

Critical appraisal of the role of glucosamine and chondroitin in the management of osteoarthritis of the knee

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Abstract: Osteoarthritis (OA) is the most common musculoskeletal disease in the United States, with rising prevalence. Medical management of OA involves acetaminophen, non-steroidal anti-inflammatory drugs, and other analgesics, all of which are of variable efficacy and are associated with significant side effects and toxicities. The purpose of this review is to critically evaluate the efficacy of glucosamine and chondroitin, both as single agents and in combination, for the treatment of knee OA. Also evaluated were the level of evidence and funding support of the included articles. Almost every included trial of glucosamine sulfate, glucosamine hydrochloride, and chondroitin sulfate has found the safety of these compounds to be equal to that of placebo, though their therapeutic efficacy in decreasing knee OA pain and improving joint function is variable. Additionally, there are data to support a role of these agents in reducing radiographic progression of knee OA. Industry involvement, however, remains prominent. Further, more comprehensive study by independent researchers free of industry ties is necessary to identify a subset of patients in whom the use of glucosamine and/or chondroitin would be most beneficial. These agents may be safely tried as an initial therapy in select OA patients prior to initiating therapy with nonsteroidal anti-inflammatory drugs, acetaminophen, and other traditional medications.

Keywords: glucosamine sulfate, glucosamine hydrochloride, chondroitin sulfate, knee osteoarthritis, nutritional supplement, nutraceutical

Introduction

Osteoarthritis (OA) affects nearly 15% of Americans, making it the most common musculoskeletal disease in the United States; its prevalence is expected to double by the year 2020.^{1,2} The total annual cost of OA has been estimated to be US\$5,700 per patient, and the cost of OA and associated conditions is estimated at more than US\$80 billion per year.³

Clinically, OA is a heterogeneous group of conditions characterized by progressive deterioration of articular cartilage, osteophyte formation, subchondral bone changes, thickening of the joint capsule, and synovitis, resulting in significant pain and loss of normal joint movement. Once considered an inevitable consequence of aging, OA is now thought to involve a complex interaction between mechanical and biological events that disrupt the normal homeostatic balance of degradation and repair in the articular cartilage, synovial membrane, and subchondral bone.^{4,5} Cytokines, particularly interleukin 1 and tumor necrosis factor alpha are thought to underlie this process, but genetics, age, sex, obesity, joint history, and muscle strength may also be contributing factors.⁶

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Current therapy for OA focuses on alleviating symptoms and preserving joint function. Non-pharmacologic management consists of patient education, self-management programs, aerobic exercise, muscle conditioning, physical and occupational therapy, bracing, patellar taping, assist devices, and joint protection.^{3,7,8} Surgical therapies for persistent symptoms and/or progressive disability include osteotomy, arthrodesis, and arthroplasty. Medical management generally involves analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs). These agents are of variable efficacy, and may be associated with a significant number of side effects and toxicities, including hepatic damage with high-dose acetaminophen, and renal insufficiency, peptic ulcer disease, and hemorrhage with chronic use of NSAIDs. The elderly, who are particularly likely to suffer from OA, are at higher risk for these problems, and may be taking such a variety of other medications for other medical comorbidities that may interact with NSAIDs or acetaminophen. Accordingly, there has been significant investigation into the role of other therapies for OA.

Glucosamine and chondroitin are components of the extracellular matrix of articular cartilage, and have been used for medicinal purposes for nearly 40 years, with a gain in popularity in the US beginning in the late 1990s.⁹ Glucosamine (2-amino-2-deoxy-D glucose) is a normal constituent of glucosaminoglycan which plays a role in the normal growth and repair of articular cartilage.^{3,8} Taken orally as either glucosamine sulfate (GS) or glucosamine hydrochloride (GH), these salts are ionized in the stomach, making glucosamine available for absorption in the small bowel. 90% is absorbed, but there is extensive first-pass metabolism, so that bioavailability approaches only 25%.¹⁰ Chondroitin sulfate (CS) is a normal constituent of aggrecan, the major proteoglycan of articular cartilage, which helps create osmotic pressure within the extracellular matrix to maintain the compressive resistance of cartilage.^{3,11} It has also been hypothesized to reduce inflammation, inhibit synthesis of degradative enzymes including matrix metalloproteinases, increase synthesis of extracellular matrix constituents, and reduce apoptosis of articular chondrocytes.⁹ Due to its larger size as compared to glucosamine, CS is not as well-absorbed; the actual absorption percentage remains controversial but has been estimated at 30%, with approximately 12% to 13% bioavailability.^{8,12}

Numerous studies have been designed to investigate the role between glucosamine, either in sulfate or hydrochloride form, and CS on pain, joint space narrowing, functionality, and other outcomes related to OA. Two of the most widely

used instruments for assessing clinical outcomes in OA of the knee are the WOMAC (Western Ontario and McMaster Universities) OA Index and the Lequesne-Algofunctional Index.^{13,14} The WOMAC Index is a three-dimensional patient questionnaire that assesses pain (5 questions), stiffness (2 questions), and physical functional disability (17 questions) on separate scales that can be aggregated into a composite index. The Lequesne Index involves 10 questions in an interview format, designed to directly aggregate symptoms and function which are not graded separately. Using these indices, clinical studies of glucosamine and chondroitin have yielded varied results, and many studies have come under criticism for their small sample sizes, lack of statistical rigor, potential for sponsor bias, inadequate concealment of the study agent, and lack of intention-to-treat principles.⁹

The purpose of this review is to critically evaluate the evidence for the use of glucosamine (both in its sulfate and hydrochloride form) and CS for the treatment of OA of the knee. This review article will focus on double-blind, placebo-controlled, randomized controlled trials using glucosamine and CS (both as single agents and in combination), published in English, which have incorporated established outcome measurement methods as noted above. These articles were identified on PubMed by using key terms including “glucosamine,” “chondroitin,” and “knee osteoarthritis,” alone and in combination, and subsequently evaluated for level of evidence using the Oxford Centre for Evidence-based Medicine criteria¹⁵ (Table 1). Articles were also evaluated regarding their funding source and author affiliations with industry to investigate the potential for conflicts of interest in the study of the therapeutic value of glucosamine and chondroitin for knee OA.

