



Hyaluronic Acid Scientific Update

Osteoarthritis (OA) is recognized as the most common cause of pain and disability among adults in the United States, with 32.5 million US adults experiencing some form of OA.¹ It primarily affects adults 45 or older; more than half of those with symptomatic knee OA are younger than 65.^{1,2} Hyaluronic acid (HA) viscosupplement injections are the standard for the treatment of early stages of symptomatic OA, providing a lubricating substance that reduces friction and absorbs shock to slow the degradation of cartilage and reduce pain, inflammation, and swelling.^{3,4}

Petrella RJ,
Petrella M

Clinical Studies

[A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intraarticular hyaluronic acid for osteoarthritis of the knee. *J Rheumatol.* 2006;33\(5\):951-956.](#)

- A randomized, placebo-controlled trial evaluating the efficacy of intra-articular HA (IA-HA) in patients with OA of the knee. The study also tested whether there was a difference in pain, functional outcomes, and patient satisfaction and quality of life in administering 3 versus 6 consecutive weekly injections.
- At 3 weeks, patients who received the HA injection showed a statistically significant improvement in WOMAC pain, stiffness, physical function, and quality of life scores. The placebo group saw inferior results compared to the HA group.
- Treatment with HA was highly satisfactory and was associated with few adverse events. No further difference was observed between groups after 3 or 6 HA injections, and the benefits were unchanged at 12 weeks.

Navarro-Sarabia F,
Coronel P,
Collantes E,
et al

[A 40-month multicentre, randomised placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. *Ann Rheum Dis.* 2011;70\(11\):1957-1962. doi:10.1136/ard.2011.152017](#)

- A randomized, double-blind study designed to compare the efficacy and safety of repeated injections of HA and its effect on disease progression over a 40-month timeframe, versus a placebo.
- Patients with knee OA were randomly assigned to receive either intra-articular injections of 2.5 ml 1% sodium hyaluronate with a mean molecular weight of 900,000 Da that was streptococcus ezoopidemicus-based or placebo injections (2.5 ml saline solution).
- At the end of the follow-up, the rate of patients responding to treatment in the HA group was 22% higher than those treated with the placebo. The number of responders steadily increased after each treatment cycle.
- All of the OARSI 2004 components (pain, function, and patient global assessment) were analyzed at the end of the study, and showed that the degree of improvement in the HA group was significantly higher than the placebo group.
- Rescue medication did not interfere with the clinical assessment of patients.
- Repeated cycles of intra-articular injections of HA not only improved knee OA symptoms during the in-between cycle period, but also demonstrated a marked carryover effect for at least 1 year after the last injections.

Concoff A,
Niazi F,
Farrokhyar F,
Alyass A,
Rosen J,
Nicholls M

[Delay to TKA and costs associated with knee osteoarthritis care using intra-articular hyaluronic acid: analysis of an administrative database.](#) Clin Med Insights Arthritis Musculoskelet Disord. 2021;14:1179544121994092. doi:10.1177/1179544121994092

- A retrospective analysis of 744,734 knee OA patients from a large claims database.
- At 1 year, the total knee arthroplasty (TKA)-free survival rate was 85.8% in patients who had HA injections compared to 74.1% for patients who did not receive HA.
- There was further reduction in TKA necessity in patients who received multiple courses of HA. Patients who received 1 course of HA therapy had a TKA hazard ratio of 0.85. That ratio decreased to 0.55 with 2 courses and to 0.43 with 3 courses, and continued to decline with each subsequent round of treatment.
- Even after patients underwent TKA, those who received HA had significantly lower OA-related health care costs compared to those who did not (\$860 per year versus \$2659 per year).
- HA injections are able to delay the need for TKA and reduce OA-related health care costs.

Kirchner M,
Marshall D

[A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee.](#) *Osteoarthritis Cartilage.* 2006;14(2):154-162. doi:10.1016/j.joca.2005.09.003

- A prospective, multicenter, randomized, double-blind trial evaluating the safety and effectiveness of a high molecular weight HA produced by biological fermentation compared to an avian-derived HA that uses crosslinking to achieve high molecular weight.
- The fermentation-derived HA group experienced a higher WOMAC score improvement from baseline, higher patient satisfaction on the patient global assessment scale, and a lower percentage of patients who required rescue medication.
- The group that received avian-derived HA reported a significantly higher incidence of post-injection effusion, proving fermentation-derived HA has a safety advantage.

Hummer CD,
Angst F,
Ngai W,
et al

[High molecular weight intraarticular hyaluronic acid for the treatment of knee osteoarthritis: a network meta-analysis.](#) *BMC Musculoskelet Disord.* 2020;21(1):702. doi:10.1186/s12891-020-03729-w

- A network meta-analysis of 14 randomized studies accounting for 2796 patients, comparing the effect of HA molecular weight on clinical outcome.
- HA products with a high molecular weight had a statistically significant reduction in pain, whereas low molecular weight products did not have a statistically significant improvement.
- WOMAC pain scores for high molecular weight HA products crossed the minimal clinically important improvement threshold, while injections with low molecular weight did not.
- High molecular weight HA injections may have superior efficacy compared to low molecular weight injections.



Malanga G,
Martins D,
Nalmachu S,
et al

Delay to TKA in patients treated with a multimodal approach using high molecular weight, biologically derived hyaluronic acid. *J Long Term Eff Med Implants*. 2021;31(3):45-50. doi:10.1615/JLongTermEffMedImplants.2021037770

- A retrospective database review of 26 727 knee OA patients.
- The purpose was to determine if a series of 3 nonavian, high molecular weight HA injections could delay the time to TKA.
- Time to TKA was compared for patients who received no HA injections, 1 series of HA injections, and multiple series of HA injections.
- Multiple courses of HA treatment delayed time to TKA by an average of 1.4 years.
- Authors concluded that multiple courses of HA injections are able to delay time to TKA.

Wang Y,
Hall S,
Hanna F,
et al

Effects of Hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: a two-year single-blind clinical trial. *BMC Musculoskelet Disord*. 2011;12:195. doi:10.1186/1471-2474-12-195

- A prospective study of 78 patients; 39 were assigned to a series of 3 HA injections every 6 months and 39 to usual care without injections.
- At 2 years, 55 subjects completed their final MRI.
- The HA group demonstrated a reduced rate of cartilage loss and a reduced cartilage defect score compared to the control group.
- HA injections may improve cartilage health and slow the degradative OA progression.

References

1. The Burden of Musculoskeletal Diseases in the United States (BMUS). *United States Bone and Joint Initiative*. Accessed December 30, 2021. <https://www.boneandjointburden.org/fourth-edition/iiia10/prevalence-aorc>
2. Arthritis by the Numbers. Arthritis Foundation. Accessed December 30, 2021. <https://www.arthritis.org/getmedia/e1256607-fa87-4593-aa8a-8db4f291072a/2019-abtn-final-march-2019.pdf>.
3. Wang Y, Hall S, Hanna F, et al. Effects of Hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: a two-year single-blind clinical trial. *BMC Musculoskelet Disord*. 2011;12:195. doi:10.1186/1471-2474-12-195
4. Altman R, Hackel J, Niazi F, Shaw P, Nicholls M. Efficacy and safety of repeated courses of hyaluronic acid injections for knee osteoarthritis: A systematic review. *Semin Arthritis Rheum*. 2018;48(2):168-175. doi:10.1016/j.semarthrit.2018.01.009