

## Use of Glucosamine and Chondroitin Sulfate in the Management of Osteoarthritis

Andrew A. Brief, MD, Stephen G. Maurer, MD, and Paul E. Di Cesare, MD

### Abstract

The goals of osteoarthritis therapy are to decrease pain and to maintain or improve joint function. The pharmacologic treatment of this condition has included the use of aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs. More recently, numerous studies have investigated the potential role of chondroprotective agents in repairing articular cartilage and decelerating the degenerative process. The reports of limited clinical experience with two of these agents, glucosamine and chondroitin sulfate, as well as the accompanying publicity in the popular media, have generated controversy. Advocates of these alternative modalities cite reports of progressive and gradual decline of joint pain and tenderness, improved mobility, sustained improvement after drug withdrawal, and a lack of significant toxicity associated with short-term use of these agents. Critics point out that in the great majority of the relevant clinical trials, sample sizes were small and follow-up was short-term.

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Osteoarthritis is the most prevalent musculoskeletal condition: more than 70% of the population 65 years of age or older demonstrate radiographic evidence of this process,<sup>1</sup> with an incidence approximately twice as high in women as in men.<sup>2</sup> Substantial patient morbidity from pain and loss of function can be attributed to this disease. Despite the high prevalence of osteoarthritis, its precise biochemical mechanisms are not yet completely understood. Characteristics of osteoarthritic cartilage include an increase in the water content and degradation of the extracellular matrix, including alteration of the proteoglycans (e.g., shorter chains and a decrease in the ratio of chondroitin to keratan sulfate). These changes predispose to progressive deterioration, with eventual loss of the articular cartilage.

The goals of osteoarthritis therapy are to decrease pain and to maintain or improve joint function. In recent years, numerous studies have investigated potential chondroprotective agents—substances that are capable of increasing the anabolic activity of chondrocytes while simultaneously suppressing the degradative effects of cytokine mediators on cartilage. It has been suggested that such agents may repair articular cartilage, or at least decelerate its progressive degradation. Among those substances that may possess chondroprotective properties are chondroitin sulfate, glucosamine sulfate, hyaluronic acid, piroxicam, tetracyclines, corticosteroids, and heparinoids.<sup>3</sup> Publicity relating to the clinical experience with the first two of these agents has created an air of contro-

versy surrounding their use as alternative agents in the treatment of osteoarthritis. The recent literature contains some limited evidence on the efficacy, potential toxicity, and long-term safety of glucosamine and chondroitin sulfate for the treatment of patients with osteoarthritis. Health-care professionals should be familiar with that evidence and should conduct further objective evaluations of their efficacy.

### Cartilage Structure and Function

Cartilage is composed of a complex extracellular matrix of collagen and elastic fibers within a hydrated gel of glycosaminoglycans and proteo-

*Dr. Brief is Resident, Department of Orthopaedic Surgery, New York University–Hospital for Joint Diseases, New York, NY. Dr. Maurer is Resident, Department of Orthopaedic Surgery, New York University–Hospital for Joint Diseases. Dr. Di Cesare is Associate Professor of Orthopaedic Surgery, Musculoskeletal Research Center, New York University–Hospital for Joint Diseases.*

*Reprint requests: Dr. Di Cesare, Department of Orthopaedic Surgery, Musculoskeletal Research Center, New York University–Hospital for Joint Diseases, 301 East 17th Street, New York, NY 10003.*

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glycans. This specialized network is stabilized by means of intermolecular and intramolecular cross-links that harness the swelling pressure exerted by the high concentration of negatively charged aggregates.<sup>4</sup> This accounts for more than 98% of the articular cartilage volume; cellular components constitute the remaining 2%. The interaction of these matrix components imparts the characteristic biomechanical properties of flexibility and resistance to compression of cartilage. The collagen component of the cartilage matrix is relatively inert, but the other constituents, such as proteoglycans, undergo a distinct turnover process during which the catabolism and removal of molecules from the extracellular matrix is in balance with the synthesis and deposition of new molecules.<sup>5</sup>