Review of studies of glucosamine and chondroitin

Glucosamine sulfate

Müller-Fassbender et al¹⁶ (Table 2) evaluated the short-term effects of glucosamine sulfate (500 mg, 3 times a day) as compared to ibuprofen (400 mg, 3 times a day) over a 4 week period. The 200 symptomatic hospital patients were evaluated weekly for improvement in the Lequesne Index. No significant differences in response rate were detected between GS and ibuprofen (48% vs 52%, $P = 0.06$), but a significant decrease was found in the incidence of adverse effects in favor of glucosamine. Thirty-five percent of patients on ibuprofen reported adverse effects (mainly gastrointestinal in origin), as compared to only 6% among patients taking GS ($P = 0.035$). Similarly, Noack et al¹⁷ conducted a 4-week study of 252 OA

Table 1 Levels of evidence

Level I	Level II	Level III	Level IV	Level V
- Individual randomized trial with narrow confidence interval - Systematic review of Level I randomized trials with homogeneity	- Individual cohort study (including low quality RCT; eg, <80% follow-up) - Systematic review of Level II studies or Level I studies with inconsistent results	- Case control study - Retrospective comparative study - Systematic review of Level III studies	- Case series - Poor quality cohort and case-control studies	Expert opinion

patients comparing GS 500 mg 3 times a day to placebo in improvement of the Lequesne Index. Patients in the GS group were found to have a significant decrease in Lequesne Index (3.2 vs 2.2, $P < 0.05$). Medications were well-tolerated. However, due to the relatively limited follow-up of patients in these studies, we must look to subsequent investigations to make more long-term conclusions on the efficacy of GS.

Reginster et al¹⁸ randomized 212 patients with knee OA to receive either 1500 mg GS or placebo daily for 3 years to assess the clinical and radiographic effects of glucosamine on knee OA. Mean joint space width of the medial compartment of the tibiofemoral joint was assessed at enrollment and after 1 and 3 years, and symptoms were scored by the WOMAC Index. Patients receiving placebo were shown to have progressive joint space narrowing which was not detected in the GS group, suggesting that GS may play a role as a disease-modifying agent for OA.

A trend toward improving WOMAC scores was seen in the GS group but without any statistical significance. Sub-analysis of this cohort (Bruyere),¹⁹ in which joint space width on anteroposterior knee radiographs was divided into quartiles and followed during the 3 year study, demonstrated that patients with less severe radiographic knee OA had the most dramatic disease progression during the study period. The GS group, compared to the placebo group, trended toward a significant reduction in joint space narrowing ($P = 0.10$).

Pavelká et al²⁰ completed a similar trial of the clinical and radiographic effects of glucosamine. 200 patients were randomized to receive either 1500 mg GS or placebo over a three year period. Changes in radiographic minimum joint space width were measured in the medial compartment of the tibiofemoral joint, and symptoms were assessed using the Lequesne Index and WOMAC scoring. Five percent of

Table 2 Summary of glucosamine sulfate trials

Study	No of patients	Length	Substance	Symptomatic relief	Radiographic progression	Sponsorship	Level of evidence
Müller-Fassbender et al ¹⁶	200	4 wks	500 mg GS 3 times per day vs ibuprofen 400 mg 3 times per day	–		Industry-supported	I
Noack et al ¹⁷	252	4 wks	500 mg GS 3 times per day vs placebo	+		Industry-supported	I
Reginster et al ¹⁸	212	3 yrs	1500 mg GS per day vs placebo	+ but not significant	+	Industry-supported	II
Bruyere et al ¹⁹	212	3 yrs	1500 mg GS per day vs placebo		+ but not significant	Industry-supported	I
Pavelká et al ²⁰	202	3 yrs	1500 mg GS per day vs placebo	+	+	Industry-supported	II
Hughes et al ²¹	80	6 mos	500 mg GS 3 times per day vs placebo	–		Industry-supported	I
Cibere et al ²²	137	6 mos	1500 mg GS per day vs placebo	–		Foundation grant	I
Herrero-Beaumont et al ²³	318	6 mos	1500 mg GS vs placebo	+		Industry-supported	II

Abbreviation: GS, glucosamine sulfate.

patients taking GS experienced severe joint space narrowing (predefined as >0.5 mm), as compared to 14% in the placebo group ($P = 0.05$). Pain and function limitation decreased in both treatment groups according to the Lequesne index and WOMAC index; however, the improvements were significantly larger in patients receiving glucosamine sulfate, with score reductions of 20% to 25% compared with baseline. No statistically significant differences in the proportion or pattern of adverse events were noted.

Hughes and Carr²¹ evaluated 80 patients over the age of 40 with radiologically defined, symptomatic OA for their improvement in global assessment of pain in the affected knee. Patients were randomized to receive either GS 500 mg three times a day or placebo for 6 months. The primary outcome measure was patients' global assessment of pain in the affected knee. No statistically significant difference was found between the two groups; placebo response rate was noted to be 33%.

