

A Review of Evidence-Based Medicine for Glucosamine and Chondroitin Sulfate Use in Knee Osteoarthritis

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Abstract: The investigation of disease-modifying treatment options for osteoarthritis (OA) has become an important aspect of orthopaedic care. The purpose of this review is to critically evaluate the evidence for the use of glucosamine and chondroitin sulfate for knee OA with the goal of elucidating their indications for clinical use. The published clinical studies of glucosamine and chondroitin sulfate on OA are reviewed within the context of evidence-based medicine. Almost every included trial has found the safety of these compounds to be equal to placebo. In the literature satisfying our inclusion criteria, glucosamine sulfate, glucosamine hydrochloride, and chondroitin sulfate have individually shown inconsistent efficacy in decreasing OA pain and improving joint function. Many studies confirmed OA pain relief with glucosamine and chondroitin sulfate use. The excellent safety profile of glucosamine and chondroitin sulfate therapy should be discussed with patients, and these supplements may serve a role as an initial treatment modality for many OA patients. **Key Words:** Glucosamine sulfate—Glucosamine hydrochloride—Chondroitin sulfate—Knee osteoarthritis—Nutritional supplement.

As the most common musculoskeletal disease in the United States, osteoarthritis (OA) has long been a topic of intense research and debate. Knowledge about the biomechanical and biochemical progression of the disease continues to improve but remains deficient.¹⁻⁵ Even worse for the some 40 million Americans incurring pain and disability from the disease, research has resulted in only minimal advances in its treatment.^{4,6} Symptomatic therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) remains the

status quo despite questionable efficacy and significant risks such as peptic ulcer disease, renal failure, and hemorrhage.⁷ With the prevalence of OA expected to double in the next 20 years and NSAID-related gastropathy currently the second most deadly rheumatic disease,^{7,8} the investigation of disease-modifying treatment options for OA has become an important aspect of orthopaedic care.

Glucosamine and chondroitin sulfate (CS), both components to the extracellular matrix of articular cartilage, have been used for medicinal purposes for nearly 40 years.⁹ After gaining popularity in Europe and Asia for the treatment of arthritis for the last 20 years, they gained popularity in the United States after the release of several lay publications in the late 1990s.¹⁰

One of the earliest studies to use glucosamine and CS for the treatment of the signs and symptoms of OA was a 1969 study by Vetter⁹ that showed a decrease in joint symptoms with topical application. In the following decades, numerous studies were designed to investigate the effects of glucosamine hydrochloride

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(GH), glucosamine sulfate (GS), and CS on outcomes such as joint space narrowing, functionality, and pain. Although many trials have been published showing significant treatment effects with these nutritional supplements, they have been largely ignored by the medical community in the United States because of their questionable quality.

Glucosamine and CS studies have been criticized for small sample sizes, confirmation of supplement quality, short length of therapy, potential bias because of manufacturer's sponsorship of the studies, inadequate masking of the study agent, and failure to adhere to the intention-to-treat principle. Despite these weaknesses, meta-analyses have concluded that these supplements likely have some efficacy in treating the symptoms of OA with possible disease-modifying effects. Combined with a strong safety profile, such conclusions have created support for glucosamine and CS in medical circles and the public eye.

The purpose of this review is to critically evaluate the evidence for the use of glucosamine and CS for OA with the goal of elucidating their indications for clinical use. It is necessary to evaluate each supplement independently (GS, GH, and CS) and jointly as a pair (glucosamine plus CS). Although placebo-controlled, "randomized," double-blind studies date back 25 years, many of the older trials are difficult to analyze because of sponsorship from manufacturers and inadequate product concealment. Specifically, this review article focuses on dou-

ble-blind, placebo-controlled, randomized controlled trials (RCTs) using glucosamine and CS for knee OA that have incorporated established outcome measurement methods.

SPECIFIC SUPPLEMENT STUDIES

Chondroitin Sulfate

In 1998 Bucsi and Poór¹¹ evaluated the use of CS on OA symptoms (Table 1). They measured clinical symptoms via Lequesne's index, the occurrence of spontaneous joint pain, and 20-minute walk time in 80 OA patients who underwent 6 months of therapy with 800 mg of CS sulfate or placebo. A statistically significant improvement was shown in all 3 tested measurements over placebo with no difference in side effects. In the same year Bourgeois et al.¹² performed a similar study to determine whether the dosing schedule of CS had any impact on the efficacy of the treatment. In this 3-month trial, 1,200 mg of CS (administered either as a single dose or as 3 equally divided doses) reduced Lequesne's index and spontaneous joint pain scores versus placebo ($P < .01$). Dosing schedules supported once-a-day administration. In a randomized clinical trial, Conrozier¹³ used an 800-mg dose in 104 patients treated for 1 year. Functional impairment recovered by approximately 50%, with significant improvement over placebo for all clinical criteria.

