

# Treatment Options for Osteoarthritis of the Knee

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## Summary

Osteoarthritis of the knee is a common, costly disorder. The etiology is multifactorial, with genetics playing a large role. Treatment should be individualized and may include nonpharmacologic, pharmacologic, and surgical treatments or surgery to improve pain. Of the pharmacologic options, glucosamine and chondroitin supplements and hyaluronans may promote cartilage growth and possibly alter the disease process. Future research will focus on combination therapy, gene therapy, and cartilage transplants.

## Key Points

- Osteoarthritis (OA) affects 20 million people in the United States.
- OA of the knee is progressive deterioration of the articular cartilage of the knee joint, which is important for optimal functioning of the knee joint.
- Significant pain results from changes in the joint. Although analgesics can help relieve the pain, they do not alter the course of the disease.
- Hyaluronans are as effective as NSAIDs for pain relief and have a longer duration of action than articular steroid injections.
- Growing evidence suggests that glucosamine, chondroitin supplements, and hyaluronans may promote cartilage growth and possibly alter the OA disease process.

OSTEOARTHRITIS IS THE MOST prevalent chronic joint disorder worldwide and is associated with significant pain and disability.<sup>1</sup> It has been estimated that OA costs approach \$150 billion annually in the U.S.<sup>2</sup> and affects 20 million people.<sup>3</sup> The disease is two times more frequent in females than males, and it affects 70 percent of the population over age 65.<sup>2</sup> This is a relentlessly progressive disease that continues to worsen with aging.

## Osteoarthritis Overview

Focusing on the knee, OA is progressive deterioration of the articular cartilage of the tibiofemoral and/or patellofemoral compartments.<sup>2</sup> The etiology of OA is thought to be multifactorial, with genetics being one of the driving forces.<sup>3</sup> Some common contributors to OA development are trauma to the articular cartilage, poor alignment of the joint, anatomy of the patella, joint instability, meniscus tear, obesity, athletic training, and smoking.<sup>3</sup> Typical symptoms of OA of the knee include

- diffuse activity-related pain
- localized pain that may radiate up or down the leg
- pain exacerbated by activity, stairs, squats, or hills
- clicking, catching, grinding, grating sounds

- mechanical symptoms
- night pain
- recurrent swelling
- post inertial dyskinesia
- pseudoinstability/pseudo locking of the joint.

Patients may experience mechanical symptoms because of loose fragments of articular cartilage. As the disease progresses, night pain develops and is uncontrollable in some cases. Disturbed sleep is often what prompts a patient to seek a knee replacement. Post-inertial dyskinesia is stiffness in the knees that occurs after a period of immobility, such as after a long flight or movie. Patients will often have episodes of their knee giving away, or instability called pseudoinstability or pseudolocking, which is a pain response.

Osteoarthritis is traditionally thought of as a noninflammatory type of arthritis, but inflammatory mechanisms can be present. Pain with OA can derive from several sources resulting from the disease process. Pain can originate from the synovial membrane, joint capsule, periarticular muscles and ligaments, and periosteum and subchondral bone, among other sources.<sup>2</sup> One source of deep pain is vascular congestion in the subchondral bone that happens late in the disease process. Another

source of pain is joint contracture secondary to fibrosis. Irritation of the synovium by osteophytes (bone spurs) that form can sometimes be a source of pain. Muscle spasms surrounding the joint can cause discomfort.

The evaluation of a patient with knee OA would include a history of symptoms and injuries, an examination of the knee, and radiographs.<sup>2,5</sup> Because articular cartilage is not visible on X-ray, OA of the knee is identified on radiographs as a narrowing of the joint space.

