ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Is glucosamine an effective treatment for osteoarthritic pain?

MICHELE HOOPER, MD
Division of the Rheumatic Diseases,
University Hospitals of Cleveland

A: GLUCOSAMINE shows promise as a treatment for osteoarthritic pain on the basis of three lines of evidence: a basic science rationale, veterinary data, and published human trials. Although results from the human trials have been especially encouraging, these studies have serious methodologic flaws. As a result, much of the data are inconclusive. A large study sponsored by the National Institutes of Health (NIH) is underway. Until the results of that study are published (projected for 2003), it would be prudent to tell patients that there is some evidence that glucosamine helps with pain, but there is insufficient evidence to support the claim of disease modification.

A definitive, NIH-sponsored study is underway

WHAT IS GLUCOSAMINE?

Glucosamine is an intermediate substrate in the synthesis of the ground substance (noncollagen portion) of cartilage. It is found in almost all human tissues but is highest in concentration in the liver, kidney, and cartilage. Studies suggest that it helps relieve pain by enhancing proteoglycan synthesis, which is impaired in osteoarthritic cartilage.

WHAT THE HUMAN CLINICAL TRIALS SHOW

McAlindon meta-analysis

McAlindon et al[1] published an excellent meta-analysis of 15 human clinical trials of glucosamine, chondroitin sulfate (another component of human cartilage) or both. These studies were randomized, controlled, double-blind trials that lasted for at least 4 weeks and were reported in the literature through 1998.

Four of the 15 studies used oral glucosamine as a treatment for osteoarthritis. The number of patients in these studies ranged from 20 to 329. Patients received 500 mg three times a day, and the length of treatment ranged from 4 to 12 weeks.

Three of the trials showed that glucosamine was superior to placebo. The fourth study showed a benefit only in the secondary outcomes.

However, three of the four studies failed to describe their randomization procedures. In three of the studies, at least one of the authors was affiliated with the glucosamine manufacturer, and in one of those studies, patients were included in the study who had minimal (grade I) joint changes that were not definitively osteoarthritis.

More recent human trials

Several clinical trials on glucosamine have been published more recently, but they also have methodological flaws that limit their usefulness.

Reginster et al[2] reported the results of a 3-year randomized placebo-controlled trial in 212 patients with osteoarthritis of the knee. Patients who took glucosamine (1,500 mg/day) experienced greater pain relief than those who took placebo, and the difference was statistically significant. In addition, the joints in the patients who took glucosamine narrowed by a mean of 0.06 mm compared with 0.31 mm in the placebo group.

Unfortunately, standard weight-bearing knee radiographs were used in this study, which are now considered unreliable for sequentially quantifying joint space narrowing. Nevertheless, the possibility of disease modification is of great interest, especially since no other compound that is currently available for the treatment of osteoarthritis seems to offer this advantage. Further study is warranted.

Das and Hammad[3] conducted a randomized, placebo-controlled, 6-month study of 93 patients with knee osteoarthritis. Patients

were treated with a combination of 2,000 mg of glucosamine and 1,600 mg of chondroitin sulfate per day.

According to the primary outcome measure, the Lequesne Index, the 72 patients with grade II and III osteoarthritis experienced a significant improvement in pain. But when the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index Pain Subscale survey (the usual outcome measure for knee osteoarthritis studies in the United States and an FDA-required tool) was applied, no benefit was evident. At best, this study can be said to show a modest improvement in patients who took glucosamine.

Müller-Fassbender et al[4] compared treatment with 1,500 mg of glucosamine per day vs 1,200 mg of ibuprofen a day. The results showed that the patients benefited equally. However, this study used hospitalized patients. Thus, the results may not be generalizable to outpatient populations.

A study sponsored by the NIH may provide more definitive data. In this study, 1,600 patients with osteoarthritis will be assigned to one of five treatment groups: 1) glucosamine; 2) chondroitin sulfate; 3) glucosamine and chondroitin sulfate; 4) celecoxib; and 5) placebo.

Pain control and efficacy will be evaluated during a 24-week period, and the progression of joint space narrowing will be measured during a 2-year period. In addition, this study will have the necessary statistical power to provide definitive answers to the questions of efficacy and disease modification.

Unlike the study by Reginster et al, the NIH-sponsored trial will use the more precise MTP flexed-knee (Buckland-Wright) radiographs. The MTP flexed knee radiographic view opens the tibio-femoral compartment maximally and has been demonstrated to be superior to other knee views in terms of diagnosis and prospective evaluation of the joint space.[5] The flexed MTP view should be adopted for all routine knee radiograph procedures.

WHAT TO TELL YOUR PATIENTS ABOUT GLUCOSAMINE

Glucosamine is less toxic than nonsteroidal anti-inflammatory drugs. However, it can worsen insulin resistance, so it should therefore be used cautiously by patients who have diabetes.

Patients who are allergic to shellfish should not use glucosamine because it is derived from crustacean chitin.

Also, glucosamine is considered a food supplement and therefore is not regulated by the Food and Drug Administration. The purity and the concentration of glucosamine can vary despite claims made by the manufacturer.

Although no study has addressed the correct dose of glucosamine or the actual time to onset of pain relief, the human clinical trials seem to suggest that a 12-week course of treatment is required at a dosage of 500 mg three times a day.

REFERENCES

1. **McAlindon TE, LaValley MP, Gulin JP, Felson DT.** Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. JAMA 2000; 283:1469–1475.
2. **Reginster JY, Deroisy R, Rovatti LC, et al.** Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001; 357:251–256.
3. **Das A, Hammad TA.** Efficacy of a combination of FCHG49 glucosamine hydrochloride, TRH122 low molecular weight sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis. Osteoarthritis Cartilage 2000; 8:343–350.
4. **Müller-Fassbender H, Bach GL, Haase W, Rovati LC, Setnikar I.** Glucosamine sulfate in osteoarthritis of the knee. Osteoarthritis Cartilage 1994; 2:61–69.
5. **Buckland-Wright JC, Wolfe F, Ward RJ, Flowers N, Hayne C.** Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and Schuss views. J Rheumatol 1999; 26:2664–2674.

ADDRESS: *Michele Hooper, MD, University Hospitals of Cleveland, Foley 201, 11100 Euclid Avenue, Cleveland OH 44106; e-mail mmhooper@aol.com.*

We still do not know whether glucosamine works