Proteoglycans—large macromolecules consisting of multiple chains of glycosaminoglycans and oligosaccharides attached to a central protein core—provide a framework for collagen and also bind water and cations, forming a viscous, elastic layer that lubricates and protects cartilage. The presence of these negatively charged aggregates imparts to the matrix of articular cartilage its strong affinity for water and is hence the most significant factor that contributes to the biomechanical properties of cartilage. The glycosaminoglycans most common in human connective tissue include keratan sulfate, dermatan sulfate, heparan sulfate, chondroitin sulfate, and hyaluronic acid. They consist of amino sugars, which are repeating disaccharide units composed of a hexuronic acid (D-glucuronic acid, iduronic acid, or L-galactose) and a hexosamine (D-glucosamine or D-galactosamine).<sup>6</sup>

Osteoarthritis results in the progressive catabolism of cartilage proteoglycans due to an imbalance between synthesis and degradation. This relative decrease in the carti-

lage proteoglycans alters the affinity of the cartilage matrix for water and, in a sense, the ability of water to easily flow in or out of the joint surface. Such structural changes in the composition of these molecules have been shown to have a negative impact on the biomechanical properties of normal adult articular cartilage and synovial fluid, rendering the articular cartilage vulnerable to the compressive, tensile, and shear forces that occur during normal joint motion. Theoretically, exogenous administration of glycosaminoglycans (e.g., glucosamine sulfate and chondroitin sulfate) to chondrocytes will ameliorate this imbalance and restore, or at least prevent further damage to, the articular cartilage of osteoarthritic joints.

Glucosamine (2-amino-2-deoxy-alpha-D-glucose) is an aminosaccharide that takes part in the synthesis of glycosaminoglycans and proteoglycans by chondrocytes. Glucosamine serves as a substrate for the biosynthesis of chondroitin sulfate, hyaluronic acid, and other macromolecules located in the cartilage matrix. Chondroitin sulfate is a glycosaminoglycan composed of a long, unbranched polysaccharide chain of alternating residues of sulfated or unsulfated residues of glucuronic acid and N-acetylgalactosamine.

Chondroitin sulfate chains are secreted into the extracellular matrix covalently bound to proteins as proteoglycans. These chains are components of several classes of proteoglycans, including aggrecan (the large-molecular-mass proteoglycan within articular cartilage). These proteoglycans function to draw water into the tissue, creating a high osmotic pressure that causes swelling and expansion of the matrix. The load-bearing properties of cartilage are attributable to the compressive resilience and affinity for water of these high-molecular-weight compounds that fill the inter-fibrillar collagen matrix.

## **Pharmacology and Pharmacokinetics**

The compound glucosamine sulfate can be derived from chitin (the second most abundant polymer on earth) or can be produced by synthetic means. Glucosamine sulfate is commercially available as an oral dietary supplement, either alone or in combination with other ingredients, including magnesium, copper, zinc, selenium salts, and vitamins A and C. Glucosamine is also commonly formulated with chondroitin sulfate. It has been safely administered to patients with a variety of medical conditions, including circulatory diseases, liver disorders, lung disease, diabetes, and depression.<sup>7</sup> An injectable form of glucosamine is available outside the United States.

Most clinical trials utilize glucosamine sulfate in oral doses of 1,500 mg daily (500 mg three times daily). Some patients exhibit a more rapid response with higher amounts (dosages of up to 1 g three times daily). Commercial products carry dosage recommendations of 500 mg three times daily to 1,000 mg twice daily. It has been suggested that individuals with peptic ulcer disease, those taking diuretics, and obese patients require a higher dose of glucosamine sulfate, as they have been noted to exhibit a below-average response to 1,500 mg daily. Such findings imply that dosing recommendations should be based on a patient's weight.

Adverse reactions to oral glucosamine are infrequent and most often not serious, consisting primarily of gastrointestinal disturbances that are reversed after discontinuation of treatment.<sup>6</sup> Other complaints include headache, nausea and vomiting, dyspepsia, heartburn, constipation, abdominal pain, edema, pain or a sensation of heaviness in the legs, palpitations, exhaustion, and skin reaction.