### Articular Cartilage

Articular cartilage covers the ends of the bones within the joint. The cartilage facilitates joint movement by providing a smooth surface, absorbs forces of impact and weight delivered to the joints, and helps maintain joint structure.<sup>2</sup>

Articular cartilage is composed of chondrocytes, matrix, and water. Articular cartilage is primarily water, as is the rest of the body. Chondrocytes make up about 1 to 5 percent of the tissue volume.<sup>2</sup> The extra cellular matrix is 70 percent type II collagen and 30 percent proteoglycans.<sup>2</sup> Under normal circumstances, articular cartilage undergoes continuous breakdown and renewal. Chondrocytes control the rate of cartilage synthesis and breakdown in part through secretion of proteolytic enzymes. Chondrocytes use amino acids, carbohydrates, and water to make glycosaminoglycans (GAGs), which are the building blocks of the matrix.<sup>2</sup> Chondrocytes release GAGs, which combine with collagen fibrils to form the matrix. The predominant GAGs in cartilage are chondroitin sulfate, keratan sulfate, and hyaluronic acid. With the exception of hyaluronic acid, all GAGs bond with a core protein to form proteoglycan monomers that provide compressive strength.<sup>2</sup> Collagen in the matrix provides tensile strength.

When considering treatment, it's especially important to consider that the articular cartilage has no blood, nerve, or lymphatic supply. Its nutrition comes either from the subchondral bone or from the synovial fluid.

With aging, the matrix experiences an increase in water, a decrease in the quality of the proteoglycans, smaller aggrecan molecules, a decrease in collagen content, and a conversion from type II to type I (scar) cartilage (see Exhibit 1).<sup>6</sup> Numerous changes occur that ultimately result in a decrease in articular cartilage strength, increased stiffness, and increased nitric oxide, an oxidating agent. Nitric oxide leads to cell death, or apoptosis of the chondrocyte. Metalloproteinases, which basically destroy articular cartilage, also increase with aging. With the onset of OA, hyaluronic acid—a component that gives the joint fluid elasticity and compression qualities—tends to be smaller and produced in smaller quantities, and works less efficiently. The aging process, unfortunately, means that synovial

fluid is less effective because of alterations in hyaluronic acid function and production. Aging also decreases the ability of chondrocytes to maintain and restore articular cartilage and, thereby, increases the risk of degeneration of the articular cartilage surface.<sup>6</sup>

### Treatment of Osteoarthritis

The two major objectives of treatment are to decrease pain and attempt to delay the progression of osteoarthritis. The management of osteoarthritic pain involves nonpharmacologic, pharmacologic, and surgical modes of therapy.

#### Nonpharmacologic Therapy

The American College of Rheumatology (ACR) guidelines recommend patient and family education, support groups, weight loss, physical therapy, exercise, and occupational therapy.<sup>4</sup>

Helping overweight patients with knee OA lose weight will improve pain and may prevent progression of the disease. Assistive devices, such as heel wedges and neoprene sleeves to correct abnormal biomechanics of the knee joint, may also be used.

#### Pharmacologic Treatment

Oral pharmacologic options for pain management include acetaminophen, nonsteroidal anti-inflammatory agents (NSAIDs), and cyclooxygenase type 2 (COX-2) inhibitors (see Exhibit 2).<sup>4</sup> Acetaminophen (Tylenol) is recommended as first line therapy for mild to moderate pain. Over the counter NSAIDs and topical analgesic creams are also options. The ACR guidelines recommend COX-2 inhibitors and prescription NSAIDs for moderate to severe pain.<sup>4</sup> Because of the adverse effects associated with these agents, many clinicians are avoiding their long-term use. Short courses are used during flare-ups.