TABLE 1. Summary of CS RCTs

Study	No. of Patients	Length	Substance	Outcome Measures
Michel et al. ¹⁸ (<i>Arthritis Rheum</i> 2005)	300	2 yr	800 mg CS v placebo	(1) Joint space narrowing and (2) pain and function
Uebelhart et al. ¹⁶ (<i>Osteoarthritis Cartilage</i> 2004)	120	1 yr	800 mg CS per day for two 3-mo periods during 1 yr v placebo	(1) Lequesne's algofunctional index and (2) walking time, global judgment, and acetaminophen consumption
Mathieu ¹⁷ (<i>Presse Med</i> 2002)	300	2 yr	CS v placebo	Joint space loss
Mazieres et al. ¹⁴ (<i>J Rheumatol</i> 2001)	130	6 mo	1 g CS per day v placebo for 3 mo with 3-mo post-therapy follow-up	Lequesne's algofunctional index
Bourgeois et al. ¹² (<i>Osteoarthritis Cartilage</i> 1998)	127	3 mo	1,200 mg CS v 400 mg CS 3 times per day v placebo	Lequesne's algofunctional index and spontaneous joint pain (visual analog scale)
Bucsi and Poór ¹¹ (<i>Osteoarthritis Cartilage</i> 1998)	80	6 mo	400 mg CS 2 times per day v placebo	Lequesne's index, spontaneous joint pain (visual analog scale), and 20-min walk time
Conrozier ¹³ (<i>Presse Med</i> 1998)	104	1 yr	800 mg every day v placebo	Lequesne's index and joint space loss
Mazieres et al. ¹⁵ (<i>Ann Rheum Dis</i> 2007)	307	6 mo	1,000 mg CS per day	Lequesne's algofunctional index

In a study by Mazieres et al.¹⁴ published in 2001, 130 patients were randomized to receive 1,000 mg of CS daily for 3 months and were followed up for an additional 3 months after therapy. Lequesne's index significantly improved ($P = .02$) and remained elevated for 1 month after treatment. These findings did not reach significance when the results were viewed with an intention-to-treat analysis. Mazieres et al.¹⁵ also evaluated 307 patients with knee OA for 6 months using CS. They failed to show any efficacy compared with controls.

Uebelhart et al.¹⁶ randomized 120 patients to receive placebo or 800 mg of CS for two 3-month periods during a period of 1 year. They showed a 36% improvement in Lequesne's index scores in the CS group whereas the placebo group only improved by 26%. This significant decrease in pain with improved function showed a long-term benefit with intermittent CS therapy.

Mathieu,¹⁷ in a double-blind prospective study of 300 patients in 2002, showed that over a 2-year period, CS reduced the radiographic progression of OA when compared with controls. In the CS group the radiologic parameters remained stable. These results were further supported by the 2005 study of Michel et al.,¹⁸ which also showed a retardation of joint space narrowing in patients who received the same nutritional supplement for a 2-year period. Together, these studies suggest a disease-modifying role of CS.

Michel et al.¹⁸ performed an RCT in 300 patients with OA, testing 800 mg of CS against placebo for 2 years. They evaluated joint space narrowing as a primary outcome, with pain and function as secondary outcomes. They found no significant symptomatic effects between the treatment groups and concluded that CS may retard radiographic progression in patients with OA of the knee. Future evaluation of these structural observations was recommended. However, large well-designed studies are necessary to prove such an effect, especially with respect to the reproducibility and consistent measurement of joint space narrowing.

Glucosamine Sulfate

GS is one of the most studied dietary supplements available today (Table 2). In the last 30 years, many trials have been conducted and published on the effects of glucosamine on the signs and symptoms of OA.⁹

Müller and colleagues¹⁹ evaluated the short-term 4-week effects of 1,200 mg of GS using Lequesne's severity index and looked at the relative risks of side effects in the GS group versus the ibuprofen group. In this short 1-month study, GS was as effective as ibuprofen and significantly better tolerated ($P < .001$). Only 6% of patients taking GS reported adverse events, whereas 35% of ibuprofen users had an adverse event (mainly gastrointestinal in origin).

TABLE 2. Summary of GS RCTs

Study	No. of Patients	Length	Substance	Outcome Measures
Bruyere et al. ²⁴ (<i>Menopause</i> 2004)	414 (all postmenopausal women)	3 yr	1,500 mg GS per day v placebo	Minimal joint space width and WOMAC for pain
Pavelká et al. ²³ (<i>Arch Intern Med</i> 2002)	202	3 yr	1,500 mg GS per day v placebo	Lequesne's index, WOMAC, and minimal joint space
Reginster et al. ²² (<i>Lancet</i> 2001)	212	3 yr	1,500 mg GS per day v placebo	WOMAC and minimal joint space
Noack et al. ²⁰ (<i>Osteoarthritis Cartilage</i> 1994)	252	4 wk	500 mg GS 3 times per day v placebo	Lequesne's severity index
Muller-Fassbender ⁴³ (<i>Am J Med</i> 1987)	200 (all inpatients)	4 wk	400 mg GS 3 times per day v ibuprofen	Lequesne's severity index
Reichelt et al. ²¹ (<i>Arzneimittelforschung</i> 1994)	155	6 wk	400 mg GS intramuscularly twice per wk for 6 wks	Lequesne's severity index
Bruyere et al. ²⁵ (<i>Osteoarthritis Cartilage</i> 2003)	212	3 yr	1,500 mg GS per day	Joint space narrowing
Cibere et al. ²⁶ (<i>Arthritis Rheum</i> 2004)	137	6 mo	1,500 mg CS per day v placebo	Lequesne's index and WOMAC
Herrero-Baumont et al. ²⁷ (<i>Arthritis Rheum</i> 2007)	318	6 mo	1,500 mg v placebo	Lequesne's index and WOMAC
Hughes and Carr ²⁸ (<i>Rheumatology (Oxford)</i> 2002)	80	6 mo	1,500 (500) mg TID GS/d v placebo	Pain scores on visual analog scale, WOMAC, and McGill pain index