Glucosamine sulfate is the most readily available form of glucosamine. Glucosamine sulfate is a small, water-soluble molecule that is readily absorbed by the gastrointestinal tract (90% absorption) by carrier-mediated transport.<sup>8</sup> It is not clear whether the glucosamine sulfate molecule is absorbed in its entirety or is degraded prior to absorption. Bioavailability in humans after first-pass metabolism by the liver is approximately 26% for the oral preparation, 96% for the intramuscular form, and 100% for the intravenous agent.

The actual metabolic uptake of orally administered chondroitin sulfate has been found to be inconsistent—possibly because of variation in the structure, biochemical properties, and molecular weights of the various preparations. Baici et al<sup>9</sup> investigated the impact of oral chondroitin sulfate on the concentration of glycosaminoglycans in human serum. In that study, chondroitin sulfate was not absorbed either in an intact form or as a sulfated oligosaccharide and did not produce any measurable change in the total serum concentration of glycosaminoglycans. The authors concluded that the theory that orally administered chondroitin sulfate alone offers chondroprotection is biologically and pharmacologically unfounded.

Morrison<sup>10</sup> found the absorption rate of chondroitin 4-sulfate to be between 0% and 8%. However, in another study,<sup>11</sup> when a radiolabeled preparation of a commercial chondroitin sulfate preparation (Condrosulf [IBSA, Lugano, Switzerland]) was administered orally to both rats and dogs, the rate of absorption of the radioisotope was 70%, although only 8.5% of the radioactivity was associated with an intact molecule of chondroitin sulfate. The same authors administered Condrosulf to healthy human volunteers and found both an in-

crease in plasma concentrations of exogenous molecules associated with chondroitin sulfate and an increase in hyaluronic acid and sulfated glycosaminoglycan content in synovial fluid. They speculated that this increase can be attributed, at least in part, to exogenous chondroitin sulfate. Despite the structural similarity between chondroitin sulfate and heparin, there are at present no data suggesting that chondroitin sulfate is relatively contraindicated if the patient is receiving anticoagulation therapy.

In vitro experiments have shown that the administration of glucosamine sulfate to human chondrocytes in tissue culture leads to its incorporation into glycosaminoglycan composition as well as to the activation of core-protein synthesis, thus promoting proteoglycan production.<sup>12,13</sup> Other reports assert that the chondroprotective action of glucosamine is due to enhanced synovial production of hyaluronic acid.<sup>14</sup> This theory proposes that the maintenance of normal hyaluronic acid levels within joint spaces may down-regulate the mechanisms that result in cartilage degradation and pain in patients with osteoarthritis.

When added to chondrocyte tissue cultures, chondroitin sulfate has been shown to (1) influence the in vitro growth and metabolism of glycosaminoglycans; (2) increase total proteoglycan production by healthy cells, and (3) inhibit the collagenolytic activity of normal chondrocytes.<sup>15</sup> Its mechanism of action may be related to its role as a substrate for proteoglycan synthesis. Other authors have proposed that the chondroprotective properties of chondroitin sulfate and glucosamine sulfate are related to the sulfate component in both of these compounds, as sulfur is an essential element for the stabilization of the extracellular matrix of connective tissue.

The potential role of glucosamine as an anti-inflammatory agent has also been investigated in studies employing animal models. According to Setnikar,<sup>3</sup> the effects of oral glucosamine are best described as antireactive rather than anti-inflammatory. Although glucosamine does not appear to be effective in inhibiting either cyclooxygenase or proteolytic enzymes involved in inflammation, its antireactive properties are likely due to its ability to synthesize proteoglycans needed for the stabilization of cell membranes and the production of intracellular ground substance. Because the anti-inflammatory mechanism of action of glucosamines is different from that of nonsteroidal anti-inflammatory drugs (NSAIDs), it is conceivable that these two treatment modalities may work synergistically to alleviate the symptoms of osteoarthritis in some patients. There is evidence that glucosamine in combination with indomethacin, piroxicam, or diclofenac sodium decreases the amount of NSAID needed to produce an antiedematous outcome.<sup>16</sup>

Chondroitin sulfate may also possess some anti-inflammatory potential. Ronca et al<sup>17</sup> showed that although it is less effective than indomethacin and ibuprofen, chondroitin sulfate effectively inhibits directional chemotaxis, phagocytosis, and the release of lysosomal contents characteristic of the inflammatory response.

