# The Conservative Treatment of Osteoarthritis of the Knee

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## abstract

Osteoarthritis has one of the highest associations for all-cause mortality in the United States. Comorbidities are common in patients with end-stage disease. In most cases, it is critical to exhaust conservative modalities of care before resorting to surgical intervention. This article discusses common conservative approaches focusing on injectable treatments that can be employed prior to total knee replacement. [*Orthopedics*. 2018; 41(5):256-260.]

The burden of osteoarthritis (OA) is reaching epidemic proportions, affecting more than 30 million individuals in the United States.[1] The number of knee replacements performed annually in the United States is expected to significantly increase during the next decade.[2] Given the close link between obesity and OA, and the high prevalence of obesity, which now affects more than one-third (36.5%) of US adults,[3] this trend will likely continue. Clinicians treating patients with knee OA face major challenges as they try to recommend the most effective conservative therapies to postpone total knee arthroplasty as long as possible. Unfortunately, despite good functional outcomes, up to 20% of patients are dissatisfied after a well-performed total knee arthroplasty; unfulfilled expectations are a principal source of dissatisfaction.[4] Due to the earlier onset of disease, an increased duration of treatment is necessary. Compared with 1990, when the average duration of treatment was 3 years, by 2010 the estimated average duration of treatment for OA of the knee had increased to 23 years. Multiple factors have led to this, including younger individuals sustaining injuries and having surgical intervention.[5-7]

In a study conducted in the United Kingdom, 25% of individuals older than 55 years reported persistent knee pain during a 1-year period.[8] Because many patients with OA of the knee have an elevated body mass index, weight loss has been shown to relieve symptoms and improve function as well as quality of life for patients with OA.[9] Additional risk factors for OA include age, female sex, diet, and anatomic variations including malalignment of the knee.[10] Furthermore, symptomatic knee OA has been reported in 10% of men and 13% of women 60 years and older.[11] The senior author (J.M.B.) typically recommends dietary changes and exercise. However, patients have reported feeling like they are in a catch-22 situation when asked to lose weight to reduce their symptoms because their pathology makes it difficult for them to exercise. Some patients may consider consulting with a bariatric surgeon, although it is difficult to obtain insurance approval for bariatric procedures to relieve the pain from knee OA. The senior author also recommends that patients address other comorbidities, such as diabetes and heart disease, to optimize OA treatment outcomes, which is critical prior to the consideration of surgical intervention.[12]

Clearly, optimizing nutrition and maintaining a near normal body mass index are

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critical for preventing OA. Weight loss has been shown to reduce the incidence of OA by up to 90% in several studies.[13,14] However, the long-term failure rate for dieting and weight loss is greater than 92%.[13] Multiple oral nutraceuticals have been recommended to improve the symptoms of OA. Glucosamine and chondroitin sulfate and nonsteroidal anti-inflammatory drugs, including cyclooxygenase-2 inhibitors, are the drugs most commonly prescribed for initial treatment. Unfortunately, there are minimal data that glucosamine and chondroitin sulfate have any long-term benefit, and nonsteroidal anti-inflammatory drugs have a high incidence of gastrointestinal complications.[13,14] Intra-articular injections are controversial, with the literature offering variable conclusions.

## Steroid Injections

Steroid injections work by inhibiting the release of prostaglandins, which are the precursors to histamine—the primary inflammatory enzyme released by mast cells and basophils. The indications for intra-articular corticosteroids are varied; however, it is commonly believed that steroid longevity ranges from 2 to 4 weeks, depending on the degree of OA and synovitis in the joint.[15] A systematic review study concluded that high–molecular-weight viscosupplementation was equivalent to intra-articular corticosteroids at 2 weeks but became more effective subsequent to the 2-week period.[16] On November 13, 2017, Zilretta (Flexion Therapeutics, Burlington, Massachusetts) was released. Zilretta is triamcinolone acetonide corticosteroid embedded in a microsphere, which results in an extended-release formulation with lower plasma concentrations. Early data indicate that patients exhibit an improvement in pain and function for up to 12 to 16 weeks after injection.[17] A recently published double-blinded, randomized, placebo-controlled multinational study of 484 patients concluded that Zilretta provided significant, clinically meaningful pain reduction compared with saline-solution placebo at the primary endpoint, week 12. A theoretical advantage of a sustained-release steroid is that due to the low plasma concentration, serum blood glucose is minimally affected.[18]

