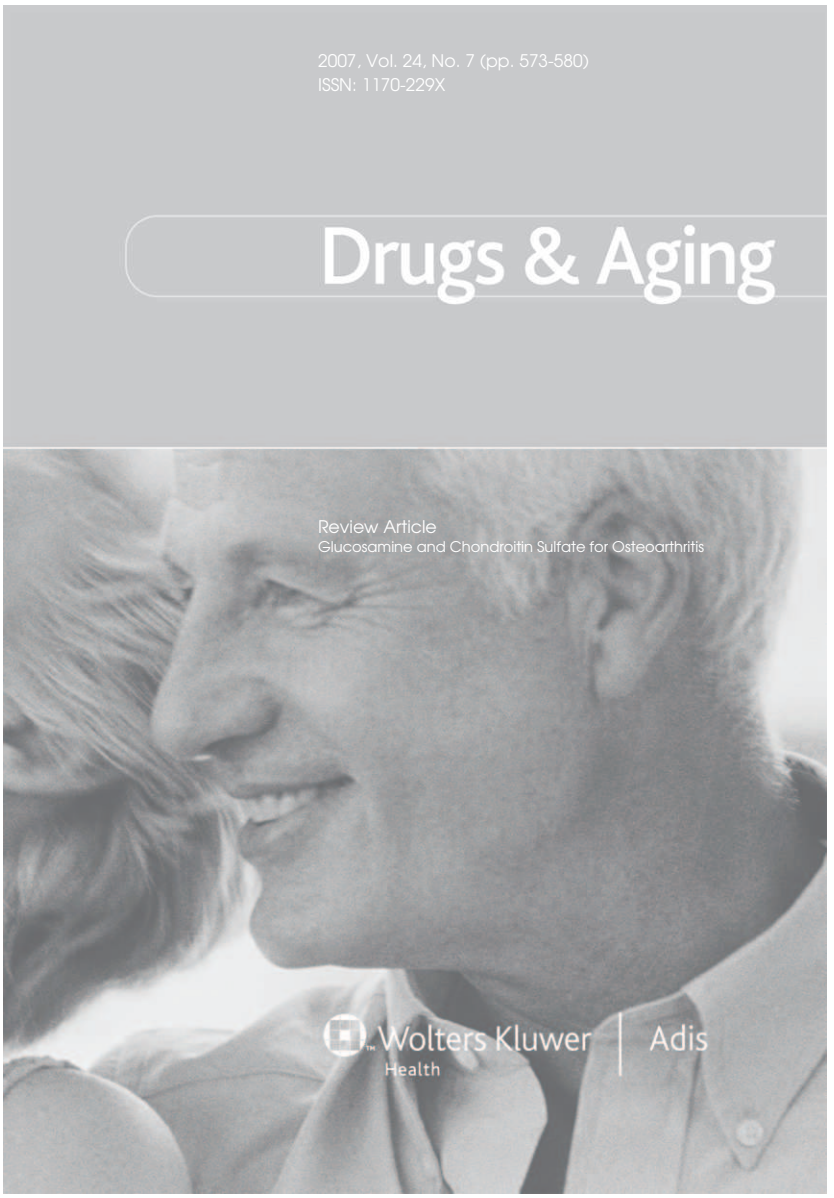

REVIEW ARTICLE

Drugs Aging 2007; 24 (7): 573-580
1170-229X/07/0007-0573/$44.95/0

Glucosamine and Chondroitin Sulfate as Therapeutic Agents for Knee and Hip Osteoarthritis

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Contents

Abstract

Osteoarthritis (OA), the most common form of arthritis, is a public health problem throughout the world. Several entities have been carefully investigated for the symptomatic and structural management of OA. This review evaluates published studies of the effect of glucosamine salts and chondroitin sulfate preparations on the progression of knee or hip OA.

