

Glucosamine and Chondroitin Sulfate

January 15, 1997
New York Times
By Jane E. Brody

I HAVE been asked repeatedly in the last two months about my knees and whether the arthritis remedy I mentioned in a column on alternative medicine was actually working. It is a combination of glucosamine and chondroitin sulfate, natural substances that are centrally involved in the formation of the cartilage that caps the ends of bones.

Deterioration of this articular cartilage and resulting abnormalities in the surrounding bone cause the stiffness, pain, crackling sounds and sometimes swelling of joints that are the hallmarks of osteoarthritis, the wear-and-tear form of arthritis that afflicts 16 million Americans.

The product had seemed to be so effective in countering the arthritic lameness of my 11-year-old spaniel that I decided to try it myself. After two months on this remedy, I am about 30 percent better. I am not pain-free and I still tend to get a little stiff after prolonged sitting, but I have stopped limping, I am playing tennis and ice skating with less pain and my knees have stopped swelling after strenuous activity. But please understand that I am only an anecdote of one, not a study that proves anything. Without a careful scientific study, any personal account of benefit leaves open to question what actually caused the improvement.

The starting dose of three capsules a day costs about \$1.67. Since it is sold as a “nutritional supplement” rather than a drug, it is not covered by health insurance.

The usual treatments for osteoarthritis are anti-inflammatory drugs, combined with muscle-strengthening activities and judicious exercise. This approach may relieve discomfort and slow deterioration of the joint, but it does not restore the health of damaged cartilage and can cause serious drug reactions.

Might Something Work?

Rebuilding damaged cartilage has long been the holy grail of orthopedics and rheumatology, and supporters of the glucosamine-chondroitin combination hope it will be the first remedy to achieve this. The individual ingredients have already been shown to improve

arthritic symptoms in more than a dozen studies in Europe, some of which were well designed. European researchers have shown, using radioactively labeled substances that glucosamine and chondroitin taken by mouth do indeed find their way to articular cartilage, and biopsies of some treated patients have shown structural improvements in damaged cartilage.

Dr. Marc Hochberg, chief of rheumatology at the University of Maryland School of Medicine, said that early studies of glucosamine and chondroitin sulfate when taken orally for osteoarthritis “appear to demonstrate that they are effective and warrant examination in a placebo-controlled, randomized trial.”

The American College of Rheumatology also noted the promise of early studies but cautioned “what looks promising at first doesn’t always pan out to be effective or safe.” The Arthritis Foundation also cited European reports indicating that the two nutrients are safe and “may be helpful in controlling pain and improving function” but added that “good, controlled, long-term studies are needed to see if the products are indeed helpful and safe.”

The combination of glucosamine and chondroitin is now being tested in well-designed human trials by a few clinical researchers in the United States. Dr. Amal Das, an orthopedic surgeon in Hendersonville, N.C., is assessing its effectiveness in 100 patients with mild to moderate osteoarthritis of the knee. For six months, the patients will receive either a dummy medication—a placebo—or a combination of glucosamine and chondroitin, and each will be thoroughly evaluated before and after the treatment for pain and disability.

Dr. Das is financing the study but Nutramax, a Baltimore company that produces a product that combines relatively large doses of glucosamine and chondroitin, is donating the product. The same product is also being evaluated by American military doctors in Norfolk, Va., for its ability to relieve arthritic back and knee pain in United States Navy Seals.

Dr. Das, who specializes in hip and knee replacement, said he had been searching for a “biological alternative to joint replacement” when he stumbled upon the European data on glucosamine and chondroitin. Glucosamine was described as reducing the pain and disability associated with osteoarthritis and chondroitin appeared to slow progression of the disease. He said he started using the treatment in patients who could not tolerate anti-inflammatory drugs. The compounds are not toxic and, in safety studies at Cornell University’s College of Veterinary Medicine, the combination product lacked side effects beyond occasional loose stools in dogs.

“If the compounds are proved to be as effective as the European studies say they are, they should be used in the United States and they should replace the anti-inflammatory medications,” Dr. Das said.

A preventive medicine specialist in Arizona who is himself using this remedy and has prescribed it for about 600 patients, including his mother and grandmother, has decided not to await results of these studies and instead summarized the European findings in a book that promotes the combination as part of a nine-point program for combating osteoarthritis. The book, despite its injudicious title, The Arthritis Cure, by Dr. Jason Theodosakis with Brenda Adderly and Barry Fox (St. Martin’s Press, \$22.95), makes no wild claims.