Noack et al.²⁰ published a 4-week study comparing GS with placebo rather than ibuprofen. This short study of 252 patients showed that GS was more effective than placebo in improving OA symptomatology. Patients in the GS arm of the trial enjoyed a 3.3-point drop in Lequesne's severity index, whereas those taking the placebo improved by 2.0 points. A 6-week study by Reichelt et al.²¹ showed GS to decrease Lequesne's index over placebo in 155 patients. Unfortunately, these studies are too short to make significant long-term conclusions.

In 2001 Reginster et al.²² published the results of a trial in which 212 patients were randomized to receive placebo or GS daily for 3 years. Glucosamine was shown to protect the joint space from the narrowing effects of OA. A trend toward improving Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores was seen without any statistically significant change.

A similar study by Pavelká et al.²³ supported the findings of Reginster et al.,²² proving statistically significant effects of glucosamine on both radiographic progression and WOMAC scores.

Bruyere et al.²⁴ used the same outcome measures of joint space narrowing and WOMAC scores to prove that the disease-modifying effects seen in the study of Pavelká et al.²³ were also found in the older postmenopausal female population. Bruyere et al.²⁵ investigated joint space narrowing in 212 knee OA patients at 3 years. Patients with less severe radiographic knee OA had the most dramatic disease progression as seen by joint space narrowing. The GS group, compared with the placebo group, showed a nonstatistical trend in significant reduction of joint space narrowing.

Cibere et al.²⁶ tested GS in a 4-center 6-month randomized, double-blind, placebo-controlled study. No differences were found in the severity of disease pain episodes (flare-ups) or other secondary outcomes between placebo- and glucosamine-treated patients. They concluded that there was no evidence of symptomatic benefits from continued GS use from this 6-month study.

Herrero-Beaumont et al.²⁷ evaluated 318 patients with knee OA in an RCT comparing GS, acetaminophen (Tylenol; McNeil Consumer Healthcare, a divi-

sion of Johnson & Johnson, Guelph, Ontario, Canada), and placebo. After 6 months, 1,500 mg of GS was found to be better than placebo and acetaminophen by use of Lequesne's index and the WOMAC.

Hughes and Carr²⁸ performed a randomized clinical trial with GS in 80 OA patients for 24 weeks. They found a 33% placebo response rate and no statistical improvement over placebo as a symptom modifier.

Collectively, these GS studies showed that GS as an individual agent may have some effect on the progression of the disease and was as safe as placebo at a dose of 1,200 to 1,500 mg/d for up to 3 years. Many studies had a short-term follow-up, and the evidence inconsistently supported the use of glucosamine as an effective alternative to higher-risk medications such as NSAIDs and cyclooxygenase II inhibitors for knee OA.

Glucosamine Hydrochloride

The hydrochloride salt of glucosamine is a common glucosamine product, yet it has received relatively little attention from researchers (Table 3). Houpt et al.²⁹ were unable to show statistically significant changes in the WOMAC pain score subset versus placebo after a short period of therapy with GH (8 weeks). All tested parameters tended to show improvement, and GH did significantly reduce the daily pain reported by patients ($P = .018$) and improved findings on clinical knee examination ($P = .026$). GH was shown to be as safe as placebo. Though failing to prove its primary outcome measure, this study suggested that GH benefited some patients with OA without the side effects of other treatment modalities. McAlindon et al.³⁰ performed a 12-week GH study on 205 patients, recruited over the Internet. By use of the WOMAC as the primary outcome, GH was safe but no more effective than placebo in treating symptoms of knee arthritis.