## Clinical Trials

### Glucosamine vs Control

The majority of clinical trials performed to evaluate the efficacy of glucosamine in the treatment of osteoarthritis have demonstrated a decrease in joint pain, tenderness, and swelling and an increase in mobility<sup>7,18-25</sup> (Table 1). In 1981, D'Ambrosio et al<sup>20</sup> examined the

**Table 1**  
**Summary of Results in Glucosamine Sulfate Trials**

Author(s)	Year	No. of Patients	Follow-up Period	Complications*	Results
Crolle and D'Este <sup>7</sup>	1980	30	3 wk	None	Overall symptom score improved by 65% after week 1, additional improvement by 15% at week 3
Drovanti et al <sup>18</sup>	1980	80	30 d	Few and minor (nausea, constipation, heartburn)	73.3% reduction in overall symptoms compared with 41.3% in placebo group; cartilage specimens from glucosamine group were "smoother" and more "orderly" than those in placebo group
Pujalte et al <sup>19</sup>	1980	20	6-8 wk	No serious events (dizziness in 1)	Considerable alleviation of self-assessed degree of articular pain, tenderness, and swelling with glucosamine
D'Ambrosio et al <sup>20</sup>	1981	30	3 wk	None	58% decrease in overall symptoms during initial week of therapy; additional 13% decline at day 21
Lopes Vaz <sup>21</sup>	1982	40	8 wk	Mild (heartburn, epigastric pain, abdominal pain, nausea, headache)	Pain scores were lower for ibuprofen compared with placebo at week 1, lower for glucosamine compared with ibuprofen at week 8
Rovati <sup>22</sup>	1992	252	4 wk	Mild (allergy and GI upset)	Reduction in symptoms was 55% in glucosamine group vs 38% in placebo group
Müller-Fassbender et al <sup>23</sup>	1994	199	4 wk	35% ibuprofen, 6% glucosamine, (mild GI upset)	Quicker response time for pain relief with ibuprofen; ibuprofen benefits stabilized after week 2; patients receiving glucosamine continued to improve
Reichelt et al <sup>24</sup>	1994	155	4 wk	Well-tolerated	Reduction in symptoms was 55% in glucosamine group vs 33% in placebo group
Qiu et al <sup>25</sup>	1998	178	4 wk	16% ibuprofen, 6% glucosamine (mild sleepiness, nausea, GI upset)	At 4 weeks, both glucosamine and ibuprofen groups showed reduction in knee pain (57% vs 51%, respectively) and swelling (77% and 78%)

\* GI = gastrointestinal.

efficacy of glucosamine in a randomized study of 30 patients with a history of chronic osteoarthritis. Half received daily intramuscular injections of 400 mg of glucosamine sulfate for 1 week, followed by 2 weeks of oral glucosamine sulfate, 1,500 mg (500 mg three times daily). The other half (control group) received daily injections of antiar-

thritic medication containing piperazine bisiodomethylate, 100 mg; piperazine thiosulfate, 100 mg; and trichloro-*t*-butanol, 5 mg, for 1 week, followed by 2 weeks of placebo. There was a 58% decrease in overall symptoms during the initial week of therapy with injectable glucosamine, followed by an additional 13% decline in overall symptoms at

day 21 ( $P < 0.05$  and  $P < 0.01$ , respectively). The composite scores were markedly lower for glucosamine compared with placebo (weeks 2 and 3), and the overall scores for patients receiving placebo therapy regressed to pretreatment levels by the completion of the study. Glucosamine sulfate was well tolerated, and no adverse effects were ob-

served. The limitations of this study included an absence of efficacy comparisons between the routes of administration.