Despite multiple double-blind, controlled clinical trials of the use of glucosamine and chondroitin sulfate in OA, controversy regarding the efficacy of these agents with respect to symptomatic improvement remains. Several potential confounders, including placebo response, use of prescription medicines versus over-the-counter pills or food supplements, or use of glucosamine sulfate versus glucosamine hydrochloride, may have relevance when attempting to interpret the seemingly contradictory results of different clinical trials. The National Institutes of Health-sponsored GAIT (Glucosamine/chondroitin Arthritis Intervention Trial) compared placebo, glucosamine hydrochloride, chondroitin sulfate, a combination of glucosamine and chondroitin sulfate and celecoxib in a parallel, blinded 6-month multicentre study of patients with knee OA. This trial showed that glucosamine hydrochloride and chondroitin sulfate alone or in combination did not reduce pain effectively in the overall group of patients with OA of the knee. However, exploratory analyses suggest that the combination of glucosamine hydrochloride and chondroitin sulfate may be effective in the subgroup of patients with moderate-to-severe knee pain.

For decades, the traditional pharmacological management of OA has been mainly symptomatic. However, in recent years, several randomised controlled studies have assessed the structure-modifying effect of glucosamine sulfate and chondroitin sulfate using plain radiography to measure joint space narrowing over years. There is some evidence to suggest a structure-modifying effect of glucosamine sulfate and chondroitin sulfate.

On the basis of the results of recent randomised controlled trials and meta-analyses, we can conclude that glucosamine sulfate (but not glucosamine hydrochloride) and chondroitin sulfate have small-to-moderate symptomatic efficacy in OA, although this is still debated. With respect to the structure-modifying effect, there is compelling evidence that glucosamine sulfate and chondroitin sulfate may interfere with progression of OA.

Osteoarthritis (OA) is the most common form of joint disease and the leading cause of pain and physical disability in older people.[1,2] For decades, the traditional pharmacological management of OA has been mainly symptomatic without well documented influence on the duration of the disease and its progression. However, in recent years, several sets of guidelines, recommendations, or points to consider have been issued by regulatory authorities or scientific groups regarding requirements for registration of drugs to be used in the treatment of OA.[3-5] The ideal outcomes currently include pain and function assessment for symptom-modifying drugs, and joint space narrowing assessed by plain radiography for structure-modifying compounds.[5] Taking advantage of these more precise recommendations, several chemical entities have been investigated in detail for the management of OA. In this review, we summarise the available evidence relating to whether glucosamine and chondroitin sulfate can effectively interfere with either the symptoms of OA or structural progression of the disease.

1. Glucosamine

Glucosamine is an aminosaccharide for which different forms (glucosamine sulfate and glucosamine hydrocholoride) have been tested as symptom-modifying OA drugs in randomised controlled trials (RCTs).

Some studies have been designed to assess the effect of glucosamine on the symptoms of lower-limb OA.[6,7] In a recent quantitative and qualitative review,[8] it was shown that glucosamine (sulfate and hydrochloride) was more effective than placebo with a 28% (change from baseline) improvement in pain (standardised mean differences [SMD] −0.61; 95% CI −0.95, −0.28) and a 21% (change from baseline) improvement in function on the Lequesne index (SMD −0.51; 95% CI −0.96, −0.05). In ten RCTs in which the Rotta preparation of glucosamine (glucosamine sulfate) was compared with placebo, glucosamine was found to be superior for pain (SMD −1.31, 95% CI −1.99, −0.64) and function on the Lequesne index (SMD −0.51, 95% CI −0.96, −0.05).