Glucosamine and CS

The highly publicized Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) was published in the *New England Journal of Medicine* early in 2006 (Table 4).³¹ The multicenter trial assigned 1,583 patients to randomly receive 1,500 mg glucosamine;

TABLE 3. Isolated GH Study for OA of Knee

Study	No. of Patients	Length	Substance	Outcome Measures
Houpt et al. ²⁹ (<i>J Rheumatol</i> 1999)	101	8 wk	GH	WOMAC pain scores
McAlindon et al. ³⁰ (<i>Am J Med</i> 2004)	205	12 wk	15 g GS per day v placebo	WOMAC

TABLE 4. *Glucosamine and CS RCTs*

Study	No. of Patients	Length	Substance	Outcome Measures
Alekseeva et al. ³³ (<i>Ter Arkh</i> 2005)	90 (all women)	6 mo	500 mg GH + 500 mg CS + diclofenac sodium 2 times per day for 1 mo and then 1 time per day for 5 mo v diclofenac sodium	WOMAC
Clegg et al. ³¹ (<i>N Engl J Med</i> 2006)	1,583	6 mo	1,500 mg GH v 1,200 mg CS v GH plus CS v 200 mg celecoxib v placebo	WOMAC and other indexes
Messier et al. ³⁴ (<i>Osteoarthritis Cartilage</i> 2007)	80	12 mo	1,500 mg GH, 1,200 mg CS	WOMAC and 6-min walk

1,200 mg CS; both GH and CS; 200 mg of celecoxib (Celebrex; Pfizer, New York, NY); or placebo for 24 weeks. Patients were allowed to take up to 4,000 mg of acetaminophen for rescue analgesia daily (no pain medications were taken within 24 hours of clinical examination). All patients in the study were aged at least 40 years, had both clinical evidence (knee pain for most days of the month for ≥ 6 months) and radiographic evidence of OA (osteophytes ≥ 1 mm), and WOMAC scores from 125 to 400. The primary outcome measure was a 20% decrease in the summed score for the WOMAC pain subscale from baseline to week 24. Over 40 secondary outcome measures were included in the study.

In the subgroup of 79 patients with moderate to severe pain (determined by a score of 300-400 on the WOMAC pain scale), GH and CS significantly reduced knee pain. In this subgroup of patients receiving GH and CS, 79% showed a 20% reduction in knee pain, whereas only 54.3% of the placebo group showed this improvement. However, GH and CS were not found to be significantly better than placebo in reducing knee pain by 20% from baseline in the pooled analysis of patients. Adverse effects were mild, infrequent, and evenly distributed across all groups tested, supporting the safety of these nutritional supplements.

Celecoxib was found to yield a statistically significant decrease in pain scores in the combined mild pain and moderate/severe pain subgroups but failed to have a significant effect on the pain scores in the moderate/severe pain subgroup. Celecoxib was also found to yield a faster decrease in pain scores, showing substantial decreases in pain scores at 4 weeks of treatment. Overall, celecoxib was found to have a significant effect on 6 of the 42 outcome measures followed in the study, whereas glucosamine and CS were found to have a significant effect on 14 of the 42 outcome measures.

This study, the largest and most rigorous of its kind, showed that GH and CS had a significant effect on

patients with more severe OA. Questions remain about the usefulness of glucosamine and CS in mild OA and their effect on other parameters such as joint function, stiffness, and joint space narrowing. Limitations of the study noted by the authors were the high rate of response to placebo (60%) and the relatively mild degree of OA pain among the participants. Concomitant treatments, such as physical therapy, were not clarified. These limitations decreased the ability of the study to detect the benefits of treatment. Studies with alternative medical therapies have shown a higher placebo response rate.³² Celecoxib at 200 mg/d had noticeably smaller effects in the GAIT study compared with earlier studies.

The GAIT study was designed to include 1,588 patients to provide the study with statistical power to detect 1 or more clinically meaningful differences based on an assumed placebo response rate of 35%. When this placebo response rate nearly doubled, the number of participants needed to obtain a similar statistical power increased substantially. With far too few patients given its placebo response rate, the data were barely able to prove its control (celecoxib) in the primary outcome measure ($P = .04$) and was unable to do so in the moderate/severe pain subgroup. Furthermore, the choice of the product tested (GH) has been called into question given the fact that GS has been more rigorously studied in the literature. The GAIT authors also chose less sophisticated methods for dealing with missing data, using the last observation-carried forward method rather than the multiple imputation method.

Alekseeva et al.³³ examined 90 women aged between 40 and 75 years with Kellgren-Lawrence stage II or III knee OA who had pain after 40 minutes of walking and regularly took NSAIDs for pain relief. The patients were randomly selected either to receive 500 mg of the glucosamine and CS supplements with optional diclofenac (50 mg) or to receive a placebo and optional diclofenac for a total of 3 months. The results were measured by the

WOMAC, daily need for NSAIDs, and evaluation of efficacy by the patient and the physician after 1 and 3 months of treatment and again 3 months after the oral supplementation had been stopped. The true WOMAC score decreased after 3 months of therapy and 3 months after the supplementation had been stopped ($P < .03$). At the end of the 3 months of therapy, the study group exhibited decreases in pain scores ($P = .008$) and increases in subjective functional ability. The patients taking the glucosamine and CS supplementation required less diclofenac. After 1 month of therapy, 4.5% stopped taking diclofenac and nearly 40% stopped taking it by the end of the study. Although limited by its size and the small subgroup that was studied (older women), this study showed that combined medications offer significant safety and effective pain relief in the short term with long-lasting effects.

Messier et al.,³⁴ in a double-blind 12-month GH/CS study with 80 patients, incorporated 6 months of exercise after 6 months of a non-exercising treatment. The primary end-point was the WOMAC and functional measures such as the 6-minute walk. At 12 months, there was no difference between groups for the 6-minute walk, knee strength, mobility, and function over the placebo treatment.