Cibere et al²² conducted a 4-center, 6-month, randomized, double blind, placebo-controlled glucosamine discontinuation trial in 137 users of GS with knee OA who had experienced at least moderate improvement in knee pain after starting glucosamine. Study medication dosage was equivalent to the dosage of glucosamine taken prior to the study (maximum 1500 mg/day). No differences were detected in severity of disease flare or other secondary outcomes in the glucosamine group compared with the placebo group, leading the authors to conclude that there is no evidence for symptomatic benefit from continued use of GS.

The Glucosamine Unum In Die (once-a-day) Efficacy (GUIDE) double-blinded multicenter trial in Spain and Portugal (Herrero-Beaumont et al)²³ randomized 318 patients with knee OA to receive GS 1500 mg/day ($n = 106$), acetaminophen 3 g/day ($n = 108$), or placebo ($n = 104$). The primary outcome variable was change in the Lequesne Index and WOMAC after 6 months. GS was shown to be more effective than acetaminophen on both indices. GS reduced the Lequesne index by 3.1 points versus 1.9 for placebo ($P = 0.032$), whereas the 2.7 point decrease with acetaminophen was not significantly different from that with placebo. WOMAC response was

21.2% for placebo, as compared to 39.6% for GS ($P = 0.004$) and 33.3% for acetaminophen ($P = 0.047$).

Glucosamine hydrochloride

Glucosamine hydrochloride (GH) has been the subject of comparatively little study. Houpt et al²⁴ (Table 3) randomized 101 patients for an 8-week trial of acetaminophen and GH versus acetaminophen and placebo after a 2 week period of only acetaminophen. WOMAC scores at week 0 and week 8 were measured. After completing the randomized 8 week trial, subjects were offered known GH capsules in an 8-week open-label trial, with follow-up telephone survey at the end of the study period. In the randomized trial, all tested parameters tended toward improvement, and GH did significantly reduce the amount of pain reported by patients ($P = 0.018$) and improved findings on clinical knee examination ($P = 0.026$). Moreover, at the end of the 8 week open label trial, 77% of all subjects (regardless of whether they had previously received GH or placebo) continued using GH, even though they had to purchase it outright. This suggests that either most subjects noted improvement or they believed that glucosamine was beneficial for their symptoms.

Also of note is a study by McAlindon²⁵ which evaluated GH in addition to GS. This was a 12-week randomized trial of glucosamine among 205 subjects with knee OA who were recruited with online advertisements and followed entirely with online assessments through a secure web database. One hundred and one subjects were randomized to receive 1.5 g/day of GS, and 104 were to receive placebo. During the study, the manufacturer of GS declined to continue providing placebo pills, and subsequent supplies were acquired from another supplier in the form of GH. At the end of the study period, no significant differences in WOMAC score were seen between the two groups. The number and type of adverse effects were similar between the groups. The potential for lack of validity of internet responses, as well as the change in supplier during this trial, may limit its conclusions.

Collectively, these studies demonstrate that GS as an individual agent may have some effect on the progression of OA, both clinically and radiographically; evidence is

Table 3 Summary of glucosamine hydrochloride trials

Study	No of patients	Length	Substance	Symptomatic relief	Radiographic progression	Sponsorship	Level of evidence
Houpt et al ²⁴	101	8 wks	acetaminophen + GH vs acetaminophen + placebo	+		Industry-supported	I
McAlindon et al ²⁵	205	12 wks	1500 mg GS/GH vs placebo	–		Foundation grant	I

Abbreviations: GS, glucosamine sulfate; GH, glucosamine hydrochloride.

not as strong for GH, given the limited number of studies. Consistent throughout all studies of both GS and GH is the fact that these agents are as safe as placebo, at doses up to 1200 to 1500 mg per day for up to 3 years. However, due to limited follow-up periods in several studies, as well as inconclusive findings in others, further study is necessary.

Chondroitin sulfate

Morreale et al²⁶ (Table 4) randomized 146 patients with knee OA to receive either CS or diclofenac sodium (DS) to compare the clinical efficacy of these agents in reducing clinical symptoms, as measured by the Lequesne Index, spontaneous pain on a visual analogue scale (VAS), and supplementary consumption of acetaminophen. During the first month, patients assigned to the CS group took 400 mg of CS and placebo each three times a day; during the second and third months, patients took only CS. Patients in the DS group took 50 mg of DS and placebo 3 times a day during the first month, and only DS during months 2 to 3. All study patients received placebo during months 4 to 6. Patients who had taken DS were found to have rapid resolution of their symptoms on the indices measured, but these effects did not persist throughout the study period. Patients who had taken CS, on the other hand, experienced later but longer-lasting

resolution of symptoms that persisted even after the 6 month study period had been completed.

In a similar assessment of the efficacy of CS in improving clinical symptoms of OA, Busci and Poór²⁷ randomized 80 patients with Kellgren-Lawrence (K-L) radiographic scores in the I-III range in a double-blind, placebo controlled trial. Patients were treated either with CS 800 mg daily (2×400 mg/day), or with placebo over a 6 month study period. Outcomes assessed were the Lequesne Index, spontaneous joint pain on a VAS, and a 20-minute walk time. Patients in the CS group showed a significant improvement in all three outcome parameters, with no difference in side effects.

Bourgeois et al²⁸ compared the effect of dosing schedules of CS on its efficacy. One hundred and twenty-seven patients with unilateral or bilateral knee OA (K-L scores of I-III) were enrolled in this 3-month treatment study. 40 were treated with CS 1200 mg/day as a single dose, 43 were treated with CS 3×400 mg/day, and 44 were given placebo. The Lequesne Index and spontaneous joint pain (VAS) were significantly improved in the CS groups ($P < 0.01$ for both parameters), while nonsignificant reductions were observed in the placebo group. No significant differences were seen in efficacy or tolerability between the divided and single dose CS groups.