Needed: Healthy Skepticism

Dr. Theodosakis emphasizes that not every patient responds to the remedy and not everyone who does respond ends up free of pain or restricted movement. But he cites a number of placebo-controlled studies of the individual ingredients that showed improvements in significantly more patients given either glucosamine or chondroitin than in those who received a look-alike inactive capsule. And he recounts the histories of patients who experienced significant improvement after taking the substances, some of whom began feeling better within a week or two.

Dr. Theodosakis also insists that improvement depends not only on taking the substances but also on following the eight other steps in his program, which include a regular regime of physical exercise, a diet rich in fish high in omega-3 fatty acids and losing excess weight.

Although glucosamine with or without chondroitin has been used for years by veterinarians, mainly in horses and dogs, most American doctors, who tend not to act based on European studies, have kept their distance.

The substances cannot be patented, which is why drug companies have not supported research. Neither have rheumatologists, who have seen scores of quack remedies for arthritis, pushed for government-sponsored studies.

Dr. Joseph B. Houpt, a rheumatologist at Mount Sinai Hospital in Toronto, said his review of the medical literature, the dramatic response of his arthritic Labrador to glucosamine and anecdotal reports from patients who had taken glucosamine had revealed “enough smoke” to prompt him to begin a controlled clinical trial. He will study its effects in 100 patients, half of whom will unknowingly receive a placebo. Dr.

Houpt insists glucosamine alone should be studied first and, if found effective, then followed by a study of the glucosamine-chondroitin combination.

Let Buyers Beware

Glucosamine and chondroitin are marketed as nutritional supplements and therefore, by Federal law, are not regulated by the Food and Drug Administration. Dr. Jason Theodosakis said he had had a number of products evaluated and found that some contained almost none of the ingredient featured on the label.

“Apparently, you don’t necessarily get what you pay for,” he said, adding that some products may contain too little of the active ingredient to be useful.

The product my dog’s vet recommended, Cosequin, is produced by Nutramax, a Baltimore laboratory that meets the Food and Drug Administration standard for food product production and is working toward pharmaceutical-quality standards. The equivalent product for people, Cosamin, is identical to the veterinary formulation. Each capsule supplies 500 milligrams of glucosamine chlorhydrate, 400 milligrams of chondroitin sulfate, 66 milligrams of ascorbate to enhance absorption and 10 milligrams of manganese, which plays a key role in the synthesis of a component of cartilage. No other combination product currently on the market supplies anywhere near these dosages, although health food stores do sell products containing large dosages of the individual ingredients.

Cosamin, which costs about \$100 for a bottle of 180 capsules, can be obtained only from a licensed health professional—physician, osteopath, chiropractor, nurse-practitioner, pharmacist, dentist or physical therapist—who can order the product from the company by calling (800) 925-5187.

ARTHRITIS UPDATE

New Weapons to Assault an Epidemic

Glucosamine and Chondroitin Sulfate

June 24, 2001
New York Times
By Larry Katzenstein

AS a New York Knick, Fred Crawford suited up with Bill Bradley and Willis Reed. Later he was a member of the Los Angeles Lakers when Elgin Baylor and Jerry West were the stars of that team. He ended his career with the Milwaukee Bucks, whose center was Kareem Abdul-Jabbar. That was three decades ago.

Late last month, as he entered a medical office on the Upper East Side of Manhattan, Mr. Crawford moved in what must have seemed like slow motion to him. Decades of constant pounding had taken their toll on his left hip. Pain and weakness prevented him from walking more than three blocks at a time. "Basketball is a tough business, but you're not thinking about that at the time," Mr. Crawford said. His diagnosis: moderately severe osteoarthritis.

Mr. Crawford is not alone. About 21 million Americans are afflicted with osteoarthritis. (According to a federal study, the figure will soar to more than 30 million by 2020, as the baby boomers grow older.) Women stand a greater chance than men of developing the disease, especially women over 65. But some arthritis experts are noticing a change in their patients: more men developing severe cases, and earlier, in their 50's rather than in their 60's and 70's, which may be attributed to more participation in strenuous sports.

At the same time, however, a variety of promising treatments and technological advances, from new drugs to viscous injections to high-tech prostheses, are keeping pace with the epidemic, offering relief to those who suffer from the nation's leading cause of disability.

Lube Job for Joints

While osteoarthritis affects the entire joint—be it knee, hip, wrist or fingers—its primary target is cartilage, the tough, slippery coating at the ends of bones that lets them glide over each other when you bend your knees or throw a baseball. With osteoarthritis, the protective cartilage wears away (which is why it is sometimes referred to as "degenerative" arthritis). As the cushioning cartilage erodes, bone eventually rubs against bone, causing the pain and stiffness that Fred Crawford knows all too well.