Meta-Analyses of Glucosamine and CS Studies

Several important meta-analyses have been published in recent years about the efficacy of glucosamine and CS therapy. By performing exhaustive searches in the literature and applying systematic quality assessment of these studies, these meta-analyses provided pooled information from the many pre-existing small studies.

McAlindon et al.³⁵ examined 15 double-blind, randomized, placebo-controlled trials of 4 weeks' duration or longer for their impact on the symptoms of hip and/or knee OA. They included studies of glucosamine and CS with various routes of administration, including oral, intramuscular, intravenous, and intra-articular. Very few of the examined studies described adequate allocation concealment or use of an intention-to-treat analysis. They also found evidence of significant publication bias, likely because of manufacturer's sponsorship of trials and the financial interests of the authors. When only the larger high-quality studies were evaluated, the effects of glucosamine and CS persisted, although they were noticeably diminished. This study also suggested that the full therapeutic benefit of these supplements likely did not occur in the first 4 weeks and that longer studies would be of significant value.

Richy et al.³⁶ examined both structural and symptomatic efficacy of CS and glucosamine. By examining structural changes via radiographic progression of joint space narrowing, this analysis was the first to evaluate the disease-modifying effects of these supplements. Evaluating the results of 15 studies that included data from 1,775 patients, the authors showed a statistically significant improvement in symptom scores with both glucosamine and CS therapy. They also were able to show a significant effect of glucosamine on the progression of joint space narrowing over a 3-year period, suggesting a disease-modifying effect of the compound (no such studies existed for CS). Importantly, the tolerance for these supplements was again shown to be equal to that of placebo.

Bjorral et al.³⁷ reviewed 63 RCTs using opioids, NSAIDs, glucosamine, CS, and acetaminophen (Tylenol; McNeil Consumer Healthcare) for knee OA including some 14,060 total patients. Acetaminophen, GS, and CS had maximum efficacies at 1 to 4 weeks with mild pain improvements. Overall clinical effects from these knee pharmacologic arthritic interventions were found to be small and limited to the first 2 to 3 weeks after the start of treatment.

Distler and Anguelouch³⁸ reviewed clinical evidence for glucosamine and CS studies analyzing RCTs. Their results were inconclusive regarding the continuous use of these nutraceuticals because of weak research design.

Reichenbach et al.³⁹ performed a meta-analysis of CS for OA of the knee or hip in 20 trials involving 3,846 patients. After analyzing the small and large studies, they found the trial quality to generally be low. They concluded that with the large-scale, methodologically sound trials, CS had minimal to nonexistent symptomatic benefit. They discouraged CS use by itself in routine clinical practice.

Leeb et al.⁴⁰ performed a meta-analysis of 7 trials of CS including 372 patients. They cited the difficulties in design with co-mixing of medications in several studies using the visual analog scale and Lequesne's index. The findings in the CS groups were significantly superior to those in the placebo groups. They called for better and longer time periods for symptom-modifying evaluations.

The Cochrane Review is perhaps the most thorough of the meta-analyses performed on glucosamine's effect on OA.⁴¹ Updated in January 2005, this meta-analysis followed 3 selection criteria: they were RCTs, they were either placebo controlled or comparative, and they were blinded (single or double were both accepted). Twenty articles were found to meet

the selection criteria, representing 2,570 patients. Cumulatively, these articles showed that glucosamine induced a 28% improvement from baseline in pain and a 21% improvement in function by use of Lequesne's index. In 8 articles that showed adequate allocation concealment, glucosamine failed to show a benefit for either pain or function. The Cochrane Review confirmed the safety findings of the incorporated studies, finding glucosamine to have adverse events equal to the placebo. Although these conclusions were significant for the number of studies they incorporate, they did have their limitations. This review was designed to include a broad selection of clinical trials, accepting short-term studies, comparative control studies, and single-blind studies. In accepting these lower-quality articles, the power of the pooled results was negatively impacted.

Other Sulfur-Containing Compounds

S-adenosylmethionine (SAMe) and methylsulfonylmethane (MSM) are market leaders among the sulfur-containing compounds advertised for joint health. Despite the public interest in these compounds, few well-designed studies have been completed. An open-label study in 1987 showed that SAMe increased joint mobility with no evaluation of pain or function.⁴² Subsequent double-blind placebo-controlled studies have supported the use of SAMe and shown it was effective as many anti-inflammatory and pain-relieving drugs.⁴³⁻⁴⁵

In 2004 Najm et al.⁴⁶ compared the efficacy of SAMe with Celebrex (Pfizer) for the symptoms of OA. In the first month of their 4-month study, celecoxib showed significantly more reduction in subjective pain reports by the participants ($P = .024$). By the second month, both study arms were equally effective in reducing pain ($P < .01$). This study noted increased functional health measures and increasing joint mobility in both treatment groups, without significant differences in side effects. These trends were not shown to be statistically significant.