The symptomatic action of glucosamine sulfate has also been compared with that of NSAIDs. In one study, glucosamine sulfate 1500 mg/day and ibuprofen 1200 mg/day achieved similar success rates (48% and 52%, respectively) after 4 weeks of therapy in 200 hospitalised patients with knee OA, notwithstanding the fact that the effect of ibuprofen tended to occur sooner than that of glucosamine sulfate (after the first week of treatment in 48% vs 28% of patients, respectively).[9] These results were

replicated in a sister study involving 68 Chinese patients, in which a non-significant difference between ibuprofen and glucosamine sulfate in terms of reduction of the symptoms of OA was observed.[10]

Despite multiple double-blind, controlled clinical trials of the use of glucosamine in OA of the knee, controversy about its efficacy with respect to symptomatic improvement continues.[11] Indeed, meta-analyses have produced conflicting results.[6-8] In the Cochrane review by Towheed et al.,[8] it was suggested that conflicting trial results might have been due to use of different formulations of glucosamine, with the most favourable trial results being associated with the prescription glucosamine sulfate preparation.

Two recently published studies have added further information regarding the clinical status of glucosamine in the treatment of OA.[12,13] The first of these was the National Institutes of Health-sponsored GAIT (Glucosamine/chondroitin Arthritis Intervention Trial), which evaluated placebo, glucosamine hydrochloride 500mg three times daily, chondroitin sulfate 400mg three times daily, the combination of glucosamine hydrochloride and chondroitin sulfate, and celecoxib 200 mg/day in a parallel, blinded 6-month multicentre study of response in knee OA.[12] The primary efficacy variable was a 20% improvement in knee pain from baseline to 24 weeks. Overall, glucosamine hydrochloride and chondroitin sulfate were not significantly better than placebo for reducing knee pain by 20%. However, for patients with moderate-to-severe pain at baseline, the rate of response (OMERACT-OARSI [Outcome Measures in Arthritis Clinical Trials – Osteoarthritis Research Society] criteria) was significantly higher with combined therapy than with placebo (79.2% vs 54.3%, respectively; p = 0.002).

The second study was the GUIDE (Glucosamine Unum In Die [once-a-day] Efficacy) trial.[11,13] This 6-month double-blind, multicentre trial, conducted in Spain and Portugal, compared placebo, glucosamine sulfate 1500mg once daily and paracetamol (acetaminophen) 3000 mg/day in patients with OA of the knee. The primary efficacy variable was a change in the Lequesne algofunctional index. Although there was a numerical difference in improvement in the Lequesne algofunctional index between paracetamol and placebo, only the improvement in the Lequesne algofunctional index for glucosamine sulfate versus placebo was significant (p = 0.032). Secondary analyses, including the OARSI responder indices, were also significantly favourable for glucosamine sulfate (p = 0.004 vs placebo).

There are several potential confounders that may have relevance when attempting to interpret the seemingly contradictory results of clinical trials such as GAIT and GUIDE.

- In North America, glucosamine hydrochloride or sulfate and chondroitin sulfate are considered nutraceuticals, whereas in most European countries these agents are marketed as pharmaceuticals. Therefore, production and marketing of glucosamine are more closely monitored in Europe. In North America, varying quantities of glucosamine have been noted in a survey of several nutraceuticals.[14]
- Most of the negative clinical trials were performed with glucosamine hydrochloride 500mg three times daily, whereas most of the positive trials were performed with the glucosamine sulfate powder for oral solution at a dose of 1500mg once daily. For example, in an 8-week double-blind, placebo-controlled study followed by 8 weeks of off-treatment observation, glucosamine hydrochloride yielded beneficial results only in response to a daily diary pain questionnaire and had no effect on the primary endpoint (WOMAC [Western Ontario MacMaster] questionnaire).[15] This obviously raises the question, so far unanswered, of the importance of sulfate and of its contribution to the overall effects of glucosamine. Although the sulfate is readily

hydrolysed from the glucosamine in the gastrointestinal tract, there are suggestions that sulfate is in itself clinically relevant.[16,17]

- Interestingly, the most clinically relevant results in GAIT were seen when sodium chondroitin sulfate was taken with glucosamine hydrochloride. Whether this may be explained by an increase in the bioavailability of sulfates when taken with glucosamine requires further study. It is of note that several of the glucosamine preparations contain other salts that could potentially influence uptake and utilisation of glucosamine.[18]
- The placebo response in many clinical trials of oral agents in treatment of knee OA has traditionally been around 30%[19] and this typical response rate was replicated in the GUIDE study. The high placebo response in the GAIT study (60.1%) is of unknown significance, but might explain the findings of this trial. Clearly, if placebo is effective in 60% of patients, it is difficult for other treatments to surpass this rate.

