

Time to Stop Glucosamine and Chondroitin for Knee OA?

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PRACTICE CHANGER

Tell patients with moderately severe osteoarthritis to stop taking their glucosamine and chondroitin, as it is less effective than placebo.

STRENGTH OF RECOMMENDATION

B: Based on a single, good-quality randomized controlled trial (RCT).¹

A 65-year-old man with moderately severe osteoarthritis (OA) of the knee presents to your office for his annual exam. During the medication review, the patient mentions he is using glucosamine and chondroitin for his knee pain, which was recommended by a family member. Should you tell the patient to continue taking the medication?

Knee OA is a common condition in the United States, affecting an estimated 12% of adults ages 60 and older and 16% of those ages 70 and older.² The primary goals of OA therapy are to minimize pain and improve function. The American Academy of Orthopedic Surgeons (AAOS) and the American College of Rheumatology (ACR) agree that firstline treatment recommendations include aerobic exercise, resistance training, and weight loss.

Initial pharmacologic therapies include full-strength acetaminophen or oral/topical NSAIDs; the latter are also used if pain is unresponsive to acetaminophen.^{3,4} If initial therapy is inadequate to control pain, tramadol, other opioids, duloxetine, or intra-articular injections with corticosteroids or hyaluronate are alternatives.^{3,4} Total knee replacement may be indicated in moderate or severe knee OA with radiographic evidence.⁵ Vitamin D, lateral wedge insoles, and antioxidants are not currently recommended.⁶



Prior studies evaluating glucosamine and/or chondroitin have provided conflicting results regarding evidence on pain reduction, function, and quality of life. Therefore, guidelines on OA management do not recommend their use (AAOS, strong; ACR, conditional).^{3,4} However, consumption remains high, with 6.5 million US adults reporting use of glucosamine and/or chondroitin in the prior 30 days.⁷

A 2015 systematic review of 43 randomized trials evaluating oral chondroitin sulfate for OA of varying severity suggested there may be a significant decrease in short-term and long-term pain with doses \geq 800 mg/d compared with placebo (level of evidence, low; risk for bias, high).⁸ However, no significant difference was noted in short- or long-term function, and the trials were highly heterogeneous.

Studies included in the 2015 systematic review found that glucosamine plus chondroitin did not have a significant effect on

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short- or long-term pain or physical function compared with placebo. Although glucosamine plus chondroitin led to significantly decreased pain compared with other medication, sensitivity analyses conducted for larger studies ($N > 200$) with adequate methods of blinding and allocation concealment found no difference in pain.⁸ There was no statistically significant difference in adverse events for glucosamine plus chondroitin vs placebo, based on data from three studies included in the review.⁸

This RCT from Roman-Blas et al evaluated chondroitin and glucosamine vs placebo in patients with more severe OA. The study was supported by Tedec-Meiji Farma (Madrid), maker of the combination of chondroitin plus glucosamine used in the study.¹

STUDY SUMMARY

Chondroitin + glucosamine not better than placebo

This multicenter, randomized, double-blind, placebo-controlled trial was conducted in nine rheumatology referral centers and one orthopedic center in Spain. The trial evaluated the efficacy of chondroitin sulfate (1,200 mg) plus glucosamine sulfate (1,500 mg) (CS/GS) compared with placebo in 164 patients with Grade 2 or 3 knee OA and moderate-to-severe knee pain. OA grade was ascertained using the Kellgren-Lawrence scale, corresponding to osteophytes and either possible (Grade 2) or definite (Grade 3) joint space narrowing. Knee pain severity was defined by a self-reported global pain score of 40 to 80 mm on a 100-mm visual analog scale (VAS).

No significant difference was noted in group characteristics; average age in the CS/GS group was 67 and in the placebo group, 65. Exclusion criteria included BMI ≥ 35 , concurrent arthritic conditions, and any coexisting chronic disease that would prevent successful completion of the trial.¹

The primary endpoint was mean reduction in global pain score on a 0- to 100-mm VAS at six months. Secondary outcomes included mean reduction in total and subscale scores in pain and function on the Western

Ontario and McMaster Universities Osteoarthritis (WOMAC) index (0–100-mm VAS for each) and the use of rescue medication.

Baseline global pain scores were 62 mm in both groups. Acetaminophen, up to 3 g/d, was the only allowed rescue medication. Clinic visits occurred at 4, 12, and 24 weeks. A statistically significant difference between groups was defined as $P < .03$.¹

Results. In the intention-to-treat analysis at six months, patients in the placebo group had a greater reduction in pain than the CS/GC group (-20 mm vs -12 mm; $P = .029$). No other difference was noted between the placebo and CS/GS groups in the total or subscales of the WOMAC index, and no difference was noted in use of acetaminophen. More patients in the placebo group had at least a 50% improvement in pain or function compared with the CS/GS group (47.4% vs 27.5%; $P = .01$).

In the CS/GS group, 31% did not complete the six-month treatment period, compared with 18% in the placebo group. More patients dropped out because of adverse effects (diarrhea, upper abdominal pain, and constipation) in the CS/GS group than the placebo group (33 vs 19; $P = .018$).¹

WHAT'S NEW

Pharma-sponsored study finds treatment ineffective

The effectiveness of CS/GS for the treatment of knee OA has been in question for years, but this RCT is the first trial sponsored by a pharmaceutical company to evaluate CS/GS efficacy. This trial found evidence of a lack of efficacy. In patients with more severe OA of the knee, placebo was more effective than CS/GS, and CS/GS had significantly more adverse events. Therefore, it may be time to advise patients to stop taking their CS/GS supplement.

CAVEATS

Cannot generalize findings

The study compared only one medication dosing regimen using a combination of CS and GS. Whether either agent alone, or different dosing, would lead to the same outcome is unknown.

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CHALLENGES TO IMPLEMENTATION

All-too-common product

CS/GC is available OTC and advertised directly to consumers. With this medication so readily available, identifying patients who are taking the supplement and encouraging discontinuation can be a challenge. **CR**

REFERENCES

1. Roman-Blas JA, Castañeda S, Sánchez-Pernaute O, et al. Combined treatment with chondroitin sulfate and glucosamine sulfate shows no superiority over placebo for reduction of joint pain and functional impairment in patients with knee osteoarthritis: a six-month multicenter, randomized, double-blind, placebo-controlled clinical trial. *Arthritis Rheumatol*. 2017;69:77-85.
2. Dillon CF, Rasch EK, Gu Q, et al. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991-94. *J Rheumatol*. 2006;33:2271-2279.
3. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of non-pharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012;64:465-474.
4. Brown GA. AAOS clinical practice guideline: treatment of osteoarthritis of the knee: evidence-based guideline, 2nd ed.

J Am Acad Orthop Surg. 2013;21:577-579.

5. Jordan KM, Arden NK, Doherty M, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis*. 2003;62:1145-1155.
6. Ebell MH. Osteoarthritis: rapid evidence review. *Am Fam Physician*. 2018;97:523-526.
7. Clarke TC, Black LI, Stussman BJ, et al. Trends in the use of complementary health approaches among adults: United States, 2002-2012. *Natl Health Stat Rep*. 2015;(79):1-16.
8. Singh JA, Noorbaloochi S, MacDonald R, et al. Chondroitin for osteoarthritis. *Cochrane Database Syst Rev*. 2015;(1):CD005614.

ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center For Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

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