Despite the presence of several studies suggesting the efficacy of MSM in reducing joint pain and enhancing mobility,^{47,48} the literature on MSM is deficient. With a paucity of research, as well as the short length of follow-up, it is difficult to recommend MSM at this time as an efficacious therapy for OA. Kim et al.⁴⁹ showed significant decreases in WOMAC pain (decrease of 25% from baseline) and physical function subcategories with MSM versus placebo. Improved performance of MSM users was seen in activities of daily life as

measured by the Short Form 36 score ($P = .05$), but this study found no significant improvement in the total aggregate WOMAC score at 3 months.

DISCUSSION

This review looked at the current research on the sulfur-containing nutraceuticals and their effects on proven outcome measures. In the literature satisfying our inclusion criteria, GS and CS have shown an inconsistent yet overall positive efficacy in decreasing OA pain and improving joint function. Most trials found the safety of these compounds to be equal to that of placebo. The literature on GH, GS, or CS as an individual supplement suggests a therapeutic value but falls short of proving a role for its independent use.

Although the study by Clegg et al.³¹ called into question the efficacy of GH and CS in mild OA, it showed the effectiveness of these supplements in the moderate/severe pain subgroup. Their study lacked the size to make up for a placebo response rate of over 60% and the relatively mild disease state of the study participants. When considered within the context of the other studies reviewed, it serves as another study to confirm the safety profile of glucosamine and CS and shows a reduction in pain scores with consistent use.

The scant literature on the sulfur-containing compounds SAM-e and MSM shows trends toward decreased pain and increased function with consistent use but fall short of proving any therapeutic benefit. However, they have a documented 3-month safety profile; there is a need for more randomized clinical trials.

Perhaps the most important trend seen in the current literature on nutraceutical use for OA is the importance of length of therapy. Although some studies have shown significant improvement in OA symptoms during a short time period, these studies involved the use of concomitant pain relievers, were poorly concealed for allocation, or were monetarily supported by manufacturers. In the more rigorous and lengthy studies comparing these compounds, effectiveness was not seen until several months into therapy. For example, in studies on CS significant effects were not seen until 3 to 6 months of treatment. In other studies the effectiveness of CS was not shown until month 9 of the treatment phase or month 4 of the post-treatment phase. In glucosamine studies a similar trend can be noted because treatment effects can be delayed until post-treatment follow-up. These findings support the need for more long-term trials and the importance of consistent use in patients who select these compounds as treatment for OA pain and disability.⁵⁰

It is important to understand that many of these glucosamine and CS studies have been financed and sponsored by industry and specific manufacturers. Not all studies document this well, and financial relationships with industry, scientific investigators, and academic institutions are widespread. These potential conflicts influence research and have been well studied.⁵¹

When considering the use of vitamin or nutrient supplementation, it is important to realize that the supplements tested in trials are not necessarily the same as the supplements sold in stores.⁵² To reduce any potential complicating factors, clinical trials must use products that have been rigorously tested with regard to the purity and quantity of the supplements. Products available in stores are not adhered to these same specifications by the Food and Drug Administration (FDA) because they do not undergo federal testing for actual content. According to the Dietary Supplement Health and Education Act of 1994, the manufacturer is responsible for determining that the supplement is present in the advertised purity and amount and that any claims made about it are adequately substantiated.⁵³

The FDA allows dietary supplement labels to include information describing the supplement's effect on the body and its biologic functions. These types of claims are referred to as structure/function claims. To make such claims, manufacturers must have some scientific data to substantiate them and not overstate the science. The FDA has the authority to declare a product mislabeled if its labeling is false or misleading. In the future the FDA intends to issue regulations on good manufacturing practices that will focus on ensuring the identity, purity, quality, strength, and composition of dietary supplements.⁵⁴ In the interim the industry has instituted its own good manufacturing practices to ensure quality products for the consumer.⁵⁵ Reputable companies provide consumers with carefully formulated supplements that are accurately labeled. These manufacturers ensure that each batch of raw materials is laboratory tested for purity and potency.

For the consumer, it is important to purchase glucosamine and CS supplements that provide the efficacious amount of each ingredient as declared by the label. Several reputable companies, both national and store brands, have been shown to sell products that contain the labeled amount of glucosamine and CS at affordable prices. As a physician, it is important to recommend a brand name that has consistently shown itself to meet or exceed its claims on content quality and quantity in the literature.

CONCLUSIONS

In the literature satisfying our inclusion criteria, GS, GH, and CS have individually shown inconsistent efficacy in decreasing OA pain and improving joint function. Many studies confirmed OA pain relief with glucosamine and CS use. The excellent safety profile of glucosamine and CS therapy should be discussed with patients, and these supplements may serve a role as an initial treatment modality for many OA patients.