Table 4 Summary of chondroitin sulfate trials

Study	No of patients	Length	Substance	Symptomatic relief	Radiographic progression	Sponsorship	Level of evidence
Morreale et al ²⁶	146	6 mos	1200 mg CS vs 50 mg diclofenac sodium vs placebo	+		Industry-supported	I
Busci et al ²⁷	80	6 mos	400 mg CS 2 times per day vs placebo	+		Industry-supported	I
Bourgeois et al ²⁸	127	3 mos	1200 mg CS vs 400 mg CS 3 times per day vs placebo	+		Industry-supported	I
Mazieres et al ²⁹	130	6 mos	1 g CS per day vs placebo for 3 mo with 3-mo post-therapy follow-up	+		Foundation grant	I
Uebelhart et al ³⁰	42	1 yr	800 mg CS per day vs placebo	+	+	Foundation grant + industry support	I
Uebelhart et al ³¹	120	1 yr	800 mg CS per day for two 3-mo periods during 1 year vs placebo	+	+	Industry-supported	I
Michel et al ³²	300	2 yrs	800 mg CS vs placebo	–	+	Not specified	II
Mazieres et al ³³	307	6 mos	1000 mg CS per day	–		Industry-supported	I
Kahan et al ³⁴	622	2 yrs	800 mg CS vs placebo	+	+	Industry-supported	I

Abbreviation: CS, chondroitin sulfate.

Mazières et al²⁹ evaluated the effects of CS on functional outcomes. Sixty-three patients received 1000 mg of CS daily and 67 patients received a placebo. A 3-month treatment period was followed by 3 additional months of observation after therapy. The main outcome measure was the Lequesne Index; secondary efficacy criteria were self-assessed pain, self-assessed impact of OA on daily living, patient and physician assessed overall change, and daily NSAID and analgesic consumption. In the completer population ($n = 114$), Lequesne Index significantly improved ($P = 0.02$) and remained elevated for 1 month after treatment in the CS group, and pain at rest was also significantly decreased ($P = 0.03$). Intent-to-treat data tended toward improvement in all efficacy criteria but did not reach statistical significance.

Uebelhart et al³⁰ evaluated the clinical, radiological, and biological efficacy of chondroitin 4- and 6-sulfate in patients with knee OA. 42 patients were randomized and treated either with 800 mg CS daily or placebo, and evaluated over a 1 year period on the basis of spontaneous joint pain, overall mobility capacity, joint space measurement, and a variety of biochemical markers of bone and joint metabolism (osteocalcin, keratin sulfate, urinary pyridinoline and deoxy-pyridinoline). By the end of 12 months, pain levels had decreased by 63% and mobility had increased by 68% in the CS group, versus 26% pain reduction and 19% mobility improvement in the placebo group ($P < 0.01$). A statistically significant difference in favor of the CS group was found for all measured radiological parameters ($P < 0.01$). Statistically significant differences in the levels of biomarkers were also noted between the two groups. Together, these latter findings indicate a role for CS in modifying disease progression.

Later study by Uebelhart et al³¹ of functional and radiological parameters examined the effect of intermittent dosing of CS on these outcomes. 120 patients with symptomatic knee OA were randomized into two groups receiving either 800 mg CS or placebo per day for 2 periods of 3 months over the course of a year. A 36% improvement was noted in the Lequesne Index, as compared to a 23% increase in the placebo group; this difference was statistically significant. Similar results were found for secondary outcome parameters including VAS, walking time, and acetaminophen consumption. Assessment of radiologic progression at month 12 demonstrated significantly decreased joint space width in the placebo group, with no change in the CS group. This study provides evidence that intermittent dosing may produce long-term improvement in function, and further suggests an inhibitory role of CS on radiological advancement of OA.

Subsequent investigation by Michel et al³² provides additional support for the role of CS as a mitigating factor in radiographic progression of OA. 300 patients with knee OA were randomized to receive either 800 mg CS or placebo once daily for 2 years. Primary outcome was joint space loss over 2 years, as assessed by a posteroanterior radiograph of the knee in flexion; secondary outcomes included pain and function. In the 150 patients who received CS, at the end of 2 years there was no change in mean knee joint space width compared to baseline. In the 150 patients who received placebo, there was a mean joint space loss of 0.14 ± 0.61 mm after 2 years ($P = 0.001$ compared from baseline). No symptomatic improvement was noted, however.

Nor was clinically significant improvement demonstrated in a randomized placebo-controlled trial by Mazières et al.³³ 307 patients with symptomatic knee OA as measured by a VAS were enrolled in this 24-week study, and were randomized to receive either CS 1 g/day or placebo. Primary outcome measures were the Lequesne index and pain on activities of daily living. Biochemical markers of bone, cartilage, and synovium metabolism (including C-terminal crosslinked telopeptide of types I and II collagen and serum hyaluronic acid) were also measured. No significant differences in pain or functional outcome were noted, and biomarkers were not significantly different between the two groups.

The radiographic and symptomatic effects of CS on knee OA were again studied by Kahan et al³⁴ in the STOPP trial (Study on Osteoarthritis Progression Prevention). 622 study subjects were randomized to receive 800 mg of CS or placebo daily for 2 years. The primary outcome was loss in minimum joint space width over the study period; secondary outcomes included VAS pain scale and WOMAC score. Significant reduction in minimum joint space width loss ($P < 0.0001$) and faster improvement in pain ($P < 0.01$) were noted in the CS group. Consistent with previous findings, no significant differences were noted in the frequency of adverse events in the study population. The authors do note, however, that the CS preparation used in this study has been approved as a prescription drug, which may limit the generalizability of these results.

