facet joint or medial branch blocks with steroids or local anesthetics, which have shown considerable improvement in the numeric rating scale (NRS) and Oswestry disability index (ODI) at 1-year follow-up.[25]

Lumbar zygopophyseal joint injections with Synvisc® (HA) were reported to yield long-term pain improvement, as well as short- and long-term functional improvement in patients with facet OA, compared with baseline. However, no significant intergroup difference was detected when compared to triamcinolone injections.[21]

In patients with lumbar radiculopathy and multilevel pathology, SNRB is useful for detecting the symptomatic pain source. A provocative response to needle placement near the root and analgesic response to medication both have diagnostic value in determining the involved nerve root.[26] For patients with lumbar radiculopathy unresponsive to 6 weeks of conservative treatment, up to four SNRBs using steroids are recommended prior to surgery. Transforaminal epidural steroid injections reduce pain by inhibiting arachidonic acid production and reducing inflammation around the dorsal root ganglion.[27]

Ko and colleagues added sodium hyaluronate and carboxymethyl cellulose (HA-CMC) to steroids and local anesthetics to reduce rebound pain occurring 3 days to 2 weeks after SNRB.[22] In another study, the same researchers compared fluoroscopically guided infraneural transforaminal HA-CMC injections versus corticosteroid injection in patients with lower leg radiating pain. They reported similar improvement in pain, function, and quality of life in both groups and recommended HA-CMC as a steroid alternative for SNRB.[23]

Lumbar degenerative spondylosis triggers a cascade of changes in ligaments, joints, and intervertebral foramina, leading to lumbar foraminal stenosis (LFS). The LFS results in disruption of root neurodynamics and blood supply, followed by pain and disability. HA exerts anti-inflammatory effects and may improve nerve gliding in the lateral recess and the intervertebral foramen, potentially reducing foraminal stenosis symptoms.

Godek and colleagues evaluated the safety of ultrasound-guided interlaminar injection of 2 mL of Sinovial® combined with an exercise program

in patients with symptomatic LFS. Although no significant improvement was observed in the Roland–Morris questionnaire (RMQ), NRS, and ODI scores after 3 months, no significant adverse effect was detected.[24]

Epidural fibrosis, scar tissue formation within the dural sac or around nerve roots following surgery or traumatic repair, is an important cause of failed back surgery syndrome.

This scar tissue compromises nerve root neurodynamics, blood supply, and axoplasmic flow, leading to pain, disability, deterioration of rehabilitation outcomes, and difficulty with revision surgery.[28] Local inflammation, fibroblast proliferation, and fibrillar connective tissue deposition are the three main stages of scar formation.[29] The extent of postoperative epidural fibrosis is determined by fibroblastic activity, immune cell infiltration, extensive tissue damage, epidural hematoma, collagen deposition, destruction of epidural fat, and the extent of laminectomy.[30]

Therefore, the theory of placing a physical barrier between the paraspinal muscles and the epidural space to inhibit scar formation has been investigated. However, the risk of infection, seroma formation, pressure necrosis, and increased fibrotic tissue must be considered.[30, 31]

A variety of barrier materials are being evaluated to reduce adhesion formation after lumbar surgery. These include autologous tissues, biodegradable polymers, and pharmacological agents such as non-steroidal anti-inflammatory drugs,[32] antibiotics,[28] dexamethasone, hydroxycamptothecine, rosuvastatin, low-dose radiation, and traditional Chinese medicines.[29] Polymeric materials act as physical barriers that can also induce the local release of anti-adhesive chemicals.

Cross-linked high-molecular-weight HA prevents epidural fibrosis and reduces fibrotic tissue density via four mechanisms: 1) prevention of local hematoma formation and physical separation from epidural tissue; 2) reduction of the inflammatory mediators secretion; 3) anti-fibrotic activity; 4) suppression of autophagy activity. Consequently, it helps maintain adequate space for the dural sac, nerve root gliding, and preserving normal blood and cerebrospinal fluid circulation.[29, 33]

The TGF-β family promotes fibroblast proliferation and plays a key role in scar tissue formation. TGF-β1, in particular, is most strongly associated with fibroblast proliferation and plays a key role in scar tissue formation. *In vivo* and *in vitro* evaluations indicated that cross-linked HA could inhibit scar tissue formation by reducing inflammatory factors such as IL-6 and by decreasing TGF-β1 expression.[28]

Multiple animal studies with different protocols were designed to evaluate the efficacy of HA sheet and gels in reducing postoperative epidural fibrosis.[28, 31, 33-47]

In 1994, Abitbol and colleagues reported that HA could reduce the biomechanical strength of post-laminectomy extradural adhesions in dogs compared to fat grafting without an interpositional membrane.[48] In 1998, another animal study demonstrated the effectiveness of sodium hyaluronate combined with chitosan in preventing epidural scar formation after laminectomy.[49]

