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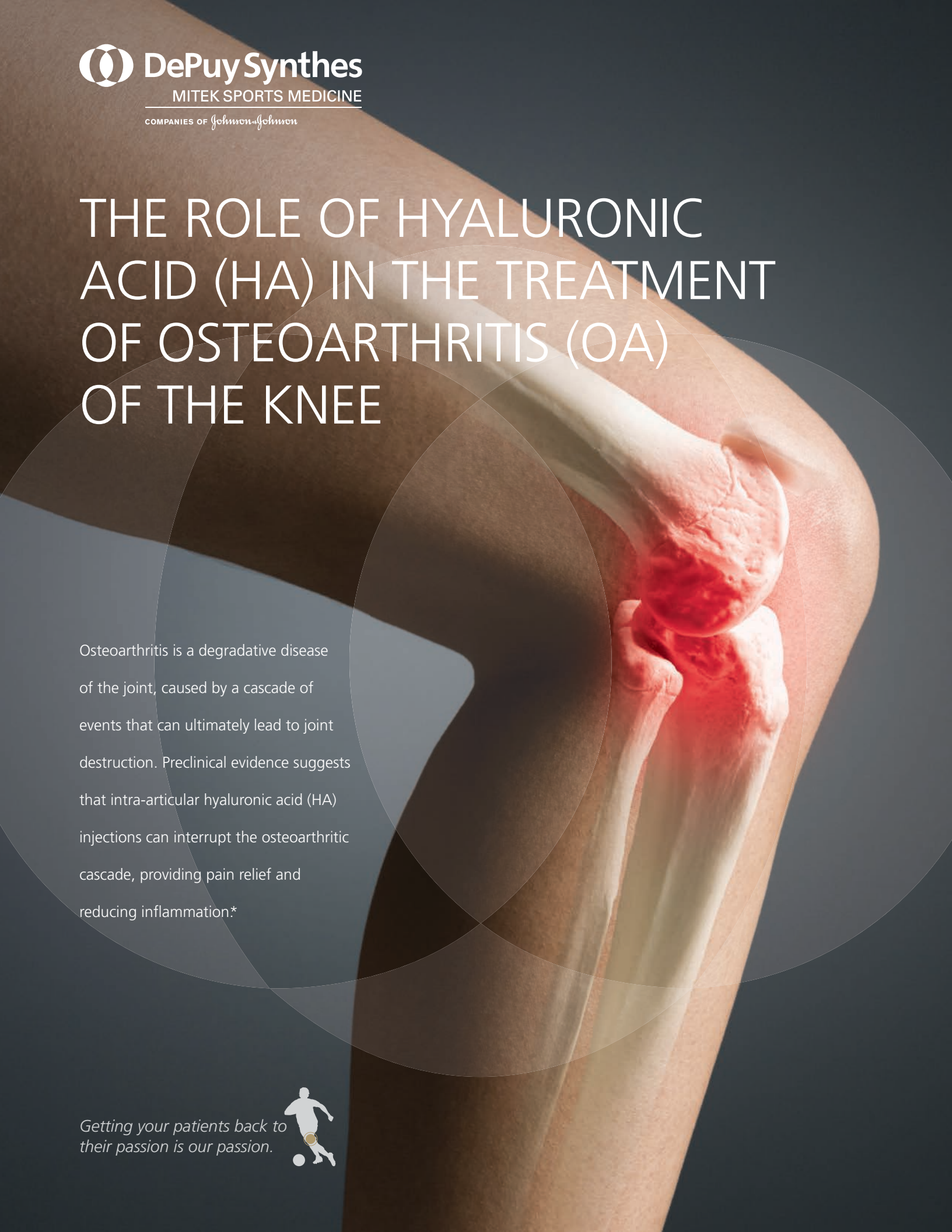
# THE ROLE OF HYALURONIC ACID (HA) IN THE TREATMENT OF OSTEOARTHRITIS (OA) OF THE KNEE



Osteoarthritis is a degradative disease of the joint, caused by a cascade of events that can ultimately lead to joint destruction. Preclinical evidence suggests that intra-articular hyaluronic acid (HA) injections can interrupt the osteoarthritic cascade, providing pain relief and reducing inflammation.*

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# HA IS CRITICAL TO HEALTHY ARTICULAR JOINTS

## HA is an important component of both cartilage and synovial fluid.

The synovium is a thin cellular membrane that lines the capsule of articulating joints.