Two other studies of glucosamine are also of interest because of the different methodologies employed.[20,21] The 12-week study by McAlindon et al.[21] deserves special mention since it is the only trial that has been conducted exclusively (including patient recruitment and follow-up) over the Internet. The results of this study suggested that glucosamine was no more effective than placebo in treating the symptoms of knee OA. However, it should be noted that this study was designed for a different purpose than assessment of glucosamine.[22]

The study by Cibere et al.[20] also deserves special mention since it is the only trial that was designed as a glucosamine discontinuation trial. For study eligibility, subjects were required to have been actively using glucosamine for OA for ≥1 month prior to study entry and also to have reported having experienced at least moderate improvement in knee pain since starting on glucosamine. The primary outcome was the proportion of disease flares in the glucosamine and placebo groups on intention-to-treat (ITT) analysis. Disease flare was seen in 28 (42%) of 66 placebo recipients and 32 (45%) of 71 glucosamine recipients ($p = 0.76$). In patients with knee OA who reported at least moderate subjective improvement with prior glucosamine use, this study provided no evidence of symptomatic benefit from continued use of glucosamine sulfate over a 24-week period. However, this trial allocated more than 35% of patients to ≤1000 mg/day of glucosamine, a dosage that is one-third lower than the approved 1500 mg/day dosage. In addition, the randomisation/withdrawal design of the trial was inadequate for drugs for which a carry-over effect is hypothesised, such as glucosamine:[3] indeed, almost 60% of patients in the study did not flare during the 6 months following the open-label glucosamine run-in period. In addition, the study was underpowered (≤70 patients/group) and there were severe imbalances in patient baseline characteristics (gender and disease severity) in favour of placebo.

To test the long-term structure-modifying effects of glucosamine sulfate on the knee OA joint, 212 patients with knee OA were randomly assigned in double-blind fashion to continuous treatment with glucosamine sulfate 1500mg once daily or placebo for 3 years.[23] Weight-bearing anteroposterior radiographs of each knee were taken at enrolment and every year for 3 years. The total mean joint space width of the medial compartment of the tibiofemoral joint was assessed by digital image analysis based on a validated computerised algorithm. After 3 years, placebo-treated patients had an average joint space narrowing of −0.31mm (range −0.48 to −0.13mm), whereas there was no joint space narrowing (mean −0.06mm; range −0.22 to 0.09mm) in the group treated with glucosamine sulfate ($p = 0.043$). Furthermore, the percentage of patients who experienced a clinically relevant (>0.5mm) mean joint space narrowing after 3 years was significantly

lower in the glucosamine sulfate group than in the placebo group (15 vs 30%, respectively; p = 0.013).

A 5-year follow-up evaluation of patients from this trial was performed to assess long-term outcomes of disease progression after the end of the study.[24] The primary endpoint of this follow-up study was the occurrence of OA-related joint surgery. Of the 177 patients participating in this follow-up evaluation, 26 (14.7%) underwent OA-related lower-limb surgery during the follow-up. Twice as many patients from the former placebo group underwent surgery, corresponding to a 48% decrease in risk with glucosamine sulfate that was borderline statistically significant (p = 0.06). The time-to-event analysis confirmed the results of the crude primary outcome, indicating a decreased (p = 0.05) cumulative incidence in OA-related lower-limb surgeries for patients formerly taking glucosamine sulfate. When only total hip and/or knee replacements were considered the trend was similar, with >40% reduction in risk after glucosamine sulfate, but the level of probability was lower and showed only a trend towards the significance threshold (p < 0.2).

