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Supplements for OA: An Unconvincing Story

Evidence supporting the use of glucosamine and chondroitin is scant, anecdotal

Terry Stanton

The glory days for glucosamine began in 1996 with the publication of *The Arthritis Cure,* by Jason Theodosakis, MD. Millions of people with painful osteoarthritis (OA) flocked to the supplement, along with its common sidekick chondroitin, hopeful that finally something could provide relief for their condition.

Medical professionals, however, tend not to embrace touted cures that haven't been tested in legitimate clinical trials and, as nutritional supplements, glucosamine and chondroitin have never been subject to Food and Drug Administration oversight or approval. But the appeal of these products was hard to ignore, especially since physicians often had little to offer patients besides analgesics and NSAIDs.

The theoretical basis for the healing mechanism of the two supplements is certainly plausible. Glucosamine and chondroitin sulfate are both components in the extracellular matrix of articular cartilage. Glucosamine is an amino sugar involved in the synthesis of glycoproteins and glycosaminoglycans—found in synovial fluid, ligaments, and other joint structures. It is thought to stimulate metabolism of chondrocytes. Chondroitin, an endogenous glycosaminoglycan, also plays a role in building the matrix.

A number of early studies, both in the lab and in vivo, yielded promising results, but larger, better designed studies focused on pain and function results were not as encouraging. A landmark study funded by the National Institutes of Health (NIH) in 2006 and involving more than 1,500 patients with knee OA found virtually no benefit from the glucosamine/chondroitin combination, and little evidence has arisen since to contradict that finding.

Not harmful, but not helpful

Because glucosamine and chondroitin have been widely demonstrated to be safe—except possibly in diabetic patients—many physicians do not discourage patients from taking them and may even mention the supplements as an option, despite a lack of compelling evidence of effectiveness.

The Academy's Clinical Practice Guideline (CPG) on the Treatment of Osteoarthritis of the Knee, however, takes a definitive stand against the supplements, recommending that glucosamine and/or chondroitin sulfate or hydrochloride not be prescribed for patients with symptomatic OA of the knee.

The Level 1 study cited by the CPG that doused much of the early enthusiasm for the supplements was the 2006 Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), funded by the NIH and published in the *New England Journal of Medicine.* The 24-week trial involved 1,583 patients who were randomly assigned to receive one of the following treatments:

- 500 mg of glucosamine hydrochloride three times daily
- 400 mg of sodium chondroitin three times daily
- 500 mg of glucosamine and 400 mg of chondroitin three times daily
- 200 mg of celecoxib daily
- a placebo

The study found that glucosamine and chondroitin, alone or together, did not reduce OA knee pain more effectively than a placebo; the celecoxib group did 17 percent better than the placebo. A small subgroup of patients with moderate to severe pain took glucosamine and did show significantly reduced knee pain, but this result has not been replicated.

"The trial was a large study; it was well done," said Anthony Luke, MD, professor of clinical orthopaedics at the University of California, San Francisco. "It was powered well and had multiple comparisons. They had to go to a small subgroup to find that anyone had any benefit."

Commenting on the study at the time, Timothy McAlindon, MD, chief of rheumatology at Tufts-New England Medical Center, noted that most ingested glucosamine is broken down in the liver; almost none gets into the blood and travels to the joints. "The amount that gets beyond the liver is minuscule," he told the *New York Times.*

"It's an attractive idea, to be able to take something orally that preserves your joints or treats arthritis," said **Joseph A. Buckwalter, MD**, chair of Orthopaedics and Rehabilitation at the University of Iowa, whose research activity includes cartilage studies. "This may have started with people eating shark cartilage with the idea that somehow it would find its way through the digestive system and into their joints. Thinking that oral doses of glucosamine and chondroitin sulfate, which make up the extracellular matrix in cartilage, would make their way to joints was the next step. But it's hard to imagine how they get past the stomach and the intestines without being broken up."

Although glucosamine sulfate had been more frequently used in previous studies, some of which indicated possible effectiveness, the GAIT study used the hydrochloride form of glucosamine. An editorial accompanying the publication of the GAIT study made the following recommendation:

"It seems prudent to tell our patients with symptomatic osteoarthritis of the knee that neither glucosamine hydrochloride nor chondroitin sulfate alone has been shown to be more efficacious than placebo. If patients choose to take dietary supplements to control their symptoms, they should be advised to take glucosamine sulfate rather than hydrochloride, and for those with severe pain, taking chondroitin sulfate with glucosamine sulfate may have an additive effect."

Some suspect that any benefit coming from the sulfate forms may be due to the sulfate component itself. Dr. Luke noted that early research was looking to detect structural changes resulting from glucosamine. "Now it's not believed that structural change will take place, but maybe some pain relief is provided; perhaps the sulfate has a modulating effect and is the important part. This hasn't gotten a lot of attention."

In 2001 and 2002, two well-respected European studies did appear to demonstrate beneficial structural changes resulting from glucosamine sulfate and generated considerable enthusiasm for its potential, as well as for further research. Both studies found that the product significantly reduced knee joint-space narrowing over 3 years.

"Those studies heightened interest," said Dr. Luke. "They showed less radiographic change compared with placebo over several years." But the clinical implications turned out to be not as significant as initially hoped. "Radiographic changes don't necessarily tell you much," he continued. "Plus they were small, like 1 millimeter.

"Evidence that glucosamine is doing anything on a structural level doesn't exist. Glucosamine and chondroitin are part of articular cartilage. The idea was by taking it, you'd get more substrate, and the cartilage would regenerate or heal. The lay person thinks that taking these supplements will help the cartilage grow back. In lab studies, cytokines and interleukins decreased, and there were signs in RNA of cartilage generation. But in the human body not much goes on."

