

Long-term Effects of Glucosamine in Osteoarthritis

Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001;357:251-6.

Study Overview

Objective. To assess long-term effects of glucosamine sulphate on anatomic and symptomatic outcomes in patients with mild to moderate osteoarthritis (OA).

Design. Randomized, placebo-controlled, double-blind clinical trial. Analysis was by study completion and intention to treat. Three methods were used to evaluate data for patients who did not complete all assessments: last measure forward, random data, and worst-case scenario (average data from the placebo group).

Setting and participants. 355 patients recruited from a single research clinic in Belgium were screened to yield 212 study subjects. Most excluded patients (74%) did not meet enrollment criteria. To be included, patients had to be older than 50 years and have primary knee OA of the medial femorotibial compartment, as diagnosed by American College of Rheumatology criteria. Patients were excluded who had a history of or currently suffered from other rheumatic diseases that could cause secondary OA; severe articular inflammation, as confirmed by physical examination, erythrocyte sedimentation rate of 40 mm/hr or more, or rheumatoid factor titer of more than 1:40; traumatic knee lesions; body mass index (BMI) of more than 30; substantial abnormalities in hematologic, hepatic, renal, or metabolic functions (not defined in article); or received intra-articular or systemic corticosteroids in the 3 months prior to enrollment.

Intervention. Subjects were randomized to receive either 1500 mg of glucosamine sulphate or identical-appearing placebo once daily for 3 years. For rescue analgesia, patients were given access to paracetamol 500 mg tablets or to one of the following medications: diclofenac 50 mg tablets, piroxicam 20 mg capsules, or proglumetacin 150 mg tablets. No other OA interventions were allowed during the study period.

Main outcome measures. The primary anatomic outcome was mean joint-space width of the medial compartment of the tibiofemoral joint. Radiographs, obtained at baseline, 1, and 3 years using a standardized technique, were digitized and automatically analyzed by a validated system [1]. The primary clinical endpoint was 3-year percent change in

total score on the Western Ontario and McMaster Universities (WOMAC) OA index [2].

Main results. Of the study cohort, 77% were women with a mean age of 66 years and BMI of 27.4 kg/m². Subjects suffered from OA for a mean 7.8 years, and half used some type of analgesic in the 6 months preceding enrollment. About one third of patients from both groups withdrew from the study for similar reasons (about half because of adverse events, the rates of which did not differ between groups). Glucosamine patients showed no significant change in mean joint-space narrowing, while placebo patients experienced significant interval narrowing (analysis of 3-year completers, 0.07 mm [95% confidence interval (CI), -0.17 to 0.32] versus -0.31 mm [95% CI, -0.57 to -0.04], respectively, $P = 0.038$; intention-to-treat analysis [worst-case scenario], -0.06 mm [95% CI, -0.22 to 0.09] versus -0.31 mm [95% CI, -0.48 to -0.13], $P = 0.043$). Percent change in WOMAC scores after 3 years yielded similar results (analysis of 3 year completers, -24.3% [95% CI, -37.0 to -11.6] in glucosamine patients versus 9.8% [95% CI, -14.6 to 34.3] in placebo patients, $P = 0.016$; intention-to-treat analysis [worst-case scenario], -11.7% [95% CI, -20.3 to -3.2] versus 9.8% [95% CI, -6.2 to 25.8], $P = 0.020$). (Lower scores reflect less symptomatology.) Two of the 3 subscales (pain and physical function) accounted for improvements observed in glucosamine patients; no improvement was noted in the stiffness subscale. In addition, no participants suffered serious adverse effects.

Conclusion

Glucosamine appears to confer a modest long-term benefit in patients with mild to moderate OA.

Commentary

Reginster and colleagues designed an excellent study that provides strong evidence supporting the benefits of glucosamine sulfate. Both the authors and an editorialist [3] discuss the methodologic difficulties in achieving reliable radiographic outcomes. Nonetheless, the significant improvement in symptom scores compared with baseline and placebo is impressive and quite arguably more important. The only major criticism that might be made is in the reporting of symptomatic outcome measures. A more helpful approach would have been to set a priori criteria for clinically significant

improvement and report the proportion of patients in each group who met these criteria at the end of the study. Without this information, assessing the intervention's clinical significance remains difficult, and it is difficult to advise patients on whether glucosamine therapy will benefit them.

Applications for Clinical Practice

With this evidence and a good safety profile, it is reasonable to recommend glucosamine to patients with OA. A few caveats should be considered, however. The study agent, prepared by a pharmaceutical company, presumptively had a validated purity and content. In the U.S., glucosamine is sold as a dietary supplement, and the quality of various products available is harder to ascertain. Second, study patients generally did not have severe OA, as indicated by their WOMAC scores and by the numbers of patients who took little analgesic medication prior to the study. While there may not be evidence suggesting that glucosamine is detrimental to patients with severe OA, more research is

needed to determine the agent's effects in this patient group. Finally, many allopaths will want to see a reduction in joint replacements before they are convinced of glucosamine's usefulness. This will require a study with many more patients followed for more than 3 years. While such research would be helpful, I do not think clinicians need to wait to recommend glucosamine to patients with OA.

References

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3. McAlindon T. Glucosamine for osteoarthritis: dawn of a new era? *Lancet* 2001;357:247-8.

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