The structure-modifying effect of glucosamine sulfate was confirmed in a similar trial involving a population of 202 men and women with a slightly worse degree of knee OA.[25] In this trial, the effect of glucosamine sulfate 1500 mg/day on rate of progression of the disease was statistically significant as early as the first year and remained so until the end of the 3-year follow-up. The investigators also described a significant (p = 0.03) reduction in the proportion of patients with worsening osteophyte score at endpoint (20% in the placebo vs 6% in the glucosamine sulfate group).

In light of these results, we can conclude that at least one formulation of glucosamine, i.e. glucosamine sulfate, has efficacy in the treatment of OA. Indeed, recent European League Against Rheumatism (EULAR) practice guidelines for knee OA have assigned the highest level of evidence, 1A, to glucosamine sulfate and accorded its use a strength A recommendation, in acknowledgement of the high quality of the studies performed.[26]

2. Chondroitin Sulfate

Chondroitin sulfate is a major component of the extracellular matrix of many connective tissues including, but not limited to, cartilage, bone, skin, ligaments and tendons. In articular cartilage, the high content of chondroitin sulfate in aggrecan plays a major role in creating the considerable osmotic swelling pressure that expands the matrix and places the collagen network under tension.

Several clinical trials have investigated the clinical effects of administration of chondroitin sulfate to patients with OA. In 127 patients with uni- or bilateral knee OA (Kellgren-Lawrence radiographic scores grade I–III), chondroitin sulfate 1200 mg/day, given either as a single daily oral dose or as 3 × 400mg, improved mean spontaneous joint pain measured on a visual analogue scale (VAS) by 50% and mean scores on Lequesne's index by 40–45% over 3 months, compared with placebo (10–15% increase in both the VAS and Lequesne's index scores).[27] In a similar population (n = 146), the same dosage of chondroitin sulfate (3 × 400 mg/day) was compared with diclofenac 3 × 50 mg/day.[28] Mean Lequesne's index score, spontaneous pain and pain on load were promptly (day 30) and drastically (by 35–50% at day 30 and 40–50% at day 90) reduced with the NSAID but reappeared after the end of the 3-month treatment period. With chondroitin sulfate, the therapeutic response appeared later (at day 60), was of greater magnitude at the end of the 3-month treatment period (80–85% increase) and lasted for up to 3 months after the end of treatment (50–80% increase at day 180).

A dose-finding study in patients with knee OA provided data supporting administration of chondroitin sulfate 800mg orally, which was shown to have nearly the same effects as the 1200 mg/day

dosage.[29] Chondroitin sulfate at a dosage of 800 mg/day was further evaluated in two other double-blind, placebo-controlled trials that included a total of 85 patients[30] with knee OA; the results obtained were within the same order of magnitude as those obtained with the 1200 mg/day dosage. Interestingly, this trial also showed a significant improvement in the chondroitin sulfate group (10% vs 0% change in the placebo group) in walking time, defined as the minimum time to complete a 20m walk.

The results of a meta-analysis following patients to ≥120 days showed chondroitin sulfate to be significantly superior to placebo with respect to the Lequesne index and pain VAS.[31] Pooled data confirmed these results and showed ≥50% improvement in the study variables in the chondroitin sulfate group compared with placebo. The authors concluded that chondroitin sulfate may be useful in OA, but further investigations in larger cohorts of patients for longer time periods are needed to prove its usefulness as a symptom-modifying drug in OA. Another study showed a trend towards efficacy of chondroitin sulfate 1 g/day compared with placebo with good tolerability after 3 months of treatment, and persistent efficacy 1 month post-treatment in patients with knee OA.[32] In the recent GAIT trial, 65.4% of patients taking chondroitin sulfate experienced a decrease of ≥20% in the WOMAC pain score compared with 60.1% of patients receiving placebo (p = 0.17).[12] It could be hypothesised, however, that the high placebo response (>60%) could have masked the symptomatic efficacy of chondroitin sulfate in this trial.

