Glucosamine and Chondroitin for Osteoarthritis: To Recommend or Not to Recommend?

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Medical treatment of osteoarthritis (OA) is challenging. Current analgesic and anti-inflammatory drugs often do not provide relief of symptoms and are less than perfectly appealing because of side effects and cost. Exercise, to be recommended for sure, is difficult for patients to stick to, and its long-term efficacy is unknown. As a consequence of this paucity of effective therapies, new therapies are badly needed. In this setting, glucosamine and chondroitin have been touted as efficacious alternative therapies for OA. One book in the lay press has proclaimed them "The Arthritis Cure" (1). As part of the regulatory drug approval process in Europe, multiple clinical trials have been carried out, most of them not published in widely read general medicine or rheumatology journals. Nonetheless, they do provide useful information about the likely efficacy and safety of these compounds and, to a lesser extent, about whether they get into the body and how they work. It is our goal to review the evidence on the efficacy and safety of chondroitin and glucosamine and what is known of their pharmacokinetics and mechanism of action. This information will form the basis for a summary recommendation regarding whether to recommend these compounds for patients, many of whom have already tried them.

Glucosamine

Glucosamine consists of the addition of an amino group to glucose. After being acetylated, glucosamine is a major constituent of glycosaminoglycans throughout connective tissues including hyaluronic acid, keratan sulfate, and other constituents of various tissues within the joint. It is likely that exogenously administered glucosamine is never incorporated into matrix oligosaccharides, which grow from energy provided by UDP-glucose.

Glucosamine has been reported to have several different effects on cartilage in in vitro and ex vivo models. Several groups have found that glucosamine at concentrations likely to be found in cartilage inhibits interleukin 1 (IL-1)-induced increases in aggrecanase activity and that it also inhibits IL-1–induced nitric oxide production, a mediator or signal of chondrocyte cell death (2,3). Adding glucosamine to chondrocyte cultures increases proteoglycan synthesis (4), which may be due to increased gene expression (5). In rat models of inflammation, glu-

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cosamine has modest but measurable anti-inflammatory effects.

Pharmacokinetic information in humans is incomplete, but animal studies suggest that this small molecule is exceedingly well absorbed after oral administration, with 87% of radioactive glucosamine appearing in either the urine or other body excretion routes outside of the bowel. In humans, after oral administration, 38% of glucosamine is excreted in urine as the complete molecule within 0–2 hours of oral ingestion (6). After absorption, much of the radioactivity of labeled glucosamine is ultimately excreted in expired air linked to carbon dioxide and water (6). After intestinal absorption, the radioactive label linked to ingested glucosamine is distributed widely throughout organs, including joints.

In a recent meta-analysis of randomized placebo-controlled trials evaluating glucosamine, we reported that all trials published to date except one had been positive, showing significant improvement in symptoms in patients randomized to glucosamine compared with patients randomized to placebo (7). The quality of trials reported to date is mixed, with some trials falling below threshold levels that would be acceptable. When we stratified trial data into trials that scored higher on quality assessments versus those that scored lower, we found that the estimate of effect in the higher quality trials was considerably less than in the lower quality trials. The high quality studies suggested efficacy in the small to moderate range of 0.3 (95% confidence interval 0.1 to 0.5) (0.2 being small, 0.5 being moderate, 0.8 being large). Thus, although glucosamine is not "the arthritis cure," the bulk of evidence suggests modest efficacy on symptoms.

It should be noted that the trials we sampled from the meta-analysis might not be all of the trials that have been performed. We found evidence of likely publication bias (small null studies going unpublished). Almost all studies had been funded and reported by sponsoring companies, and many did not include intent-to-treat analyses. Further, many did not include in their reports evidence of avoiding allocation bias, the likely selection of patients prior to randomization so as to be chosen for one group or another. One example is when open randomization occurs, and patients can find out the treatment to which they are randomized. Allocation bias has been shown to be associated with a systemic overestimate of the efficacy of treatments (8). Thus, even in the higher quality trials, enough bias remains that any accurate estimate of the efficacy of glucosamine is difficult to arrive at with validity.

Since our meta-analysis, one additional randomized placebo-controlled trial of glucosamine has been published, a negative, or null, study (9). In this study, 98 patients with OA of the knee were randomized to glucosamine or placebo for two months. Outcomes at one and two months did not remotely suggest efficacy (the improvements in placebo and glucosamine groups were almost identical in an intent-to-treat analysis).

Evidence for the effect of glucosamine on structural changes in OA is meager. Results of an abstract presented prominently at the 1999 American College of Rheumatology meeting (10), a 3-year randomized trial with glucosamine, suggested that treatment delayed joint space loss in the knee compared with placebo. While these data were suggestive, x-rays were not obtained using state of the art techniques, and loss to followup marred the final analysis. Additional data on this issue are needed.

One of the advantages of glucosamine is its apparent safety. Indeed, in almost all of the randomized trials published, glucosamine patients have experienced no more side effects than those randomized to placebo. The most common side effects have included gastric intolerance (but this is often similar to the rate experienced by those taking placebo), which may be due, in part, to concurrent nonsteroidal drug use. Side effect profiles beyond 2–3 years are unknown.

It is uncertain whether diabetic patients are at risk of hyperglycemia or heightened insulin resistance during treatment with glucosamine. A manufacturer reports no effects on glucose metabolism when glucosamine is given orally, although one study in nondiabetic individuals reported a modest increase in fasting insulin levels (11). Intravenous administration of glucosamine appears to increase insulin resistance or decrease insulin secretion (12). The inhibition by glucosamine of glucokinase, at least in rats, induces a drop of in vivo insulin secretion, an effect that may or may not be relevant in human beings (13).