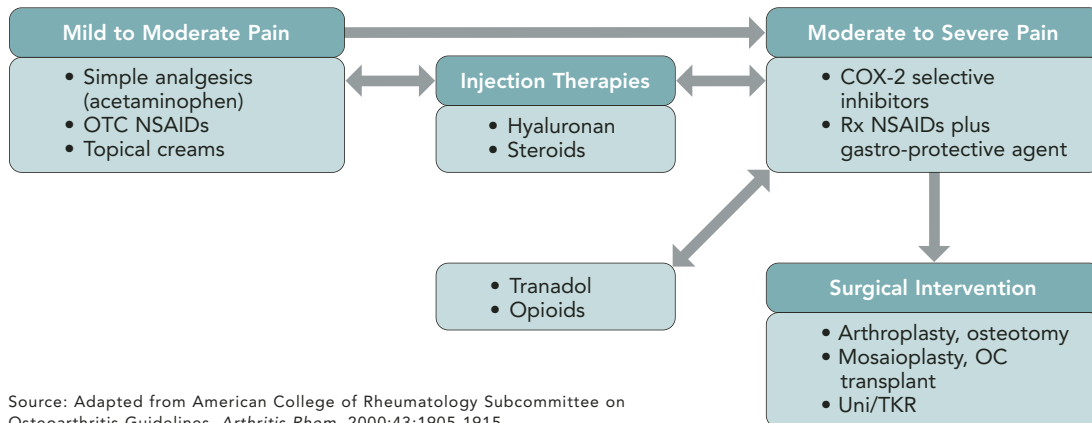
Corticosteroid injections are also used for acute flare-ups. Although the role of corticosteroid injections in OA is not well defined, many times these agents are used to decrease inflammation in a joint so that the patient can move better and be able to fully participate in and benefit from physical therapy.

#### Exhibit 1: Changes in Articular Cartilage

##### Microscopic

- Chondrocytes
  - > Increase cell activity
  - > Decrease beta-1 integrin expression
- Matrix
  - > Increase water content
  - > Decrease PG content
  - > Decrease collagen content/quality

**Exhibit 2: Medical Treatment**  
**ACR 2000 Guidelines: Pharmacologic/Surgical Therapy**



Source: Adapted from American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum.* 2000;43:1905-1915.

### Hyaluronan Injections

Because of the many significant systemic adverse effects of analgesics and the fact that they only control pain and do not alter the course of the disease, many clinicians have begun using intra-articular hyaluronan injections earlier in the course of the OA disease process. The ACR guidelines also recommend early considerations of these agents.<sup>4</sup> When initially approved, these agents were primarily used for patients who had failed other forms of therapy.

Five hyaluronan injection products are available in the U.S. (see Exhibit 3). The products differ in size of the hyaluronan and origin. Four products are extracted from rooster combs.<sup>7-8</sup> The fifth, Euflexxa®, is different in that it's bioengineered through bacteria fermentation, thereby avoiding patient exposure to proteins from an animal source.<sup>8</sup> These agents are FDA approved for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative nonpharmacologic therapy and simple analgesics (e.g., acetaminophen).<sup>7-8</sup>

Hyaluronan has many action mechanisms (see Exhibits 4 and 5).<sup>9-10</sup> There is laboratory evidence that hyaluronan injections may stimulate synovial membrane cells to make more hyaluronan and aggrecan, which, theoretically, may be reversing osteoarthritis.<sup>9</sup> Hyaluronan injections also have been shown to have disease-modifying activity.<sup>9</sup> This stems from 1) the complex biochemical effects of hyaluronans in the synovium and extracellular matrix of the articular cartilage, including interactions between exogenously administered hyaluronans and articular cartilage, subchondral bone, matrix proteoglycans, and collagens; 2) the effects of hyaluronan administration in animal models of OA, including total or partial meniscectomy and anterior cruciate ligament transection; and 3)

results of clinical trials using one product, Hyalgan (sodium hyaluronate, molecular weight 500-730 kDa) that evaluated structural outcomes, such as joint-space width, chondrocyte density and vitality, and arthroscopic evaluation of chondropathy. Growing evidence supports the notion that, in addition to relieving the symptoms of OA, hyaluronans also modify the structure of the diseased joint and the rate of OA disease progression, at least early in the evolution of the disease process.<sup>9</sup> Viscosupplementation does not appear to be very effective when used late in the disease process.