- Synovial fluid HA is produced by synovial fibroblasts.[1]
- HA gives synovial fluid its characteristic viscoelastic and lubricating properties, which help protect cartilage from shear forces and traumatic shock.[2]
- HA in healthy joints interacts with cell surface receptors on synoviocytes and chondrocytes to maintain joint homeostasis.[1,3,4]

Hyaline cartilage, the most common form of cartilage, covers the surfaces of articulating bones in synovial joints.

- Chondrocytes produce the extracellular matrix of cartilage, which is composed of collagen, proteoglycan, and HA.
- In cartilage, HA is chemically bound to proteoglycan domains by link protein, providing structural stability to the tissue. Proteoglycan molecules ensure maximum hydration of cartilage, imparting its characteristic turgidity and resiliency.[5]

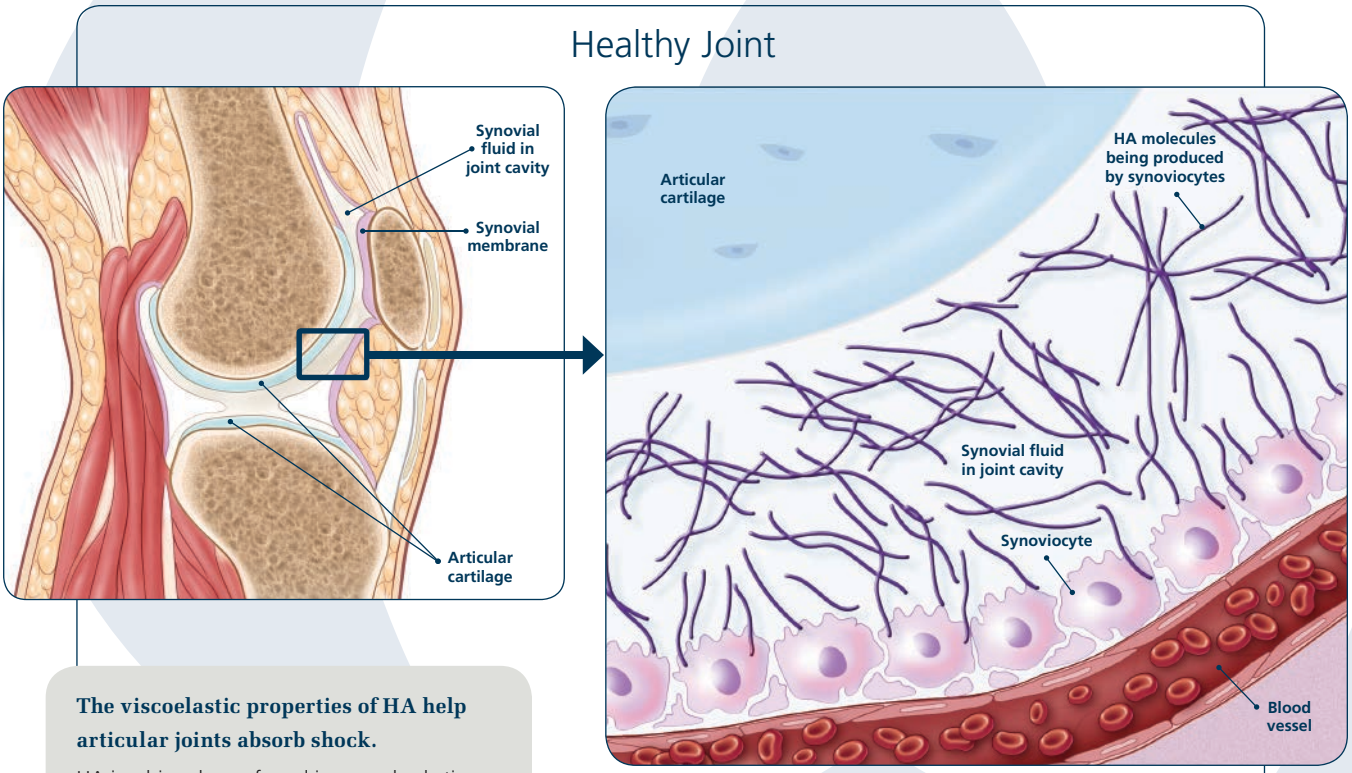


**Figure 1.**

**The viscoelastic properties of HA help articular joints absorb shock.**

HA is a biopolymer found in many body tissues. In synovial fluid, its high molecular weight imparts viscoelasticity and lubricity, helping the joint to absorb shock and contributing to the biomechanical stability of the joint.[2]