## Platelet-Rich Plasma

Thus far this year, Google site "hits" for platelet-rich plasma (PRP) have already exceeded 20 million. A systematic review of PRP in knee OA noted that although the data were inconclusive, it may be effective.[19] In a meta-analysis of PRP in knee OA, leukocyte-poor PRP had better results than leukocyte-rich PRP and hyaluronic acid, but local adverse reactions were higher with PRP.[20] In a review of 6 level 1 studies, it was concluded that PRP may have beneficial effects for patients with mild to moderate OA on Western Ontario and McMaster Universities Osteoarthritis Index and International Knee Documentation Committee scores at 6 months.[21] In some studies, PRP was not found to be more effective than high–molecular-weight viscosupplementation; however, leukocyte-rich PRP was used as the comparator in some of these studies.[22,23] Other authors have concluded in level 1, prospective, randomized studies that PRP and high–molecular-weight hyaluronic acid yield similar results and result in moderate improvement in patients' symptoms from knee OA.[24]

## Stem Cells

Mesenchymal stem cells have been isolated from bone marrow, adipose tissue, synovium, blood, and amniotic fluid. Bone marrow mesenchymal stem cells are the most extensively studied. It has been reported that adipose tissue stem cells have the most stability, are significantly pluripotential, and have increased chondrogenicity. In a review of 7 randomized controlled trials using stem cell treatment for patients with knee OA, the overall results led to the conclusion that mesenchymal stem cell injections could potentially be efficacious for decreasing pain and may improve physical function.[25] A systematic review from 1990 to 2013 of 9 animal and 7 human studies using bone marrow mesenchymal stem cells confirmed that "mesenchymal stem cells have shown potential for improving function and decreasing inflammation in animal studies with translation to patients still in question."[26] However, in a series of 37 patients with knee OA who were subjected to adipose stem cell injections, all had improved symptoms and appearance at second-look arthroscopy.[27] Mesenchymal stem cells appear to be the most helpful in younger patients with mild to moderate knee OA and chronic patellar tendinosis.[28]

## Hyaluronic Acid

Hyaluronic acid has been in use since 1997, when it was first approved for humans.[29] Endogenous hyaluronan is the major hydrodynamic component of joint synovial fluid. It is produced by type B synoviocytes and fibroblasts of the synovial membrane and has a molecular weight of $5\times10^6$ Da in a young individual.[30] There are more than 10 different products available in the United States; however, only 2 are considered high molecular weight and/or are cross-linked (**Table**).[31-33]

Cross-linking increases the residence time (amount of time the material remains in the joint) and the half-life of the compound by up to 8.8 days. With cross-linking, trace amounts of the injected hyaluronic acid can be found in the joint up to 26 weeks later. Without cross-linking, the half-life of hyaluronic acid can be as short as 3 to 20 hours and excretion of the hyaluronic acid additive will occur in the first 24 hours after.[29,31,34,35] By prolonging the residence time, there is an increase in the production of endogenous hyaluronan and increased inhibition of matrix metalloproteinases.[36] In a review of 68 randomized studies with a minimum follow-up of 26 weeks, high–molecular-weight/cross-linked compounds (>3 million Da) had greater efficacy than low–molecular-

Table

**Molecular Weight and Elasticity Comparison of Hyaluronan With Normal and Osteoarthritis Synovial Fluid**

| Synovial Fluid and Various Hyaluronic Products | Molecular Weight (Million Daltons) | Elasticity (Pascals at 2.5 Hz) |
|---|---|---|
| Healthy, young synovial fluid[32] | 6 | 117 |
| Osteoarthritic synovial fluid[31,33] | 1.9 | 1.9 |
| Synvisc-One[a] (cross-linked) | 6 | 111 |
| Gel-One[b] (cross-linked) | "Infinite" | 111 |
| Hyalgan[c] (sodium hyaluronate) | 0.5 to 0.7 | 0.6 |
| Supartz[d] (sodium hyaluronate) | 0.6 to 1.2 | 9 |
| Orthovisc[e] (high–molecular-weight hyaluronan) | 1 to 2.9 | 60 |
| Euflexxa[f] (1% sodium hyaluronate) | 2.4 to 3.6 | 92 |