Crolle and D'Este<sup>7</sup> found that glucosamine sulfate caused a 65% improvement in overall symptom score compared with placebo administration during week 1, followed by an additional 15% improvement over the following 2 weeks ( $P<0.01$ ). No appreciable adverse effects were noted.

A larger, randomized, double-blind, placebo-controlled study was conducted in 1980 in Italy by Drovanti et al.<sup>18</sup> Eighty patients with established osteoarthritis received either oral glucosamine sulfate (500 mg three times daily) or placebo for 30 days. Those treated with glucosamine sulfate experienced a 73.3% reduction in overall symptoms, compared with 41.3% in the placebo group ( $P<0.001$ ). Physicians rated the results of glucosamine therapy as excellent or good in 29 of 40 patients who received it, compared with 17 of 40 who received placebo ( $P<0.005$ ).

Another prospective, double-blind trial by Pujalte et al<sup>19</sup> in 1980 evaluated the use of glucosamine sulfate in 20 ambulatory patients with osteoarthritis of the knee. Half the patients received oral glucosamine sulfate, 500 mg three times daily; the other half received placebo for 6 to 8 weeks. There was a greater improvement in overall composite scores for patients who received glucosamine sulfate than in those given placebo ( $P<0.01$ ). Further analysis of the results revealed that 80% of the patients who received glucosamine sulfate, but only 20% of those who received placebo, experienced diminished or complete resolution of joint pain and tenderness ( $P<0.01$ ). Those who were treated with glucosamine sulfate encountered earlier relief of pain, joint tenderness, and swelling than placebo patients ( $P<0.01$ ).

The largest multicenter, randomized, double-blind, placebo-controlled parallel-group study was performed by Rovati<sup>22</sup> in Europe. A total of 252 patients with osteoarthritis in the knee were treated with either oral glucosamine sulfate (500 mg three times a day) or placebo over a 4-week period. Of the 241 patients who completed the trial, 55% of those who received glucosamine sulfate had a significant reduction in symptoms, compared with 38% who received placebo ( $P<0.05$ ).

In the multicenter, prospective, randomized, placebo-controlled trial reported by Reichelt et al,<sup>24</sup> 155 patients received intramuscular injections of 400 mg of glucosamine sulfate or 0.9% saline solution bi-weekly for 6 weeks. Use of NSAIDs, other analgesics, or oral corticosteroids was not permitted. In the 142 patients who completed the study, there was a significant ( $P=0.012$ ) difference in response rate between patients treated with glucosamine (55% [40 of 73]) and those treated with placebo (33% [23 of 69]).

### Chondroitin Sulfate vs Control

A number of clinical trials have examined the effects of chondroitin sulfate<sup>26-32</sup> (Table 2). The most frequently studied therapeutic agents containing chondroitin sulfate are derivative products, such as glycosaminoglycan polysulfate (Arteparon [Luitpold, Munich, Germany]), galactosaminoglycan polysulfate, and chondroitin sulfate (Condrosulf and Structum [RobaPharm, Allschwil, Switzerland]).

In one randomized, double-blind, placebo-controlled clinical trial, Bucsi and Poór<sup>30</sup> examined the efficacy of oral chondroitin sulfate (Condrosulf) in 80 patients with symptomatic osteoarthritis of the knee. Chondroitin sulfate, 800 mg, or placebo was given daily for 6 months. At the completion of the trial, there was a 43% reduction in joint pain in the

chondroitin sulfate group, compared with only 3% in the placebo group ( $P<0.01$ ). The chondroitin sulfate group also exhibited significantly greater improvement in walking time ( $P<0.05$ ), and the patients' pain scores improved consistently (by 15%, 24%, and 37% at months 1, 3, and 6, respectively), while the scores for the placebo group showed little variation ( $P<0.01$ ).

Uebelhart et al<sup>31</sup> reported the results of a randomized, double-blind, controlled trial involving 46 patients with symptomatic osteoarthritis of the knee. Chondroitin sulfate was well tolerated and significantly diminished joint pain ( $P<0.05$ ) and improved overall mobility ( $P<0.001$ ).