The structure-modifying effect of chondroitin sulfate has also been investigated. In a pilot double-blind study, joint space width measurement on digitalised radiographs of the extended knee was used to compare the effects of chondroitin sulfate 800 mg/day and placebo in patients with knee OA.[33] There were 23 patients in each group. After 1 year, mean joint space width was unchanged in the treated group but was decreased by a mean 0.4mm in the placebo group ($p < 0.005$). No significant difference was found for joint space width at the narrowest site. The small number of patients for whom endpoint values were available (12 in the placebo group and 14 in the chondroitin sulfate group) limits the relevance of these results.

Another study randomised a total of 120 patients with symptomatic knee OA into two groups receiving either chondroitin sulfate 800 mg/day or placebo for two periods of 3 months within 1 year.[34] Radiological progression was assessed, as a secondary outcome, by automatic measurement of medial femoro-tibial joint space width on weight-bearing x-rays of both knees. Radiological progression at month 12 showed significantly decreased joint space width in the placebo group with no change in the chondroitin sulfate group.

More recently, a double-blind, placebo-controlled trial randomly assigned 300 patients with knee OA to receive either chondroitin sulfate 800mg or placebo once daily for 2 years.[35] The primary outcome was joint space loss over 2 years as assessed by a posteroanterior radiograph of the knee in flexion. The 150 patients who received placebo had progressive joint space narrowing, with a mean ± SD joint space loss of 0.14 ± 0.61mm after 2 years ($p = 0.001$ compared with baseline). In contrast, there was no change in mean joint space width in the 150 patients receiving chondroitin sulfate (0.00 ± 0.53mm, p-value not significant compared with baseline). Similar results were found with respect to minimum joint space narrowing. The differences in loss of joint space between the two groups were significant for mean joint space width (0.14 ± 0.57mm, $p = 0.04$) and for minimum joint space width (0.12 ± 0.52mm, $p = 0.05$).

Recently, the results of a new large study were presented at the annual scientific meeting of the American College of Rheumatology.[36] This pro-

spective, randomised, double-blind, parallel-group, multicentre study compared orally administered chondroitin 4&6 sulfate 800 mg/day or placebo over 24 months in patients with knee OA. More than 600 male and female patients aged 45–80 years with tibio-femoral knee OA (pain and radiological signs) were recruited in Europe and North America. The primary efficacy outcome was the minimal joint space narrowing measured over 2 years on digitalised x-rays (Lyon schuss view). In the ITT analysis, patients from the placebo group had a mean (± standard error) joint space narrowing of 0.24 ± 0.03mm after 2 years, which was significantly prevented in the group treated with chondroitin sulfate (0.10 ± 0.03mm) [$p < 0.01$]. The per-protocol analysis confirmed the results obtained in the ITT analysis. Moreover, the interaction time × treatment showed a statistically significant difference in pain VAS and WOMAC (both $p < 0.01$) in favour of chondroitin sulfate.

Taking these well designed randomised controlled trials into account, we believe there are sufficient clinical data available to support the view that oral chondroitin sulfate is a valuable symptomatic treatment for OA disease with some potential structure-modifying effects.

3. Adverse Effects

The safety of OA treatments is also of great importance. A recent study of the safety of glucosamine and chondroitin sulfate showed that the evidence strongly supports safety at intakes of up to 2000 mg/day for glucosamine and 1200 mg/day for chondroitin sulfate, and these levels have been identified as the respective observed safe levels.[37] These values represent the highest levels tested in human clinical trials. The complete absence of adverse effects at these levels supports a confident conclusion about the long-term safety of these agents.

4. Conclusion

Glucosamine sulfate and chondroitin sulfate have shown small to moderate symptomatic efficacy in OA, although this finding is still debated. There is also some evidence to suggest a structure-modifying effect of glucosamine sulfate and chondroitin sulfate. However, it should be kept in mind that all conclusive results for these substances were obtained using prescription drugs containing these agents and should not be extrapolated to over-the-counter or food supplements, of which the content, pharmacokinetics and pharmacodynamics are not guaranteed.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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