In 2005, Akeson designed a study to evaluate post-laminectomy fibrosis in a rat model. He observed that proliferative scars increased 3–8 weeks after laminectomy, leading to scar tissue formation and nerve root adherence to adjacent pedicles and discs. However, placing a 0.2-mm bioabsorbable macropore roof barrier sheet between the muscles and epidural space, along with applying HMWHA gel, reduced intraspinal adhesions compared to the control group. Notably, a thinner 0.02-mm intracanal barrier sheet resulted in fibrotic mass formation within the canal.[50]

Conflicting data suggested that direct injection of liquid HA into a laminectomy defect might increase dural pressure and induce spinal arachnoiditis.[31] As the half-life of HA in the epidural space appears to be less than 1 day, such side effects may be temporary.

To overcome rapid HA degradation, self-crosslinking sodium hyaluronate was proposed.[28, 36, 41] While low doses of this self-crosslinking gel could effectively prevent epidural adhesion long-term, high doses might cause temporary motor deficits due to spinal cord compression.[51]

Different combinations of HA were investigated. It was shown that HA with 1, 4-butanediol diglycidyl had better anti-adhesion effects than sodium carboxymethylcellulose.[35] Other formulations reported to effectively prevent epidural fibrosis include: IIbuprofen-conjugated hyaluronate/polygalacturonic acid hydrogel,[39] decellularized adipose matrix/adipose stromal cells-incorporated HA hydrogel,[38] Poloxamer-based thermo-sensitive sol-gel,[40] oxidized HA/adipic acid dihydrazide hydrogel,[42] 1, 4-butanediol diglycidyl ether-crosslinked hyaluronan,[45] HA carboxymethylcellulose alginate hydrogel,[46] and Pirfenidone-loaded HA methacryloyl hydrogel.[47]

Given all the data, HA reduces inflammation and fibroblast activity, lubricates and hydrates tissue, modifies cell signaling, and creates a physical barrier to prevent new scar tissue formation in the epidural space. In contrast,

hyaluronidase is an enzyme that dissolves existing adhesions and scar tissue by breaking down HA, reducing its viscosity, and degrading fibrotic tissue. These properties make hyaluronidase useful for epidural adhesiolysis in failed back surgery syndrome.[52, 53]

HA enhances the cohesion and mechanical properties of calcium phosphate cement.[54, 55] Similarly, adding HA to polymethylmethacrylate (PMMA) cement increases its viscosity, injectability, and compressive strength.[56] Therefore, HA may improve the long-term outcome of vertebroplasty. It decreases the elastic modulus of PMMA, reduces the mechanical imbalance and mismatch between treated and untreated vertebra, and thereby lowers the risk of adjacent vertebral body collapse associated with stiff cement. HA also provides a proper porous environment for the process of bone regeneration.[57]

The limited regenerative capacity of the central nervous system (CNS) and the absence of a natural extracellular matrix to guide regenerating axons are key challenges in neural tissue repair. Therefore, some studies focused on the potential therapeutic effects of mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP) to provide a supportive microenvironment and neurotrophic factors for endogenous neural stem cell differentiation. Concurrently, various scaffolds are being evaluated to offer improved mechanical support for cell growth and to bridge the injury site.[58-62]

HA is a major component of the extracellular matrix and plays an essential role in promoting lesion healing. Accordingly, HA-based adhesive hydrogels are being evaluated in animal models for spinal cord injury repair.[63]

## Conclusion

Viscosupplementation and regenerative medicine have introduced a new paradigm in treatment approaches. HA, along with platelet-rich plasma, prolotherapy, and mesenchymal stem cells, comprises a range of materials now used globally in managing musculoskeletal disorders. As surgical treatments face inherent limitations and potential complications, clinicians are increasingly moving toward minimally invasive methods. The application of viscosupplementation and regenerative medicine aims to improve patient outcomes where feasible. HA has been investigated for various diagnostic and therapeutic applications in spinal diseases. This review highlighted its potential roles as a diagnostic biomarker, a component in tissue engineering for intervertebral disc degeneration, an agent for managing spinal pain, a preventive measure for postoperative epidural fibrosis, and an adjunct in the minimally invasive treatment of vertebral compression fractures. Although the efficacy of HA as a viable alternative or adjunct to existing spinal therapies has been investigated, further experimental and clinical studies are required. Future work must explore the regulatory considerations, refine clinical applications, and develop potential interdisciplinary management strategies before definitive, generalized recommendations can be established.

## Authors' Contribution

SA.R: Conceptualization, and reviewing the manuscript; SM.R: Conceptualization, and reviewing the manuscript; E.K: Conceptualization, study design, drafting, and reviewing the manuscript; AH.MK: Study design, and reviewing the manuscript; A.ND: Study design, and reviewing the manuscript; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Conflict of Interest:** None declared.

## Declaration of AI

The authors declare that no AI tools were used in the preparation of this manuscript.

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