In Rovetta's double-blind, placebo-controlled study, chondroitin sulfate was given by 50 intramuscular injections over 25 weeks to 40 patients with osteoarthritis in the knee.<sup>26</sup> A statistically significant ( $P<0.01$ ) therapeutic effect on all symptoms of joint pain was observed. Oliviero et al<sup>27</sup> also reported favorable effects of chondroitin sulfate in diminishing joint pain and improving mobility when given both orally and intra-articularly to elderly patients with osteoarthritis. In recent studies, several authors have alleged that, in addition to providing symptomatic relief, chondroitin sulfate is directly responsible for an increase in cartilage height and radiographic improvement of osteoarthritic changes when compared with placebo.<sup>31,32</sup> However, no compelling data exist as yet to substantiate such claims.

### Glucosamine Sulfate or Chondroitin Sulfate vs NSAIDs

The efficacy and safety of glucosamine sulfate for the treatment of osteoarthritis have been compared with those of NSAIDs in several recent studies. A double-blind, randomized trial involving 40 outpatients with unilateral knee osteoarthritis compared the efficacy of

**Table 2**  
**Summary of Results in Chondroitin Sulfate Trials**

Author(s)	Year	No. of Patients	Follow-up Period	Complications	Results
Rovetta <sup>26</sup>	1991	40	25 wk	None (drug "well tolerated")	Higher therapeutic effect on all symptoms of osteoarthritis
Oliviero et al <sup>27</sup>	1991	200	6 mo	3% "mild" adverse effects	Considerable improvement in both pain and mobility
Morreale et al <sup>28</sup>	1996	146	3 mo	Few, minor	NSAIDs gave prompt reduction of clinical symptoms, but symptoms reappeared at the end of treatment; benefits of chondroitin sulfate appeared later but lasted for up to 3 months after end of treatment
Bourgeois et al <sup>29</sup>	1998	127	3 mo	No major events	Significant ( $P<0.01$ ) reduction in joint pain with both doses vs placebo
Bucsi and Poór <sup>30</sup>	1998	80	6 mo	Few, minor (1 GI upset)	43% reduction in joint pain vs 3% in control group
Uebelhart et al <sup>31</sup>	1998	42	1 yr	None (drug "well tolerated")	Decreased joint pain and improved overall mobility; also stabilized medial femorotibial joint width
Verbruggen et al <sup>32</sup>	1998	119	3 yr	Not documented	Radiographic demonstration of decrease in number of patients with "new" erosive finger-joint osteoarthritis (8.8% vs 29.4%)

glucosamine sulfate and ibuprofen over an 8-week period.<sup>21</sup> Patients received either glucosamine sulfate, 500 mg, or ibuprofen, 400 mg, three times daily for 8 weeks. At week 1, the mean pain score for the ibuprofen group was significantly lower than that for the glucosamine sulfate group ( $P<0.01$ ). At week 8, the pain score for the glucosamine sulfate group was significantly lower than that for the ibuprofen group ( $P<0.05$ ). Unlike the response to ibuprofen, the response to glucosamine sulfate continued to improve throughout the trial period ( $P<0.05$ ). The attending physician rated the overall efficacy as good in 8 of 18 glucosamine sulfate-treated patients (44%) but in only 3 of 22 ibuprofen-treated patients (14%). The limitations of this study included small sample size and short treatment follow-up.

Another randomized, double-blind, parallel study compared the efficacy of orally administered glucosamine sulfate and ibuprofen in 199 patients with osteoarthritis of the knee.<sup>23</sup> Patients received daily doses of ibuprofen, 1,200 mg (400 mg three times daily), or glucosamine sulfate 1,500 mg (500 mg three times daily). A difference with respect to response time was found between the groups, with glucosamine requiring 2 weeks to achieve the same degree of pain relief achieved with ibuprofen in the first week. As in the previously cited study, the benefits of ibuprofen appeared to stabilize after the first 2-week period, while patients taking glucosamine sulfate continued to improve in subsequent weeks. At the end of the treatment period, it was shown that both agents reached

a similar therapeutic level and that there was no significant difference in success rates between the groups: 52% for the ibuprofen group versus 48% for the glucosamine-treated group ( $P = 0.67$ ). A significant disparity in the incidence of adverse effects of the two treatments was found, however: 35% in the ibuprofen group versus 6% in the glucosamine sulfate group ( $P<0.001$ ).