REFERENCES

1. Adachi N, Ochi M, Deie M, Ito Y, Izuta Y. Lateral compartment osteoarthritis of the knee after meniscectomy treated by the transplantation of tissue-engineered cartilage and osteochondral plug. *Arthroscopy* 2006;22:107-112.
2. Spahn G, Mückley T, Kahl E, Hofmann GO. Factors affecting the outcome of arthroscopy in medial-compartment osteoarthritis of the knee. *Arthroscopy* 2006;22:1233-1240.
3. Ikeuchi M, Takahashi T, Tani T. Localized synovial hypertrophy in the anteromedial compartment of the osteoarthritic knee. *Arthroscopy* 2005;21:1457-1461.
4. Bae DK, Yoon KH, Song SJ. Cartilage healing after microfracture in osteoarthritic knees. *Arthroscopy* 2006;22:367-374.
5. Stuart MJ, Lubowitz JH. What, if any, are the indications for arthroscopic debridement of the osteoarthritic knee? *Arthroscopy* 2006;22:238-239.
6. US Senate Committee on Health, Education, Labor and Pensions, Subcommittee on Aging. *Center for Disease Control's role in combating the burden of arthritis*. Washington, DC: Department of Health & Human Services, 2004.
7. Fries JF, Williams CA, Block DA, Michel BA. Nonsteroidal anti-inflammatory drug-associated gastropathy: Incidence and risk factor models. *Am J Med* 1991;91:213-222.
8. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: Systematic review of randomised controlled trials. *BMJ* 2002;325:619.
9. Vetter G. Topical therapy of arthroses with glucosamine (Dona 200). *Munch Med Wochenschr* 1969;11:1499-1502 (in German).
10. Theodaski J, Adderly B, Fox B. *The arthritis cure*. New York, NY: St Martin's, 1997.
11. Bucsi L, Poór G. Efficacy and tolerability of oral chondroitin sulfate as a symptomatic slow-acting drug for osteoarthritis (SYSADOA) in the treatment of knee osteoarthritis. *Osteoarthritis Cartilage* 1998;6:31-36 (suppl A).
12. Bourgeois P, Chales G, Dehais J, Delcambre B, Kuntz JL, Rozenberg S. Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3 × 400 mg/day vs placebo. *Osteoarthritis Cartilage* 1998;6:25-30.
13. Conrozier T. Anti-arthrosis treatments: Efficacy and tolerance of chondroitin sulfates (CS 4&6). *Presse Med* 1998;27:1862-1865 (in French).
14. Mazieres B, Combe B, Phan Van A, Tondut J, Grynfeldt M. Chondroitin sulfate in osteoarthritis of the knee: A prospective, double blind, placebo controlled multicenter clinical study. *J Rheumatol* 2001;28:173-181.
15. Mazieres B, Hucher M, Zaim M, Garner P. Effect of chondroitin sulfate in symptomatic knee osteoarthritis: A multicentre, randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2007;66:639-645.
16. Uebelhart D, Malaise M, Marcolongo R, et al. Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate:

