James J. Stevermer, MD, MSPH; Nina V. Rogers, MD
Department of Family and Community Medicine, University of Missouri–Columbia (Dr. Stevermer); Department of Family Medicine, University of Chicago (Dr. Rogers)

PURLs EDITOR
John Hickner, MD, MSc
Cleveland Clinic

Arthritis pain? These supplements provide little relief

Taken alone or together, these 2 supplements don't relieve the pain of hip or knee osteoarthritis.

PRACTICE CHANGER

Tell patients with large joint arthritis that glucosamine and chondroitin have been found to be little better than placebo.[1]

Wandel S, Juni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ*.2010;314:c4675.

STRENGTH OF RECOMMENDATION
A: Based on a good-quality meta-analysis.

ILLUSTRATIVE CASE

A 64-year-old woman with osteoarthritis (OA) of both knees reports that acetaminophen does not relieve the pain, and both ibuprofen and naproxen give her an upset stomach. She wonders if glucosamine and chondroitin would help relieve the pain. How should you respond?

Degenerative joint disease is a common and frustrating problem for patients and clinicians. Symptomatic knee OA has a prevalence of 16% among adults older than 45 years, and is one of the top 5 reasons for disability in noninstitutionalized adults.[2] With no highly effective treatment for OA of the hip or knee other than joint replacement surgery, patients often turn to unproven over-the-counter remedies. Individuals with OA spend about $2600 per year out-of-pocket on disease-related expenses.[2]

Trials of these supplements have had mixed results

Glucosamine and chondroitin have been touted as beneficial, and sales have grown rapidly over the last decade, reaching nearly $900 million in the United States in 2008 alone.[3] There have been many randomized trials of these supplements, with inconsistent results.

Larger and higher quality studies have found little or no effect, while smaller studies reported that glucosamine and chondroitin helped to relieve joint pain. A meta-analysis published in 2000 found 15 studies and reported moderate to large effect sizes, but the authors noted that quality issues and publication bias probably exaggerated the benefit.[4] An updated Cochrane meta-analysis of 25 randomized controlled trials (RCTs), published in 2009, found little benefit from glucosamine. A subgroup analysis found that one company's preparation appeared to be beneficial, but all 14 studies of that particular formulation had some connection with the manufacturer.[5]

STUDY SUMMARY

Effects of glucosamine and chondroitin, alone or together, were small

The meta-analysis we review in this PURL only included RCTs with an average of ≥100 patients with hip or knee OA in each group.[1] This was based on the minimum sample size needed to detect a small or moderate difference between the 2 groups (roughly 1 cm on a 10-cm visual analogue scale [VAS]). The authors found 10 eligible RCTs with a total of 3803 patients; the average age of participants ranged from 58 to 66 years. Most of the trials studied knee arthritis, and most were sponsored by pharmaceutical firms.

Included studies had to compare glucosamine sulphate, glucosamine hydrochloride, chondroitin sulphate, or a combination, either with a placebo or head-to-head. Minimum daily doses were 800 mg chondroitin and 1500 mg glucosamine. The primary outcome was absolute pain intensity over the duration of the study. The authors summarized pain scores every 3 months for up to 2 years; they also analyzed changes in joint space narrowing in the studies reporting that measure.

The authors used a sophisticated framework that adjusted for comparisons over time and between studies, allowing them to increase the power, and likely the accuracy, of their comparisons. They reported outcomes as effect sizes, then translated the findings to a real-world outcome by converting results to a 10-cm VAS. Typically, an effect size of 0.2 standard deviation (SD) units is considered small, 0.5 SD units is a moderate difference, and 0.8 SD units is large. The authors set their threshold for a clinically important difference at 0.37 SD units, which translated to a 0.9 cm change on a 10-cm VAS—a generally accepted minimal clinically significant difference in pain.