Glucosamine and chondroitin

The Glucosamine/chondroitin sulfate Arthritis Intervention Trial (GAIT) trial³⁵ was developed to evaluate the efficacy of glucosamine, chondroitin, and combination therapy for knee OA over a 24-week period (Table 5). Patients (1583) at 16 centers with symptomatic knee OA were randomized to receive 500 mg of GH 3 times daily, 400 mg of

CS 3 times daily, 500 mg of GH + 400 mg of CS 3 times daily, 200 mg of celecoxib (Celebrex®; Pfizer) daily, or placebo. Patients were allowed to take up to 4000 mg of acetaminophen daily as rescue analgesia, except during the 24 hours before a clinical evaluation for joint pain; NSAIDs, narcotics, and other analgesics were not permitted. Patients were evaluated at baseline, and at 4, 8, 16, and 24 weeks after randomization. All patients in the study were at least 40 years old, had both clinical evidence (knee pain for at least 6 months and on the majority of days during the preceding month) and radiologic evidence (KL grade II or III) of OA, as well as WOMAC scores of 125 to 400. The primary outcome measure was a response to treatment, defined by expert consensus as a 20% decrease in WOMAC score from baseline to week 24. Over 40 secondary outcome measures were also included in the study.

For GAIT patients overall, compared to placebo, there was no difference in the rate of response for GH alone ($P = 0.30$), CS alone ($P = 0.17$), or for the combination of GH + CS ($P = 0.09$). The rate of response for celecoxib was significantly better than for placebo ($P = 0.008$). However, in the subgroup of patients with moderate to severe pain (determined by a score of 301–400 on the WOMAC pain scale), the combination of GH and CS was significantly

better than placebo (79.2% vs 54.3%, $P = 0.002$). Celecoxib, GH alone, and CS alone were not significantly better than placebo ($P = 0.06$, $P = 0.17$, $P = 0.39$, respectively). Among the secondary outcomes of the study, the only statistically significant improvement was that of joint swelling/effusion in the CS group ($P = 0.01$), giving further support to the previously-suggested role of CS in preventing the radiologic progression of OA. Post-hoc analysis of this finding was conducted by Hochberg et al³⁶ to further assess this observation. Patients with relatively earlier OA (milder symptoms, baseline KL grade 2 radiographic changes) were found to be more responsive to CS than patients who had KL grade 3 changes. In the GAIT trial overall, the rate of use of rescue acetaminophen was low and not significantly different among the groups or within each pain stratum. Adverse effects were mild, infrequent, and evenly distributed across all groups tested.

The GAIT trial suggests a role of combination glucosamine and chondroitin therapy in patients with more severe OA. However, the authors note a number of limitations to this study, including high rate of response to placebo (reported in other OA trials) and the relatively mild degree of OA pain among the study participants. Moreover, though the treatment effects were more substantial in the subgroup of

Table 5 Summary of glucosamine + chondroitin trials

Study	No of patients	Length	Substance	Symptomatic relief	Radiographic progression	Sponsorship	Level of evidence
Clegg et al ³⁵	1583	24 wks	500 mg GH TID vs 400 mg CS TID vs 500 mg GH + 400 mg CS TID vs 200 mg celecoxib daily vs placebo	– except in select groups		Foundation grant, but with author industry affiliation and donated supplies	I
Hochberg et al ³⁶	1583	24 wks	500 mg GH TID vs 400 mg CS TID vs 500 mg GH + 400 mg CS TID vs 200 mg celecoxib daily vs placebo	+ only in pts with mild OA		Foundation grant, but with author industry affiliation and donated supplies	I
Sawitzke et al ³⁷	572	24 mos	500 mg GH TID vs 400 mg CS TID vs 500 mg GH + 400 mg CS TID vs 200 mg celecoxib daily vs placebo		+ but not significant	Foundation grant, but with author industry affiliation and donated supplies	I
Messier et al ³⁸	89	12 mos	1500 mg GH + 1200 mg CS daily vs placebo × 6 months, then exercise was added to both groups × 6 months	+/-		Industry-supported	I
Leffler et al ³⁹	34	16 wks	1500 mg GH + 1200 mg CS + 228 mg manganese ascorbate	+		Foundation grant	II
Das et al ⁴⁰	93	6 mos	1000 mg GH + 800 mg CS + 152 mg manganese ascorbate twice daily vs placebo	+/-		Industry-supported	I

Abbreviations: GH, glucosamine hydrochloride; CS, chondroitin sulfate; OA, osteoarthritis; TID, 3 times daily.

patients with moderate to severe pain, the relatively small number of patients in this subgroup may have limited the study's power to demonstrate benefits in the non-combination therapy groups.