The 60-year-old Mr. Crawford had been scheduled for hip-replacement surgery in April. But he canceled after hearing about a less drastic but more controversial alternative known as visco-supplementation—a lube job for arthritic joints.

In visco-supplementation, a clear, thick liquid is injected into the joint in three weekly injections costing about \$1,000 for the series. (Some health insurance plans cover the cost.) The relatively painless injections are intended to provide temporary relief for arthritic pain and stiffness. The key ingredient is hyaluronic acid, a chemical found naturally in the fluid of the knee and other joints that aids in lubrication.

The Food and Drug Administration approved two visco-supplementation products, Synvisc and Hyalgan, in 1997 and a third, Supartz, earlier this year. They are currently approved for treating symptoms of osteoarthritis of the knee that have not responded to drugs or other treatments. (None has yet been approved for osteoarthritis of the hip, so Mr. Crawford's injections, using Synvisc, are an "off-label" but permissible treatment.)

Visco-supplementation has drawn attention, not all favorable, partly from how it has been promoted. Full-page ads in magazines and newspapers contend that Synvisc offers "drug-free relief for osteoarthritis knee pain," which is technically true, as the products are classified as medical devices rather than drugs. But experts are also split over visco-supplementation's effectiveness.

"I think it doesn't work, and there's actually pretty strong evidence from clinical trials that it doesn't work," said Dr. David Felson, the director of the Arthritis Center at the Boston University School of Medicine. He said that the three large-scale clinical trials of visco-supplementation for knee osteoarthritis "show no effect compared with placebo injections of saline."

But visco-supplementation has its proponents, too. One is Mr. Crawford's doctor, Vijay Vad, a rheumatologist at the Hospital for Special Surgery in New York. Dr. Vad has "visco-supplemented" nearly 600 knees and 70 hips—the first 25 as part of a recently completed clinical trial. For best results, he emphasizes, "careful selection of patients is essential."

According to Dr. Vad, the prime candidates for visco-supplementation are men in their 40's or 50's with moderately severe osteoarthritis of the hip or knee who have failed to improve with oral medications, physical therapy or cortisone injections. Following the

injections, Dr. Vad insists that patients engage in a rehabilitation program that includes exercise and aquatherapy.

Mr. Crawford, for one, is a believer. “I have less pain and have already noticed improvement in my range of motion,” he reported shortly after the last of his three Synvisc injections. He said he was looking forward to playing doubles tennis and taking his bicycle out of storage. But as for basketball, “I’m going to leave that to Kobe and Shaq.”

The Surgical Solution

Dr. Richard Laskin, an orthopedic surgeon and co-chief of the knee service at the Hospital for Special Surgery, recently reviewed his hospital’s database for the last 20 years, tallying up the numbers of men who had been candidates for hip or knee replacement surgery and noting their ages. One finding stood out: between 1980 to 1990 and 1990 to 2000, male patients in their 50’s had tripled.

“Why am I seeing so many more men in their 50’s when I used to see them much later?” Dr. Raskin asked. “It’s because when they were in their 20’s, they skied or played rugby or soccer or whatever and damaged their knees—tore their anterior cruciate ligament or their medial meniscus, for example, and more men tended to do that than women.” (Ligaments are bands of tissue that help stabilize a joint by binding together the bones within it; meniscuses are pads of tissue that help to cushion the knee joint.)

Even without directly damaging cartilage, traumatic injury to a joint greatly increases the risk of developing osteoarthritis years later. Tearing a ligament or meniscus makes the joint unstable, creating abnormal stresses on cartilage during movement. Athletes who suffer a major injury to the knee or hip, for example, are up to seven times more likely to develop osteoarthritis in that joint than the average person.

Often, the best solution is to replace the knee. A quarter of a million such operations are done each year for severe arthritis, and the results are striking, with almost total relief in most cases. Until recently, though, the drawback for younger patients was that these artificial joints often wore out after about 20 years, so orthopedists preferred to delay surgery until 65.

But thanks to an implant introduced earlier this year, patients may not need to wait. Laboratory comparisons show that the new knee, with a surface of oxidized zirconium ceramic, a highly durable material, wore down only about one-tenth as fast as standard implants.

“If they can last 30 to 35 years, then even for my 50-year-old patients you’re talking about their lifetime,” Dr. Laskin said. “That’s what we’ve been looking for all these years.”

The Cox-2 Breakthrough

For more than three decades, nonsteroidal anti-inflammatory drugs—aspirin, ibuprofen, naproxen and others—have been mainstays of medical treatment for the pain, stiffness and inflammation of osteoarthritis. But these drugs, referred to by doctors as Nsaid’s, can also cause major gastrointestinal problems, including ulcers and bleeding.