Modawal and colleagues conducted a meta analysis of 11 trials of hyaluronan injections or derivatives.<sup>10</sup> Their conclusion was that intra-articular viscosupplementation with hyaluronan injections was moderately effective in relieving knee pain in patients with osteoarthritis for up to 10 weeks after the last injection but not at 15 to 22 weeks.<sup>10</sup>

A Cochrane analysis published in 2005 found that at 5 to 13 weeks post-injection there was an 11 to 54 percent improvement in pain and a 9 to 15 percent improvement in function.<sup>11</sup> This analysis concluded that viscosupplementation is an effective treatment for OA of the knee with beneficial effects on pain, function and patient global assessment, and at different post-injection

### Exhibit 3: Hyaluronan Injections

**Products**

- Hyalgan, Supartz, Orthovisc
  - > Extracted, separated, and purified tissue
  - > Avian combs
- Synvisc
  - > High MW cross-linked HA polymers
  - > Avian combs
- Euflexxa®
  - > Bioengineered via bacterial fermentation

#### Exhibit 4: Hyaluronan Injections

##### Potential Mechanisms

- Restore elastoviscosity
- Inhibit inflammatory cell activity
- Anti-nocioceptive (PGE2, bradykinin)
- Entrap endogenous receptor endings
- Coat pain fiber receptor endings
- Stimulate hyaluronan synthesis

periods, but especially at the 5- to 13-week post-injection period. It should be noted that the magnitude of the clinical effect is different for different products, comparisons, time points, variables, and trial designs. However, there are few randomized head-to-head comparisons of different viscosupplements, and conclusions regarding the relative value of different products cannot be made.<sup>11</sup>

In general, hyaluronan injection has comparable efficacy against NSAIDs and longer-term benefits when compared against intra-articular corticosteroids.<sup>11</sup> Few significant adverse events are reported with hyaluronans.<sup>7-8</sup> The majority of adverse effects are local reactions at the injection site. There is a potential for allergic reactions with the rooster-derived products in patients with avian allergies.<sup>7</sup>

#### Pharmacoeconomics of Hyaluronans

Torrance and colleagues evaluated the cost effectiveness and cost utility of hyaluronan injections using data from a one-year double-blind trial conducted in Canada. Pharmacoeconomic analyses in U.S. dollars have not been published.<sup>12</sup> Over the year, the hyaluronan treatment group had higher costs (\$2,125 to \$1,415 = CAN\$710,  $P < 0.05$ ), more patients improved (69 percent to 40 percent = 29 percent,  $P = 0.0001$ ), and increased quality-adjusted life years (QALYs) (0.071,  $P < 0.05$ ). The incremental cost-effectiveness ratio was \$2,505/patient improved. The incremental cost-utility ratio was \$10,000/QALY gained. The authors stated that their results provide strong evidence for adoption of hyaluronan treatment in Canada in the patients and settings similar to those studied in the trial.

#### Supplements

The supplements glucosamine and chondroitin sulfate have some clinical evidence to support their use in altering the course of OA.<sup>13</sup> Both are building blocks of articular cartilage. Both also appear to have some anti-inflammatory activity. Although not all patients appear to gain benefit, many do and are able to decrease their dosage of analgesics. The adverse effects of these agents tend to be minor gastrointestinal reactions. Based on other studies that looked at joint space narrowing over time, the combination of these two supplements appears to slow the progression of joint space narrowing.

#### Exhibit 5: Hyaluronan Injections

##### Potential Mechanisms

- Chondroprotective
  - > Stimulate TIMP-1 synthesis
  - > Inhibit pmn mediated cartilage degradation
  - > Attenuate effects of IL-1, degradative enzymes, and oxygen free radicals on chondrocyte injury and matrix degradation

Whether this is the disease slowing or a rebuilding of articular cartilage is unknown at this time.

#### Surgery

Various surgical procedures are used to relieve the pain and deformities caused by OA. Examples include arthroscopy and lavage to remove cartilage fragments, chondrocyte transplantation, implantation of joint spacers, reshaping of the knee bones, and knee replacement.

#### Conclusion

Pain is a significant part of the OA disease process. Current therapy aims to reduce pain and alter the progression of the disease. Analgesics, which have many adverse effects, improve pain. Hyaluronan injections and glucosamine and chondroitin supplements appear to reduce pain and improve the disease process. **JMCM**

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