Sawitzke et al³⁷ published a 24-month, double-blind, placebo-controlled study from 9 centers as a prospective observational study of GAIT enrollees to determine whether glucosamine or chondroitin, either alone or in combination, had a structure-modifying effect in OA of the knee. 572 patients with KL grade II or III changes and joint space width of at least 2 mm on baseline were enrolled. Patients who had been randomized to 1 of the 5 groups in the GAIT study continued to receive their study medications, including celecoxib and placebo, and were evaluated on the basis of PA radiographs at baseline, 12 months, and 24 months to detect mean change in joint space width (JSW). No significant differences in JSW loss were detected over the 2 year study period between the treatment groups and the placebo group, nor was the likelihood of radiographic progression in any treatment group significant compared to placebo. All treatment groups showed numerically less JSW loss than did the placebo group in KL grade II knees, and numerically more JSW loss in KL grade III knees than in placebo, but these differences did not reach statistical significance. The authors of this study note limited power due to a smaller than anticipated sample size, increased variability of measurement, and a smaller than expected loss in JSW. As previously described above, prior studies have demonstrated slowing of JSW loss among patients receiving glucosamine and chondroitin separately. Despite the statistical limitations, this study suggests that combination of these agents may interfere with their individual actions in slowing the progression of OA in advanced cases, though there is some evidence for benefit in more moderately arthritic (KL grade II) knees.

Messier et al³⁸ sought to determine whether using 1500 mg of GH and 1200 mg of CS is effective, both separately and combined with exercise, as compared to a placebo plus exercise program in improving functional outcomes in patients with knee OA. Eighty-nine participants were randomized to receive either a combination of GH and CS ($n = 45$) or placebo ($n = 44$) for 6 months, followed by an additional 6 month period during which identical exercise programs were added to each group. Patients were assessed at 6 months and 12 months using the WOMAC scale. Mean function did not vary significantly between the study groups at 6 months ($P = 0.52$) or at 12 months ($P = 0.50$), but mean WOMAC function combining both groups improved significantly over time ($P = 0.005$). The placebo group was noted to have

significantly better balance than the GH/CS group at 6 months ($P = 0.01$) and at 12 months ($P = 0.05$). The authors concluded that the GH/CS group was not superior to placebo during the pill-only and pill plus exercise phases of this trial.

Several studies have examined the role of glucosamine and chondroitin in conjunction with manganese for management of OA. Leffler et al³⁹ performed a trial of combination GH (1500 mg/day), CS (1200 mg/day), and manganese ascorbate (228 mg/day) in 34 male troops from the US Navy's diving and special warfare commands. Mean subject age was 43.6 years. Subjects had chronic pain and radiographic DJD of the knee or low back, and were followed over a 16-week crossover period (8 weeks of treatment, 8 weeks of placebo). For the knee, statistically significant improvement in patient assessment of treatment result ($P = 0.02$) and VAS for pain ($P = 0.048$) were demonstrated in the treatment group. The generalizability of this study beyond the relatively young population of heavily active males may be limited, however.

Das et al⁴⁰ further evaluated the combination of GH, CS, and manganese ascorbate on the treatment of OA. 93 patients were randomized to receive either 1000 mg of GH, 800 mg of CS, and 152 mg of manganese ascorbate twice daily or to receive placebo for 6 months. Patients in the intervention group with radiographically mild or moderate OA ($n = 72$), defined as having KL grade II or II OA, showed significant improvement in the Lequesne Index at 4 and 6 months ($P = 0.003$ and $P = 0.04$, respectively). No improvement in WOMAC score was noted at any time interval. Patients with severe OA (KL grade IV) did not show significant improvement in either Lequesne Index or WOMAC. Adverse events were not different between the two groups.

Meta-analyses of glucosamine and chondroitin

McAlindon et al⁴¹ (Table 6) examined 15 published and unpublished double blind, randomized, placebo-controlled trials lasting 1 month or longer that tested glucosamine or chondroitin for knee or hip OA, including oral, intramuscular, intravenous, and intra-articular routes of administration. Only one study was found to describe adequate allocation concealment, and only two reported an intent-to-treat analysis. Evidence for publication bias for both glucosamine and chondroitin was also found, as most of the included trials were either supported or performed by a manufacturer. Effect sizes were 0.44 (95% confidence interval [CI] 0.24 to 0.64) for glucosamine and 0.78 (95% CI 0.60 to 0.95) for chondroitin. When only high-quality or large trials were

Table 6 Summary of meta-analyses of glucosamine and chondroitin trials

Study	No of trials	Substance	Symptomatic relief	Radiographic progression	Sponsorship	Level of evidence
McAlindon et al ⁴¹	15	glucosamine, CS	+		Foundation grant	I
Richy et al ⁴²	15	GS, CS	+	+ for GS, insufficient evidence for CS	"Authors have no relevant financial interest"	I
Bjorndal et al ⁴³	63	GS, CS, opioids, NSAIDs, acetaminophen	+ but small		Foundation grant	I
Leeb et al ⁴⁴	7	CS	+		Not specified	I
Reichenbach et al ⁴⁵	20	CS	–		Foundation grant	II
Hochberg et al ³⁶	6	CS		+	Industry support	I
Towheed et al ⁴⁶	25	glucosamine	+/-		No sources of support. Authors in past had industry ties. 1 author holds patent on glucosamine-type substances	I

Abbreviations: CS, chondroitin sulfate; GS, glucosamine sulfate; NSAIDs, nonsteroidal anti-inflammatory drugs.

included, the effects of glucosamine and CS persisted but effect sizes were noticeably diminished. The authors conclude that glucosamine and chondroitin are safe and likely have some efficacy and utility in treating OA symptoms, but that methodological problems with numerous trials may tend to over-exaggerate their overall benefit.

Richy et al⁴² performed a meta-analysis to assess the structural and symptomatic efficacy of at least 4 weeks of oral GS and CS in knee OA via radiographic progression of joint space narrowing and 1 of several clinical measures such as the Lequesne Index, WOMAC, and VAS for pain. Fifteen studies including data from 1775 patients (1020 glucosamine and 755 chondroitin) were analyzed. The authors found a statistically significant improvement in symptom scores with both GS and CS therapy. Highly significant ($P < 0.001$) evidence of a structural efficacy of glucosamine on minimum joint space narrowing over a 3-year period was also shown, providing additional evidence for a disease-modifying role of glucosamine. CS studies of joint space narrowing were of insufficient quality and detail to assess effects on joint space narrowing, and this analysis was withdrawn from the study. Safety was excellent for both compounds.