They found that all 3 interventions (glucosamine alone, chondroitin alone, and a combination) were statistically better than placebo, with very little difference in outcomes over time. Compared with placebo, VAS improvements were 0.4 cm for glucosamine (95% confidence interval [CI], 0.1-0.7), 0.3 cm for chondroitin (95% CI, 0-0.7) and 0.5 cm for the combination (95% CI, 0-0.9). All of these improvements in pain were less than the authors' defined minimum clinically significant improvement of 0.9 cm on a 10-cm scale.

Among the 6 trials that reported on joint space narrowing, the changes were minute and not statistically significant. There was a net difference between treatment and placebo groups of less than 0.2 mm (an effect size ≤0.16 SD units). There was no evidence of increased risk of adverse effects or increased dropout rates with any of the substances.

WHAT'S NEW

Study results leave little room for doubt

This meta-analysis used more sophisticated comparison techniques and used only larger (and probably better quality) studies than previous meta-analyses. However, inclusion and exclusion were not based on any study quality criteria.

The authors found that glucosamine and chondroitin, used alone or in combination, provide little benefit in terms of pain relief of OA of the knee or hip compared with placebo, and contend that we should recommend against patients buying them. This meta-analysis is consistent with the American Academy of Orthopedic Surgeons 2008 guideline for knee OA, which recommends not using glucosamine and/or chondroitin based on good evidence.[6]

CAVEATS

Rate of joint replacement was not considered

This meta-analysis did not study the effect of these supplements on joint replacement. In a 5-year follow-up study after completion of 2 of the RCTs included in this meta-analysis, the relative risk of total joint replacement was 0.43 (95% CI, 0.2-0.92) for those in the glucosamine group (who had taken 1500 mg glucosamine sulphate for 12-36 months) compared with placebo (NNT=12).[7] However, the authors were only able to follow up with 81% of the original participants. In the meta-analysis reported here, the difference in joint space narrowing was unlikely to be clinically significant or to lead to a difference in joint replacement rates.

Among the studies included in the meta-analysis, commercially funded trials had a greater decrease in pain with glucosamine or chondroitin compared with independent trials. This did not change the overall outcome of the meta-analysis, thereby supporting the validity of the results.

CHALLENGES TO IMPLEMENTATION

These supplements are available OTC

There are few barriers to advising patients not to use these products. Since glucosamine and chondroitin are available over-the-counter, however, patients have ready access to them, even if their doctors don't recommend them. Several meta-analyses have not found

Five years after completion of 2 of the RCTs included in the meta-analysis, the relative risk of total joint replacement was 0.43 for those in the glucosamine group compared with placebo.

an increased risk of harm from these products (other than the expense).[1,5] JFP

ACKNOWLEDGEMENT

The PURLs Surveillance System is 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.

References

1. Wandel S, Juni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ*. 2010;341:c4675.
2. Centers for Disease Control and Prevention (CDC). Arthritis. Last updated June 25, 2010. Available at: http://www.cdc.gov/arthritis/basics/osteoarthritis.htm. Accessed June 5, 2011.
3. Heller L. US glucosamine grows slow, lags global sales. Last updated March 2, 2009. Available at: http://www.nutraingredients-usa.com/Consumer-Trends/US-glucosamine-grows-slow-lags-global-sales. Accessed May 7, 2011.
4. McAlindon TE, LaValley MP, Gulin JP, et al. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA*. 2000;283:1469-1475.
5. Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2009;(2):CD002946.
6. National Guideline Clearinghouse (NGC). Guideline summary: American Academy of Orthopaedic Surgeons treatment of osteoarthritis of the knee (non-arthroplasty). Rockville, MD: Agency for Healthcare Research and Quality, 2008. Last updated December 6, 2008. Available at: http://www.guidelines.gov/content.aspx?id=14279. Accessed May 16, 2011.
7. Bruyere O, Pavelka K, Rovati LC, et al. Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. *Osteo Cartilage*. 2008;16:254-260.