- A one year, randomized, double-blind, multicenter study versus placebo. *Osteoarthritis Cartilage* 2004;12:269-276.
17. Mathieu P. Radiological progression of internal femoro-tibial osteoarthritis in gonarthrosis. Chondro-protective effect of chondroitin sulfates ACS4-ACS6. *Presse Med* 2002;31:1386-1390 (in French).
 18. Michel BA, Stucki G, Frey D, et al. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: A randomized, controlled trial. *Arthritis Rheum* 2005;52:779-786.
 19. Rothenfluh DA, Reedwisch D, Müller U, Ganz R, Tennant A, Leunig M, et al. Construct validity of a 12-item WOMAC for assessment of femoro-acetabular impingement and osteoarthritis of the hip. *Osteoarthritis Cartilage* 2008;16:1032-1038.
 20. Noack W, Fischer M, Förster KK, Rovati LC, Setnikar I. Glucosamine sulfate in osteoarthritis of the knee. *Osteoarthritis Cartilage* 1994;2:51-59.
 21. Reichelt A, Forster KK, Fischer M, Rovati LC, Setnikar I. Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee. A randomised, placebo controlled, double-blind study. *Arzneimittelforschung* 1994;44:75-80.
 22. Reginster JY, Derolsy R, Rovati LC, et al. Long-term effects of glucosamine sulfate on osteoarthritis progression: A randomized, placebo-controlled clinical trial. *Lancet* 2001;357:251-256.
 23. Pavelká K, Gatterová J, Olejarová M, et al. Glucosamine sulfate use and delay of progression of knee osteoarthritis. *Arch Intern Med* 2002;162:2113-2123.
 24. Bruyere O, Pavelka K, Rovati LC, et al. Glucosamine sulfate reduces osteoarthritis progression in postmenopausal women with knee osteoarthritis: Evidence from two 3 year studies. *Menopause* 2004;11:138-143.
 25. Bruyere O, Honore A, Ethgen O, et al. Correlation between radiographic severity of knee osteoarthritis and future disease progression. Results from a 3-year prospective, placebo-controlled study evaluating the effect of glucosamine sulfate. *Osteoarthritis Cartilage* 2003;11:1-5.
 26. Cibere J, Kopec JA, Thorne A, et al. Randomized, double-blind, placebo-controlled glucosamine discontinuation trial in knee osteoarthritis. *Arthritis Rheum* 2004;51:738-745.
 27. Herrero-Beaumont G, Ivorra JA, Del Carmen Trabada M, et al. Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: A randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. *Arthritis Rheum* 2007;56:555-567.
 28. Hughes R, Carr A. A randomized, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. *Rheumatology (Oxford)* 2002;41:279-284.
 29. Hout JB, McMillan R, Wein C, Paget-Dellio SD. Effect of glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee. *J Rheumatol* 1999;26:2423-2430.
 30. McAlindon TE, Formica M, LaValley M, Lehmer M, Kabbara K. Effectiveness of glucosamine for symptoms of knee osteoarthritis: Results from an internet-based randomized double-blind controlled trial. *Am J Med* 2004;117:643-649.
 31. Clegg D, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006;354:795-808.
 32. Kaptchuk TJ. The placebo effect in alternative medicine: Can the performance of the healing ritual have clinical significance? *Ann Intern Med* 2002;136:817-825.
 33. Alekseeva LI, Chichasova NV, Benevolenskaia LI, Nasonov EL, Mendel' OI. Combined medication ARTRA in the treatment of osteoarthritis. *Ter Arkh* 2005;77:69-75 (in Russian).
 34. Messier SP, Mihalko S, Loeser RF, et al. Glucosamine/chondroitin combined with exercise for the treatment of knee osteoarthritis: A preliminary study. *Osteoarthritis Cartilage* 2007;15:1256-1266.
 35. McAlindon TE, LaValley MP, Gulin JP, et al. Glucosamine and chondroitin for treatment of osteoarthritis: A systematic quality assessment and meta-analysis. *JAMA* 2000;283:1469-1475.
 36. Richey F, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster JY. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: A comprehensive meta-analysis. *Arch Intern Med* 2003;163:1514-1522.
 37. Bjorral JM, Kloving A, Ljunggren AE, Stordal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomized placebo-controlled trials. *Eur J Pain* 2007;11:125-138.
 38. Distler J, Anguelouch A. Evidence-based practice: Review of clinical evidence on the efficacy of glucosamine and chondroitin in the treatment of arthritis. *J Am Acad Nurse Pract* 2006;18:487-493.
 39. Reichenbach S, Sterchi R, Scherer M, et al. Meta-analysis: Chondroitin for osteoarthritis of the knee or hip. *Ann Intern Med* 2007;146:580-590.
 40. Leeb BF, Schweitzer H, Montag K, Smolen JS. A metaanalysis of chondroitin sulfate in the treatment of osteoarthritis. *J Rheumatol* 2000;27:205-211.
 41. Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev* 2005;CD002946.
 42. König B. A long-term (two year) clinical trial with S-adenosylmethionine of the treatment of osteoarthritis. *Am J Med* 1987;83:89-94.
 43. Muller-Fassbender H. Double-blind clinical trial multicenter study comparing S-adenosylmethionine, naproxen, and placebo in the treatment of osteoarthritis. *Am J Med* 1987;83:1-4.
 44. Maccagno A, Di Giorgio EE, Caston OL, Sagasta CL. Double-blinded controlled clinical trial of oral S-adenosylmethionine versus piroxicam in knee osteoarthritis. *Am J Med* 1987;83:72-77.
 45. Vetter G. Double-blind comparative clinical trial with S-adenosylmethionine and indomethacin in the treatment of osteoarthritis. *Am J Med* 1987;83:78-80.
 46. Najm WI, Reinsch S, Hoehler F, Tobis JS, Harvey PW. S-adenosylmethionine (SAME) versus celecoxib for the treatment of osteoarthritis symptoms: A double-blind cross-over trial. *BMC Musculoskelet Disord* 2004;5:6.
 47. Jacob SW, Herschler R. Dimethyl sulfoxide after twenty years. *Ann N Y Acad Sci* 1983;411:13-17.
 48. Usha PR, Naida MUR. Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. *Clin Drug Invest* 2004;24:353-363.
 49. Kim LS, Axelrod LJ, Howard P, Buratovich N, Waters RF. Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: A pilot clinical trial. *Osteoarthritis Cartilage* 2006;14:286-294.
 50. Owens S, Wagner P, Vangsness CT Jr. Recent advances in glucosamine and chondroitin supplementation. *J Knee Surg* 2004;17:185-193.
 51. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: A systematic review. *JAMA* 2003;289:454-465.
 52. Russell AS, Aghazadeh-Habashi A, Jamali F. Active ingredient consistency of commercially available glucosamine sulfate products. *J Rheumatol* 2002;29:2407-2409.
 53. Joint supplements: Brands to try and brands to avoid. *Consumer Reports*. June 2006.
 54. Dickinson A. Docket No. 96N-0417, good manufacturing practices for dietary supplements. Available from: URL: http://www.crnusa.org/pdfs/CRN_FDA_GMPS081103_Process.pdf. Accessed March 2, 2007.
 55. Hathcock JN, Shao A. Risk assessment for glucosamine and chondroitin sulfate. *Regul Toxicol Pharmacol* 2007;47:78-83.