Glucosamine and chondroitin sulfate did not improve pain in osteoarthritis of the knee

Clegg DO, Reda DJ, Harris CL, et al. **Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis.** N Engl J Med. 2006;354:795-808.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Phys Med & Rehab ★★★★★★★ Rheumatology ★★★★★★☆

QUESTION

In patients with osteoarthritis of the knee, are glucosamine, chondroitin sulfate, or both more effective than placebo for relief of pain?

METHODS

Design: Randomized placebo-controlled trial (Glucosamine/chondroitin Arthritis Intervention Trial [GAIT]).

Allocation: Unclear allocation concealment.*

Blinding: Blinded (clinicians and patients).*

Follow-up period: 6 months.

Setting: 16 clinical centers in the United States.

Patients: 1583 patients ≥ 40 years of age (mean age 59 y, 54% women) who had knee pain for ≥ 6 months and on most days of the preceding month; radiographic evidence of osteoarthritis (tibiofemoral osteophytes ≥ 1 mm [Kellgren and Lawrence grade 2 or 3]); a score of 125 to 400 on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC); and American Rheumatism Association functional class I, II, or III. Exclusion criteria were concurrent medical or arthritic conditions that could confound evaluation of the index joint, predominant patellofemoral disease, previous trauma or surgery to the index knee, or coexisting disease that could preclude successful completion of the trial.

Intervention: Glucosamine hydrochloride, 1500 mg/d (n = 317); sodium chondroitin sulfate, 1200 mg/d (n = 318); both glucosamine plus chondroitin sulfate (n = 317); celecoxib, 200 mg/d (n = 318); or placebo (n = 313) for 24 weeks.

Outcomes: 20% decrease in WOMAC pain score. Secondary outcomes included WOMAC stiffness and function scores, Outcome Measures in Rheumatology Clinical Trials–Osteoarthritis Research Society International (OMERACT–OARSI) response, Health Assessment Questionnaire (HAQ) pain and alternative disability scores, patient's and physician's global assessment of disease status, and adverse events. The study had 85% power to detect ≥ 1 clinically meaningful difference between groups.

Patient follow-up: 79.5% (intention-to-treat analysis).

MAIN RESULTS

Patients who received glucosamine, chondroitin sulfate, or both did not differ from the placebo group for 20% decrease in WOMAC pain score (Table). The glucosamine-plus-chondroitin group had an improvement in OMERACT–OARSI compared with the placebo group (Table). The rate of response to the celecoxib control group was 10% higher than that for the placebo control group (P = 0.008). Groups did not differ for any other outcomes. Adverse events were mild and infrequent and did not differ between groups.

CONCLUSION

In patients with osteoarthritis of the knee, glucosamine, chondroitin sulfate, or both did not differ from placebo for pain relief.

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*See Glossary.

Glucosamine, chondroitin sulfate, or both vs placebo for osteoarthritis of the knee†

Outcomes at 6 mo	Comparison with placebo	Event rates	RBI (95% CI)	NNT (CI)
20% decrease in WOMAC pain score	Glucosamine	64% vs 60%	6.6% (–5.7 to 21)	Not significant
	Chondroitin	65% vs 60%	8.9% (–3.5 to 23)	Not significant
	Glucosamine + chondroitin	67% vs 60%	11% (–1.6 to 25)	Not significant
OMERACT–OARSI response	Glucosamine	61% vs 57%	6.5% (–6.6 to 22)	Not significant
	Chondroitin	64% vs 57%	12% (–1.6 to 27)	Not significant
	Glucosamine + chondroitin	66% vs 57%	15% (1.9 to 31)	12 (7 to 89)

†WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index (score range 0 to 500); OMERACT–OARSI = Outcome Measures in Rheumatology Clinical Trials–Osteoarthritis Research Society International. Other abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

Glucosamine and chondroitin sulfate are popular nutritional supplements that are thought to relieve pain and slow the progression of osteoarthritis. Despite enthusiasm for these treatments among consumers and physicians, evidence supporting their efficacy has recently been called into question. Earlier studies showing benefits for these substances have not been replicated, and a meta-analysis has suggested that previous impressions of efficacy were caused partially by study design flaws, small sample sizes, and publication bias (1). Nonetheless, another systematic review has concluded that the benefit is real (2).

The GAIT trial by Clegg and colleagues was well designed to provide a more definitive conclusion. The response to placebo was a surprisingly high 60%, which could have diluted a true treatment effect; and after 24 weeks of treatment, there was no statistically significant difference between groups for the primary endpoint. Supporters of this regimen may suggest that a benefit (albeit a small one) did exist when a different pain scale was used and that there may have been more substantial benefit among patients with severe symptoms. We are also awaiting the results of an upcoming report from the same cohort that will attempt to confirm previous work suggesting that the treatment slows disease progression.

For now, we have learned that the positive effects of treatment are unlikely to be clinically important for most patients and that the study population had a substantial placebo effect. Most physicians will conclude that it would make more sense to tell their patients to take 2 aspirin and call them in the morning.

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References

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2. **Richy F, Bruyere O, Ethgen O, et al.** Arch Intern Med. 2003;163:1514-22.