In 1998, the food and drug agency approved celecoxib (Celebrex), the first of a new class of anti-inflammatories known as Cox-2 inhibitors. A second, rofecoxib (Vioxx), was approved in 1999. Celebrex and Vioxx cost much more than standard drugs and are no better at relieving arthritis symptoms. Their crucial advantage is that they inhibit the Cox-2 enzymes that cause pain and inflammation while, in contrast to standard anti-inflammatories, largely sparing the “good” Cox-1 enzymes that protect the stomach lining.

“Celebrex and Vioxx aren’t immune from causing the same nasty side effects as other Nsaid’s,” said a rheumatologist in New York, Dr. Mark Eberle. “But in well-conducted studies comparing Cox-2’s with traditional Nsaid’s such as ibuprofen, naproxen and diclofenac, the Cox-2’s were only about 25 percent as likely to cause such problems.”

But because of their specificity, Cox-2’s lack a useful side effect that standard anti-inflammatories have, which is the ability (because these drugs interfere with blood platelets) to reduce the risk of clots that can cause heart attacks. So people who rely on aspirin for its anti-clotting effect cannot depend on Celebrex or Vioxx to provide the same benefit.

The Sunshine Treatment

A connection between vitamin D and osteoarthritis might seem unlikely. But since vitamin D is important for strong bones, and bones are joined to cartilage, it makes sense. Now, mounting evidence suggests that osteoarthritis is likely to worsen for those who are deficient in vitamin D—a common deficiency affecting nearly 60 percent of adults, according to one recent survey.

Initial reports of a link emerged from the Framingham Heart Study, best known for revealing risk factors for heart disease but also a source of valuable information

on other diseases. Residents of Framingham, Mass. who had osteoarthritis of the knee were periodically monitored for vitamin D intake, blood-serum levels of vitamin D, and changes in the severity of their disease.

In a study of 556 people over a period of about 10 years, people who consumed little vitamin D and had low levels in their serum were three times more likely to experience a worsening of their knee osteoarthritis than those with high intakes and high serum levels. Low serum levels of vitamin D were also associated with loss of cartilage in the knee.

“When we initially published that data, I frankly was a little bit nervous as to whether we were correct,” said Dr. Felson of the Boston University medical school, an author of the study. But he added that a very large study on osteoarthritis of the hip, published in 1999, corroborated their findings “almost exactly.”

Based on the Framingham results, the amount of vitamin D in a typical multivitamin—400 International Units—should keep cartilage healthy. An eight-ounce glass of milk fortified with vitamin D contains about 100 units, and occasional exposure to sun can help too.

The Arthritis “Cure”

After The Arthritis Cure became a best seller in 1997, even its principal author, Dr. Jason Theodosakis, agreed that “cure” was too strong a term for the effects of glucosamine and chondroitin sulfate, the two dietary supplements whose properties were lauded in the book. (Both are basic building blocks of cartilage and have anti-inflammatory properties.) But while claims for their ability to rebuild cartilage remain to be proven, recent studies provide further evidence for the safety and effectiveness of these supplements: They work against symptoms of osteoarthritis and may prevent the further breakdown of cartilage.

“I tell my patients, ‘I believe in God, the Tooth Fairy and glucosamine,’ “ said Dr. Steven K. Magid, a rheumatologist at the Hospital for Special Surgery. “I’ve just had so many patients tell me that they do get pain relief from these supplements.”

Five physicians interviewed for this article were asked about The Arthritis Cure supplements, and all said they had recommended them to patients. Two were particularly impressed with a study done in Belgium and published this year in The Lancet, the London-based medical journal.

The Belgian study involved 212 patients with knee osteoarthritis who took either 1,500 milligrams of

glucosamine sulfate or a placebo daily for three years. Their knees were X-rayed at the start of the study and again after one and three years. The 106 patients on placebo experienced progressive loss of cartilage, while those on glucosamine experienced no significant cartilage loss. Also, symptoms of placebo users worsened slightly during the study but improved among glucosamine users.

The best choice may be a combination product, since chondroitin sulfate, glucosamine’s partner, may work even better. In a review of 15 clinical studies of glucosamine and chondroitin published last year in the Journal of the American Medical Association, the authors reported finding “moderate” treatment effects for glucosamine and “large effects” for chondroitin. A federally sponsored clinical trial of glucosamine and chondroitin sulfate, now under way, may provide a clearer idea of the supplements’ benefits.