Many variables

One obstacle to conclusive findings is that OA research is inherently complex and conclusions are elusive, especially for conservative treatments. "Often people are taking many different drugs. Mild to moderate OA can affect patients very differently—one patient might be running marathons, while another can't walk three blocks. It is hard to demonstrate benefits when the clinical outcome is pain, which is variable. Something structural would be convincing, but that doesn't appear to be happening," said Dr. Luke.

Furthermore, conservative treatments in general don't draw large-scale funding and interest. "Often not a lot of money is invested in evaluating these treatments," Dr. Luke said, "even though a huge number of people are treated nonsurgically."

Trials since the GAIT study, including a 2-year follow-up to the GAIT itself, have largely failed to demonstrate a benefit from glucosamine and chondroitin. For instance, a 2010 randomized controlled trial of patients in Norway with lower back pain and OA found that taking 1,500 mg

daily of glucosamine sulfate provided no more benefit than a placebo.

"The literature is confusing because some studies seem to show an effect, and others don't, but in the big, well-done studies, the effect, if any, is minimal," said Dr. Buckwalter. "Some patients swear by it, but overall, the impact isn't much different than taking a placebo."

Few options

Despite the lack of favorable evidence, Dr. Luke—like many physicians—doesn't discourage patients from taking the supplements.

"I don't recommend it, but if they ask me, I'll talk about it. The placebo effect might help in about 20 percent of patients. NSAIDs have side effects, and if we don't have a surgical solution, I don't see a problem with considering glucosamine. I tell patients to take it for 4 to 6 weeks. If they like the effect, keep going."

Because glucosamine is made from the endoskeletons of shellfish, persons with allergies may be advised to use it cautiously and watch for a reaction, or to avoid it.

Letha Y. Griffin, MD, of Peachtree Orthopaedic Clinic in Atlanta, takes a similar tack and notes that the supplements are routinely prescribed for animals. "I tell patients that it's an option, and we're not sure if it works," she said. "If they are going to use it, I recommend buying a brand name. Patients with significant arthritis are probably not going to benefit as much as those with mild to moderate arthritis. The good news about the supplements is that they don't seem to have side effects. I also think a smaller dose—500 mg glucosamine and 400 mg chondroitin—may be adequate."

Dr. Griffin has observed an effect in animals. "You give it to an old dog, and he seems to do better. He can get down the steps," she said. "Dogs don't know they're being treated, so there's no placebo effect."

"There are definitely proven mechanisms of action in vitro for glucosamine-type products, which primarily involve antidegradation effects," said **James L. Cook, DVM, PhD,** director of the Comparative Orthopaedic Laboratory at the University of Missouri, who conducts basic science and clinical research on articular cartilage. "The combination of glucosamine and chondroitin sulfate consistently show better in vitro effects than either alone. However, the clinical evidence is lacking in small animals. No studies in small animals have high evidentiary value. That said, I do recommend trying them to many clients because they are safe and many clients report high perceived efficacy in their dogs."

C. Wayne McIlwraith, BVSc, PhD, a veterinarian and director of the Orthopaedic Research Center at Colorado State University, has written about nutraceuticals and conducted research in large animals. "In vitro data show both glucosamine and chondroitin sulfate are effective," he said. "However, in vitro data are somewhat meaningless because the product has not gone through the animal's gastrointestinal tract. Dr. Sheila Laverty at the University of Montreal Veterinary School questions whether current recommended doses are sufficient to achieve any

effect with oral administration. In vivo studies are needed, but companies have no incentive to do them because oral supplements aren't required to prove efficacy."

Dr. Griffin said that some of her patients who take the supplements report positive results and that many variables may be in play. She also noted that *The Arthritis Cure* stressed a whole-body approach to management. "When we talk about 'homeopathic' remedies and nutraceuticals, we treat all types of OA as one. Maybe the effect on genetic arthritis is different than on posttraumatic arthritis. The wear patterns and responses may differ. It might be pointless to take glucosamine/chondroitin if the patient is morbidly obese. Ideally, the patient is also losing weight and exercising, so supplements are part of a whole program."

A new approach?

Whatever the evidence, or lack of it, for the efficacy of glucosamine and chondroitin, Americans continue to spend $1 billion or more annually for the supplements. In a 2010 article on the future of glucosamine research, Joel A. Block, MD, a professor of rheumatology at Rush University Medical Center, and colleagues noted that as long as these supplements are seen as safe to use, people will keep using them. They also make the point that conducting additional studies modeled after those that have strongly demonstrated ineffectiveness is a poor use of resources; instead, future research "aimed at elucidating mechanisms of action for glucosamine salts for translational purposes needs to be based on the use of

- standardized in vitro cell and tissue culture systems
- well-characterized animal models of osteoarthritis pathology
- therapeutically relevant preparations and concentrations of glucosamine
- standardized outcome measures that include the inflammatory and pain pathway relevant to human osteoarthritis."

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Bottom Line

- Glucosamine and chondroitin, classified as food supplements and not regulated by the FDA, are substances that occur naturally in cartilage.
- Common forms of glucosamine are sulfate and hydrochloride, while chondroitin is typically a sulfate; it is possible that the sulfate component acts as a pain modulator.
- Early laboratory and clinical studies showed promise for glucosamine and chondroitin, but a large NIH-funded trial cast doubt on their efficacy, and subsequent studies have had similar findings.
- Glucosamine and chondroitin are considered safe for most people, and many physicians do not discourage their use if the patient thinks they are beneficial.

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