Chondroitin

Unlike glucosamine, preparations of chondroitin sulfate, usually derived from beef trachea, contain large molecules of chondroitin 4 and 6 sulfates. Despite the size of these molecules, data from rats, dogs, and humans suggest that the orally administered compound is absorbed (14), although in humans the percentage absorbed is only about 15%. In humans, maximal absorption occurs in approximately 1 hour, and serum levels of chondroitin in humans rise after oral ingestion. Unlike glucosamine, most of hours, high molecular mass chon-

droitin reaches its maximal concentration in 1.6–2.7 hours. Technetium-labeled chondroitin sulfate localizes in human joint tissues (15). Clearance of the molecule and its metabolism has not been well described.

Chondroitin appears to have both modest anti-inflammatory and metabolic effects on cartilage synthesis or degradation. Animal studies suggest that chondroitin sulfate administered at doses substantially higher than those given clinically decreases granuloma formation after cotton or sponge implants and inhibits leukocyte migration and enzyme release in carrageenan-induced pleurisy. It is not clear whether conventionally administered doses of chondroitin would have similar anti-inflammatory effects. In rabbit knees injected with chymopapain, chondroitin either orally or intramuscularly modestly prevented proteoglycan loss. Additional work on mechanism of action is needed.

In our aforementioned meta-analysis evaluating placebo-controlled randomized trials of glucosamine and chondroitin (3), we included 9 trials of chondroitin. These trials constituted all of the placebo-controlled trials of chondroitin we could find that had extractable data. All reported that chondroitin was significantly more efficacious than placebo. Like trials evaluating the efficacy of glucosamine, many of the chondroitin trial reports did not score highly in methodologic quality, and those with higher quality scores reported, on average, lower levels of efficacy. Further, even the higher quality trials contained methodologic shortcomings that should inject caution into interpreting summary efficacy estimates—only two presented intent-to-treat data, and none had adequate reports of allocation concealment. Even so, the summarized estimate for chondroitin efficacy among the better quality trials was an effect size of 0.8, an effect generally considered large.

While no trials evaluating the efficacy of chondroitin have been published since our meta-analysis, one small trial of combined chondroitin (1,200 mg/day), glucosamine (1,500 mg/day), and manganese was more efficacious than placebo in knee OA patients (16). Intent-to-treat analysis and allocation concealment were both features of this trial.

Two small trials have suggested that chondroitin treatment inhibits structural progression on radiographs. In a randomized study of chondroitin in hand OA, Verbruggen et al reported that those who received chondroitin had many fewer new central erosions, a prominent feature of hand OA, than persons who received placebo (17). In a study of knee OA using conventional radiographs and digitized analysis, Uebelhart and colleagues reported a delay in joint space loss in those randomized to chondroitin (18). The trials were small (maximal total size 46), and dropout rates were substantial in both of these studies, raising concerns about how to interpret their results.

As with glucosamine, few subjects experience side effects when taking chondroitin preparations, the most frequent being gastrointestinal symptoms. In general, side effect rates for those randomized to chondroitin have been similar to those assigned to placebo. Data on side effects for those taking chondroitin beyond one year are unavailable.

Practical considerations in interpreting trial reports on glucosamine and chondroitin and in recommending use

Most new drugs tested for rheumatic diseases are developed and evaluated by industry, which report their results. Many of these trials are carried out and reported with fastidious care and are of exceedingly high quality. Chondroitin and glucosamine trials are almost entirely funded by industrial sponsors, and most have been reported in either abstract form or in obscure journals. Thus, the rheumatology community is appropriately skeptical because the evidence about the drugs' efficacy and safety has not been subjected to rigorous scientific scrutiny. The lack of Food and Drug Administration (FDA) review of these nutriceuticals, which would assure consumers that evidence supports efficacy, adds to this concern, although these products have been approved by European drug regulatory agencies. Fortunately, the National Institutes of Health has embarked on a trial to evaluate the efficacy of both of these compounds.

Nonetheless, at this time, the preponderance of evidence suggests that both of these nutriceuticals offer modest symptom relief to OA patients, with the effect for chondroitin perhaps greater than that for glucosamine. There is strong evidence that their short-term safety profile is excellent, with a possible caveat being glucosamine in patients with diabetes. Thus, we recommend these compounds to our patients, expressing to them our own concerns that the evidence on their usefulness is incomplete and discussing with them cost and possible safety issues (vide infra). Because clinical trial data suggest that the onset of efficacy is delayed up to one month and is often maximal after that time, we suggest that patients take these pills for at least a month (and preferably longer) to decide whether they work.

In deciding whether to recommend glucosamine and/or chondroitin to your patients, other considerations loom. Since neither of these is prescription

medicine, third-party insurers will not pay for their use, and patients need to buy them with their own funds. The drugs can be expensive, although prices vary considerably. They are available in pharmacies, in warehouse retailers, from mail-order vitamin suppliers, and on the Internet.

Because they are not regulated as drugs, the purity of compounds available is not assured. Further, there is the possibility that, as animal products, glucosamine and chondroitin may contain other unwanted constituents. For example, concern has been raised that cows from which chondroitin is extracted may be infected with bovine spongiform encephalopathy. As for whether specific brands actually contain advertised compounds, results of independent laboratory testing of some brands is reported on a website (www.drtheo.com). Unfortunately, only companies producing the relatively expensive brands pay for this independent testing.

Lastly, the rise of glucosamine and chondroitin as popular lay treatments for OA speaks to our increasing need for rigorous, carefully reviewed, and scrutinized trials, either in the context of FDA evaluation or using public funding. In the absence of either regulatory oversight or nonsponsor-funded trials, it will be increasingly difficult to ensure that we can have access to accurate information on the efficacy and safety of treatments.

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