[a]*Sanofi, Inc, Bridgewater, New Jersey.*
[b]*Zimmer Biomet, Warsaw, Indiana.*
[c]*Fidia Pharma USA Inc, Florham Park, New Jersey.*
[d]*Bioventus LLC, Memphis, Tennessee.*
[e]*DePuy Synthes, Warsaw, Indiana.*
[f]*Ferring Pharmaceuticals, Parsippany, New Jersey.*

weight compounds (<3 million Da) in all studies.[37]

The concentration and molecular weight of hyaluronan molecules are decreased by 33% to 50% in OA synovial fluid, and the loss of glycosaminoglycan in cartilage causes brittleness and decreases the resiliency of the matrix.[38,39] Viscosupplementation enhances chondrocyte metabolism, decreases chondrocyte apoptosis, and stimulates synthesis of endogenous hyaluronic acid, which decreases shear secondary to increased viscosity and decreased elasticity of the synovial fluid.[40] Other effects of high–molecular-weight viscosupplementation include chondrocyte death when added to bupivacaine.[41] High–molecular-weight viscosupplementation appears to be helpful for patients with Kellgren II and III OA, but its effect in Kellgren IV disease is minimal. However, in a level 1, 2-year follow-up study, it did decrease the progression of cartilage degeneration in patients with mild to moderate OA.[42] It appears to be helpful after arthroscopy of the knee for patients with grade II and grade III chondromalacia.[43]

When pharmacologic interventions were compared regarding their effectiveness for knee OA, the results of a network meta-analysis confirmed that high–molecular-weight/cross-linked viscosupplementation was the most efficacious treatment for pain but was not superior to the other interventions for function and stiffness.[44]

In 2013, the American Academy of Orthopaedic Surgeons recommended against the use of viscosupplementation based on a small series of studies using the minimum clinically important improvement criterion and minimal clinically important difference as the metric for determining efficacy. In 2014, Bannuru et al[45] outlined how this metric was used inappropriately in the clinical practice guideline review. Since the 2013 publication of the nonarthroplasty treatment of OA guidelines by the American Academy of Orthopaedic Surgeons, there have been more than 33 noncoverage decisions affecting more than 50 million patients in the United States. This has occurred despite multiple articles confirming the efficacy of high–molecular-weight/cross-linked viscosupplementation.[44,46-50] In a 2016 article on viscosupplementation for knee OA, Johal et al.[51] concluded that "a careful examination of the most recently published articles suggests that viscosupplementation is a safe option with a clinically important reduction in pain for younger patients with knee OA in those formulations with higher molecular weight or hyaluronic acid cross-linking." Furthermore, in 2 separate studies, the greater the number of high–molecular-weight hyaluronic acid injections, the greater the delay in total knee arthroplasty.[52,53] Finally, when the cost-effectiveness of viscosupplementation was compared with that of nonsteroidal anti-inflammatory drugs and analgesics, quality of life years were significantly increased with high–molecular-weight hyaluronic acid, thus representing a greater effect and a decrease in cost.[54]

## Conclusion

The conservative treatment of OA of the knee is important and should be exhausted prior to total knee replacement. Total knee replacement does not fulfill patient expectations, as more than one-third continue to report residual symptoms and only 66% feel that their knee is "normal."[33] Improvement in the microbiology of the cartilage cell has not been proven for PRP and stem cells, and they are not reimbursed by payers. However, many patients have noted improvement in symptoms subsequent to injections. Research beyond animal studies will hopefully provide answers regarding the effectiveness of these bioinjectables. Although in most series high–molecular-weight/cross-linked hyaluronic acid has been shown to be helpful, the lack of insurance coverage has resulted in a decrease in its use nationwide. Steroid injections reduce inflammation and offer temporary relief and, with the introduction of a corticosteroid that improves the residence time within the knee joint, may offer a sustained improvement in symptoms. The use of injectable treatments is important prior to surgical intervention in

patients with knee OA. A conservatively directed, logical approach should be used for each patient with knee OA prior to consideration of surgery.

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