Bjorndal et al⁴³ reviewed 63 randomized placebo-controlled trials encompassing 14,060 patients to determine the short-term pain-relieving effects of 7 commonly used pharmacologic agents used to treat OA knee pain. These agents were GS, CS, acetaminophen, opioids, NSAIDs (both oral and topical, including COX-2 selective inhibitors), and intra-articular glucocorticoid injections. GS, CS, and acetaminophen had maximum mean efficacies at 1 to 4 weeks, but changes in VAS pain scale were small. Overall clinical

effects of these pharmacologic interventions were shown to be small and limited to the first 2 to 3 weeks after the start of treatment.

Leeb et al⁴⁴ performed a meta-analysis of 7 trials of 372 patients to examine the efficacy of CS on improvement of the Lequesne Index and pain VAS. The authors note that, despite the fact that all selected studies claim to be randomized, double blind designs in parallel groups, CS was given along with analgesics or NSAIDs, which introduces another confounding variable into the analysis. Nonetheless, at 120 or more days of administration, CS was shown to be significantly superior to placebo, as measured by the Lequesne Index and pain VAS. Additionally, the authors called for further investigation in larger cohorts of patients for longer time periods in order to provide additional evidence for the role of CS in the treatment of knee OA.

Further study of the effect of chondroitin on OA outcomes was undertaken by the meta-analysis performed by Reichenbach et al⁴⁵ in which 20 trials (3846 patients) were evaluated. The goal of this study was to determine the effects of chondroitin on pain and joint space width and to explore whether reported beneficial effects could be explained by bias affecting individual trials or by publication bias. The authors note that trial quality was generally low, and that significant heterogeneity among the trials limits interpretation of the results. Pooling of 3 trials with larger sample sizes and intention-to-treat analysis (which included 40% of patients) to control for this heterogeneity, an effect size near 0 was found for any clinically relevant benefit of chondroitin. No evidence was found to suggest that chondroitin is unsafe. The authors conclude that there is no robust evidence to support

the use of chondroitin, and thus discourage its use in routine clinical practice.

Hochberg et al¹¹ evaluated randomized clinical trials of at least 52 weeks duration which specifically examined the effects of CS on structural outcomes of joint space width. 5 reports describing three RCTs and 1 abstract presented at the 2006 annual meeting of the American College of Rheumatology were included. In these studies, 800 mg of oral CS was administered daily. Using pooled data, this meta-analysis found that patients randomized to receive oral CS had a significant reduction in the annual rate of decline of joint space width (0.07 mm/year) as compared to patients who had received placebo ($P < 0.0001$).

Regarding meta-analyses of the effects of glucosamine on OA, the Cochrane Review⁴⁶ examined 25 studies with 4963 patients. This comprehensive meta-analysis followed 3 selection criteria – enrolled studies were RCTs, they were either placebo controlled or comparative, and they were blinded (single and double were both accepted). A total of 1905 participants were randomized to treatment with glucosamine and 3058 were randomized to the comparator groups (placebo or active comparator). Analysis restricted to the studies with adequate allocation concealment failed to show any benefit of glucosamine for pain and WOMAC subscales; however, it was found to be better than placebo using the Lequesne index (standardized mean difference [SMD] -0.54 ; 95% CI -0.96 to -0.012). Collectively, the 25 included RCTs favored glucosamine with a statistically significant improvement in pain (22% decrease from baseline) and an 11% improvement in function using the Lequesne Index, but WOMAC outcomes did not reach statistical significance. RCTs in which the Rotta brand of glucosamine was compared to placebo found glucosamine superior for pain (SMD -1.11 ; 95% CI -1.66 to -0.57) and function (Lequesne Index SMD -0.47 ; 95% CI -0.82 to -0.012). Glucosamine was as safe as placebo in terms of the number of adverse reactions reported by study participants.

Discussion

A variety of international societies and consortia have published treatment guidelines regarding the use of glucosamine and chondroitin for knee osteoarthritis. These include the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), the Osteoarthritis Research Society International (ORSI), and the UK's National Institute for Health and Clinical Excellence (NICE). The ACR guidelines⁷ felt it premature to make specific recommendations about glucosamine and chondroitin for patients

with knee OA given several methodologic issues with studies published up to that point. The EULAR guidelines⁴⁷ note growing evidence to support the use of glucosamine sulfate and chondroitin sulfate for their symptomatic effects on knee OA but do not provide a management algorithm. The OARSI guidelines⁴⁸ conclude that treatment with glucosamine and/or chondroitin sulfate may provide symptomatic benefit in patients with knee OA, but recommend discontinuing treatment if no response is appreciated within 6 months; again, no management algorithm was addressed. Finally, the NICE guidelines⁴⁹ did not endorse the use of either glucosamine or chondroitin for knee OA.

This review examined single studies as well as meta-analyses of glucosamine and chondroitin, both as single agents and in combination, to establish their effects on proven outcome measures such as pain and functional limitation in patients with knee OA. Of the 32 studies included, 26 were Level I evidence, and the remaining 6 studies were Level II. Qualitatively, our review of the evidence finds a mild yet overall positive benefit for glucosamine and chondroitin regarding their effects on symptomatic improvement of knee OA, and thus supports the EULAR and OARSI findings. Overall benefit for radiographic progression of disease is also noted in our review of the evidence but not addressed in published guidelines.