A more recent study from China was performed on 178 patients with osteoarthritis of the knee.<sup>25</sup> Patients were randomized into two groups, one treated for 4 weeks with glucosamine sulfate, 1,500 mg (500 mg three times daily), and the other with ibuprofen, 1,200 mg (400 mg three times daily). At 4 weeks, administration of either glucosamine sulfate or ibuprofen resulted in reduced knee pain relative to baseline

values (by 57% and 51%, respectively) and knee swelling (by 77% and 78%, respectively). However, there was no statistically significant difference in the effectiveness of the two agents. Glucosamine sulfate was significantly ( $P = 0.01$ ) better tolerated than ibuprofen as measured by the incidence of adverse drug reactions (6% in the glucosamine sulfate group vs 16% in the ibuprofen group).

Morreale et al<sup>28</sup> compared the efficacy of chondroitin sulfate in the treatment of knee osteoarthritis with that of NSAIDs (diclofenac sodium). Patients treated with NSAIDs showed a prompt reduction in clinical symptoms; however, these symptoms re-emerged soon after the discontinuation of therapy. Patients treated with chondroitin sulfate tablets, despite having a slower initial response, exhibited a more favorable outcome 3 months after discontinuation of treatment.

A notable limitation of all the aforementioned studies comparing glucosamine sulfate or chondroitin sulfate with NSAIDs is the absence of a control (placebo) group.

### Combination Therapy

One recent study examined the effects of simultaneous administration of glucosamine and chondroitin sulfate on osteoarthritis.<sup>33</sup> In a 16-week randomized, double-blind, placebo-controlled crossover trial, a combination of glucosamine hydrochloride (1,500 mg/day),

chondroitin sulfate (1,200 mg/day), and manganese ascorbate (228 mg/day) was given to 34 male subjects from the US Navy diving and special warfare community with chronic back pain and radiographic evidence of osteoarthritis of the knee or low back. A summary disease score incorporated physical examination scores, pain and functional questionnaire responses, and running times. The study demonstrated greater effectiveness of this combination regimen compared with placebo in symptomatic relief as measured by the summary disease score ( $-16.3%$  [ $P < 0.05$ ]), patient assessment of treatment effect ( $P < 0.05$ ), and visual analog scale for pain ( $-28.6%$  [ $P < 0.05$ ]). This study neither demonstrated nor excluded a therapeutic benefit for this combination of drugs in the treatment of spinal degenerative joint disease. In the limited number of studies on combination therapy, there is no suggestion of an increased incidence of adverse effects when these two agents are administered together.

### Summary

Glucosamine and chondroitin sulfate have been widely acclaimed in the popular press as a panacea for the treatment of osteoarthritis. These agents are proposed to act by virtue of their chondroprotective

properties. Thus far, the vast majority of studies conducted that have supported both glucosamine and chondroitin sulfate for the relief of the symptoms of osteoarthritis have been based on clinical trials with short-term follow-up. These studies have demonstrated a progressive and gradual decline of joint pain and tenderness, improved mobility, and sustained improvement after drug withdrawal. In addition, there are fewer side effects when compared with other drugs used to treat the symptoms of osteoarthritis, as well as a lack of toxicity associated with short-term use of these agents.

Many unanswered questions remain surrounding their long-term effects (whether beneficial or adverse), the most effective dosage and route, and product purity. A well-designed prospective study of glucosamine sulfate and chondroitin sulfate demonstrating that these agents are effective for the prevention and treatment of osteoarthritis has yet to be conducted. Such a lack of substantial and conclusive evidence underlies the refusal of the Arthritis Foundation to support the use of glucosamine sulfate or chondroitin sulfate for the treatment of osteoarthritis or any other form of arthritis. Despite these controversies, patients continue to use such alternative forms of therapy to alleviate the painful effects of this prevalent disease process.

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