# SYNOVITIS CONTRIBUTES TO THE OSTEOARTHRITIC CASCADE AND JOINT DEGRADATION

## Inflammation of the synovium is believed to be a major source of osteoarthritic pain.

- In osteoarthritic joints, synovial inflammation can lead to swelling, effusion, and pain. Synovitis is now recognized as being a prominent component of OA, with as many as 70% of OA patients showing evidence of synovitis.[6,7]
- Osteoarthritic synoviocytes produce less HA, with a lower molecular weight compared to healthy joints. They also produce increased levels of inflammatory cytokines and degradative enzymes that can accelerate cartilage degradation.[1,8-10]

## The role of the synovium and HA in the osteoarthritic cascade.

OA results from a complex interplay of biomechanics, joint trauma, lifestyle, genetics, and overall physical health. Regardless of how it is initiated, osteoarthritis is a cascading disease[11]:

- Excess mechanical stress, traumatic injury, or other destabilizing events can initiate cartilage breakdown. Cartilage fragments are then released into the synovial fluid.
- Cartilage debris is phagocytosed by synovial macrophages. When excessive cartilage breakdown occurs, the increased presence of cartilage fragments can lead to inflammation of the synovium.
- Inflamed synovial cells produce inflammatory cytokines and degradative enzymes that accelerate joint destruction, including cartilage and subchondral bone. HA synthesis by synoviocytes is decreased, and the HA that is synthesized has a lower molecular weight, compromising its ability to interact with cell surface receptors.[1,12]
- In vitro and in vivo studies have shown that high molecular weight exogenous HA can interrupt the osteoarthritic cascade by downregulating the production of inflammatory cytokines and enzymes, restoring the production of native HA, and slowing the progression of OA. These effects have been shown to be dependent upon concentration and molecular weight.[1,13-15]