Some of the described studies have shown significant improvements in OA symptoms over short periods of time, but these findings have not been consistent compared to more rigorous and longer studies involving larger patient populations. The lack of a statistically significant response in the GAIT trial for glucosamine and chondroitin, for example, casts some doubt on the clinical efficacy of these agents in mild OA, but does suggest that selective use in patients with more advanced disease may be of some benefit. Follow-up of patients after treatment has also been variable, supporting a need for more lengthy trials involving outcome measurements after a course of supplementation has been completed in order to account for delayed treatment effects. In terms of the side effects of these agents, it can be reliably concluded that the overall safety profile of GS, GH, and CS is equal to that of placebo.

The relationship between clinical symptoms of knee OA and structural changes measured radiographically is not entirely clear. Severity of knee pain and functional limitation does not consistently relate to the degree of radiographic OA, nor has radiographic change alone been linked consistently with symptoms of disease.⁵⁰ However, several studies have examined cartilage changes over time as prognostic factors

for subsequent joint surgery. Cicuttini et al⁵¹ identified the rate of tibial cartilage loss as a risk factor for subsequent replacement of the affected knee, independent of age, sex, baseline level of pain, and radiologic severity of disease. Bruyere et al⁵² demonstrated that minimum joint space narrowing after 3 years was also found to be highly predictive of the risk of requiring OA-related knee surgery within a further period of 5 years.

Evaluation of articular cartilage using MRI may provide additional insight into disease progression, as it has been noted that 11% to 13% of cartilage volume is lost before the first changes of radiographic joint space narrowing can be detected.⁵³ Assessing knee articular cartilage volume from MRI has been shown to be a reliable measure, with low coefficients of variation (approximately 2%).^{54,55} Though it is still unclear which components of knee cartilage are the most useful to measure, assessing the radiographic progression of disease using MRI imaging may provide additional evidence for efficacy of disease-modifying agents. Consequently, despite inconclusive findings regarding the efficacy of glucosamine and chondroitin for relieving clinical manifestations of OA at the current time, the role of these agents in modifying the ultimate course of disease should not be discounted, particularly given their excellent safety.

Many glucosamine and chondroitin studies have been financed and supported by industry or manufacturers of the supplements under study. Not all studies clearly document the widespread financial relationships between study investigators, their academic institutions, and industry groups involved in the products under study. As noted in tables 2–6, financing was variable among the included studies. Seventeen studies were directly sponsored by industry; 10 studies were funded by non-profit foundations (though in 3 studies, one or more authors had industry ties and the study supplies were donated by industry); 1 study was funded both by industry and by a nonprofit foundation; no sources of support were identified in 4 studies (though the authors of 1 study had past ties to industry). These potential conflicts of interest have been well-studied and do, in fact, influence research.⁵⁶ While it is impossible to know the extent to which sponsorship influences the results discussed above in this review, the need for further study of glucosamine and chondroitin by independent investigators without industry support or financial ties is a necessary step in proving their clinical utility.

Another potential problem is the fact that, while clinical trials use products that have been rigorously tested for purity and quantity of the supplements, products available for

purchase in stores do not undergo federal testing for actual content.⁹ For example, in a study of 14 commercially available glucosamine preparations, Russell et al⁵⁷ notes variability in the amount of free base glucosamine ranging from 41% to 108% of the mg content stated on the label. Such differences in compound purity can certainly be expected to alter bioavailability and therefore affect therapeutic efficacy.

According to the Dietary Supplement Health and Education Act of 1994, manufacturers are required to ensure that their products are safe before they are marketed and that any claims made about the product are supported by adequate data; however, generally these companies are not required to submit these data to the FDA.⁵⁸ Once the product is marketed, it then becomes the FDA's responsibility to show that the product is unsafe before it can take action to either restrict use or remove it from the market. Unlike drug manufacturers, dietary supplement manufacturers and distributors are not required to record, investigate, or send the FDA reports they receive of adverse events that may be related to their product.⁹ Consequently, in the absence of clinical trials such as those detailed previously in this review, safety information on these products is limited to voluntary adverse event reporting, labeling claims, and product literature. It is therefore important for physicians to recommend appropriate brands in order to ensure that patients receive a product of sufficient quality and quantity to achieve any therapeutic effects.

This survey of the literature for the clinical and radiographic effects of glucosamine and chondroitin on knee OA is not a systematic review or meta-analysis of the data; definitive conclusions cannot be drawn from this narrative discussion. Our study was limited to articles published in English, causing the exclusion of 3 additional studies (1 GS, 1 CS, and 1 combination GS + CS) identified in our literature search. Evaluation of the English abstracts of these studies revealed positive results for the intervention as compared to placebo. Accordingly, we do not feel that the validity of this literature review was compromised by exclusion of non-English language studies.

Conclusion

Glucosamine and chondroitin have individually and collectively shown inconsistent efficacy, even in meta-analyses, in decreasing knee pain and improving joint function associated with OA, though there is some evidence to suggest that these agents may help prevent radiographic progression of disease. This variability suggests the need for further, more comprehensive study to identify a subset of patients in whom the use of glucosamine and/or chondroitin would be most beneficial. Though clinical outcomes may be variable on a

patient-to-patient basis, the literature consistently demonstrates an excellent safety profile of these agents; given this fact, even modest improvement could have clinical utility. These agents may be safely tried as an initial therapy in select OA patients prior to initiating therapy with NSAIDs, acetaminophen, and other traditional medications.

Disclosures

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