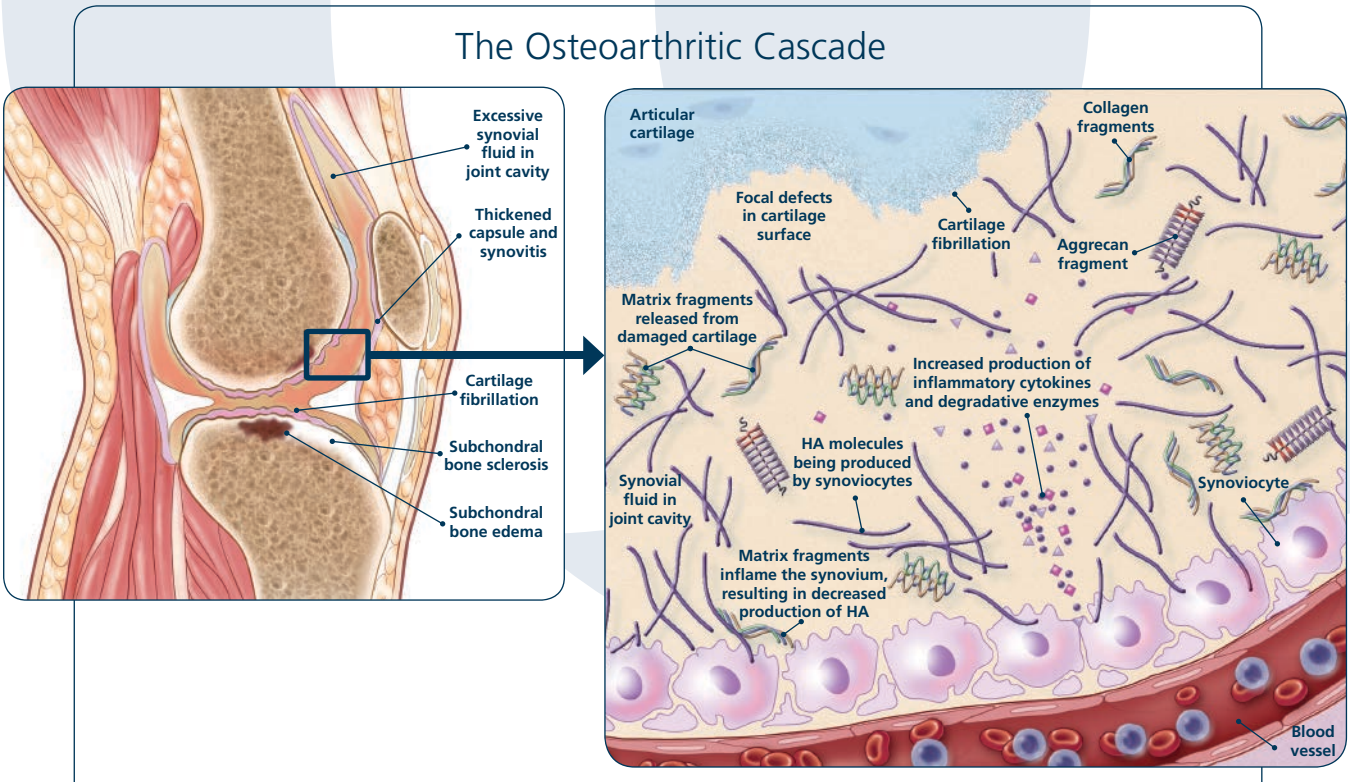


Figure 2.

# POTENTIAL THERAPEUTIC BENEFITS OF HA SUPPLEMENTATION IN THE KNEE

## Intra-articular injections of HA may stimulate native HA production and inhibit inflammatory agents that lead to pain and joint deterioration.

### Preclinical studies suggest that there is an optimal molecular weight (MW) of HA required to stimulate native HA production.[1]

- Low MW molecules of HA bind only weakly to surface receptors, resulting in little to no stimulation of native HA biosynthesis by osteoarthritic synoviocytes.
- Excessively high MW molecules of HA cannot bind strongly to synoviocyte surface receptors due to steric hindrance, inhibiting their ability to stimulate HA biosynthesis.
- Optimal MW molecules bind strongly to synoviocyte surface receptors, maximizing the stimulation of native HA biosynthesis.

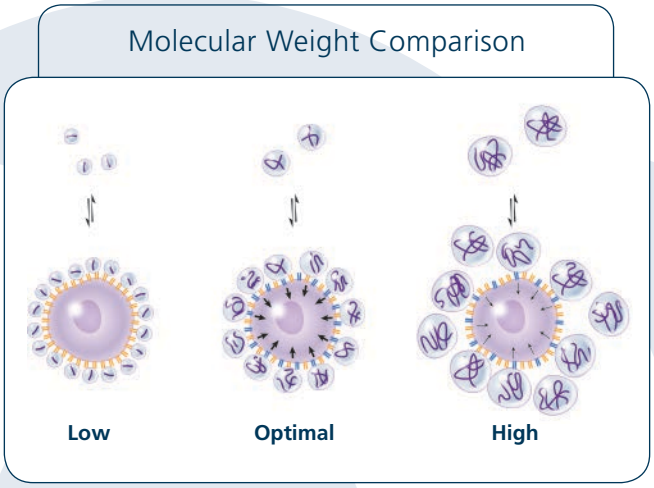


**Figure 3.**

## Intra-articular HA may help dampen the inflammatory component of the osteoarthritic cascade.

- In vitro studies have shown that HA binds to CD44 receptors on the surfaces of cells that are involved in the inflammatory process.[3,16,17]
- The analgesic effects of intra-articular HA extend beyond its residence time in the osteoarthritic joint.
- In vitro and in vivo studies have demonstrated that exogenous HA may help restore native HA production and provide chondroprotection by inhibiting the production of inflammatory cytokines and proteases that can lead to cartilage damage in osteoarthritic joints.[1,13,14,18]

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*Pain relief statements are based on preclinical data which have not been shown to quantitatively predict clinical performance.

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