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## Review

# What is the current status of chondroitin sulfate and glucosamine for the treatment of knee osteoarthritis?

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## ABSTRACT

Chondroitin sulfate and glucosamine sulfate exert beneficial effects on the metabolism of *in vitro* models of cells derived from synovial joints: chondrocytes, synoviocytes and cells from subchondral bone, all of which are involved in osteoarthritis (OA). They increase type II collagen and proteoglycan synthesis in human articular chondrocytes and are able to reduce the production of some pro-inflammatory mediators and proteases, to reduce the cellular death process, and improve the anabolic/catabolic balance of the extracellular cartilage matrix (ECM). Clinical trials have reported a beneficial effect of chondroitin sulfate and glucosamine sulfate on pain and function. The structure-modifying effects of these compounds have been reported and analyzed in recent meta-analyses. The results for knee OA demonstrate a small but significant reduction in the rate of joint space narrowing. Chondroitin sulfate and glucosamine sulphate are recommended by several guidelines from international societies for the management of knee and hip OA, while others do not recommend these products or recommend only under condition. This comprehensive review clarifies the role of these compounds in the therapeutic arsenal for patients with knee OA.

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## Contents

1. Introduction .....	00
2. Methods .....	00
2.1. CS and GlcN in clinical trials .....	00
2.1.1. Glucosamine (GlcN) .....	00
2.1.2. Chondroitin sulfate (CS) .....	00
2.1.3. GlcN and CS in combination .....	00
2.2. GINc and CS in guidelines .....	00
3. Discussion and conclusions .....	00
Contributors .....	00
Competing interest .....	00
Funding .....	00
Provenance and peer review .....	00
References .....	00

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## 1. Introduction

Osteoarthritis (OA), one of the most disabling arthritic conditions, is now clearly defined as a disease of the whole organ; namely, the synovial joint [1]. It is acknowledged that cartilage is not the sole tissue affected by OA, but that the subchondral bone and the synovial membrane (SM) undergo metabolic and structural modifications as the disease progresses [2].

The complexity of OA pathogenesis is a matter of fact and its management represents a challenge for the scientific community. Recently, different OA phenotypes have been described including obesity-related OA, mechanical-induced OA and aging-related OA. This suggests that OA treatment could be stratified and tailored to the relevant phenotype [3]. A key challenge will be to identify phenotypes for particular treatments. Until now, the management of OA has consisted mostly of symptom management, i.e. reduction of pain and improvement of joint function, which relies on the combination of non-pharmacologic and pharmacologic approaches as has been proposed by the main published guidelines [4–10]. Although important, the control of symptoms is not the only goal that needs to be achieved in OA patients. Indeed the ideal treatment for OA should preserve the joint structures, keeping in mind the improvement in the quality of life of patients [11] and exhibit a good safety profile. It is paramount to take into account the side effect due to the chronic use of OA therapies, such as NSAIDs [12].

Glycosaminoglycans such as chondroitin sulfate (CS) and glucosamine (GlcN) are two natural compounds considered as Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOA). Moreover, some of these compounds were also demonstrated to possess disease-modifying (DMOAD) potential based on the measurement of joint space narrowing on radiographs. Nevertheless, the use of these products as well as the relevance of their clinical efficacy are constantly under debate since they could be sold “over the counter” as dietary supplements in North America whereas they are registered drugs in Europe. This narrative review will provide an update on the potential mechanisms of action of CS and GS and the results of clinical trials will be further documented and discussed.

## 2. Methods

The literature search was performed using the PubMed/Medline databases between January 2009 and January 2014. Searches were performed in PubMed using the search terms “glucosamine”, “chondroitin sulphate”, “pharmaceutical-grade”, “osteoarthritis”, “randomized clinical trials”, “humans”. The MEDLINE database was searched for all randomized controlled trials, meta-analyses (MAs), systematic reviews, and review articles of chondroitin sulfate and glucosamine sulphate in OA.

Only articles published in English were included and clinical studies including knee OA patients were considered. Studies on the therapeutic effects of injectable substances were excluded.

### 2.1. CS and GlcN in clinical trials

In the following sections we review the evidence for CS and GlcN in published clinical trials.

#### 2.1.1. Glucosamine (GlcN)

The DMOAD effect of GlcN was analyzed in recent MAs [13,14]. Wandel et al. reported no relevant clinical effect based on an effect size (ES) on joint pain of  $-0.17$  ( $-0.28$  to  $-0.05$ ) and on joint space width (JSW) of  $-0.16$  ( $-0.25$  to  $0.00$ ) [13]. However, this MA showed numerous limitations and the interpretation of the data was hazardous with regards to the data [15]. Several expert groups in the field of OA have questioned the validity of the conclusions. Pitfalls of this MA were addressed in part in the report from the

British Medical Journal post-publication review meeting, which states that the data of the study did not directly support the strong negative conclusion of the study (Groves T. Report from BMJ post publication review meeting. Available at: [http://www.bmj.com/content/341/bmj.c4675.full%20./reply#bmj\\_el.247719](http://www.bmj.com/content/341/bmj.c4675.full%20./reply#bmj_el.247719) [accessed 19.06.11]).

The other MA, including only two trials [14], reported a small to moderate protective effect of GlcN-S on the minimum JSN after 3 years in knee OA. This was in accordance with the data of a recent trial indicating that GlcN-S prevented total knee replacement (TKR) [16]. In contrast, no effect was observed in hip OA with GlcN-S [17]. It is noteworthy that the Glucosamine/chondroitin Arthritis Trial (GAIT) study, the largest randomized controlled trial (RCT), did not report any significant effect for GlcN-HCl in knee OA patients [18]. The question of the importance of GlcN formulation was addressed in the MA by Wu et al. [19]. They concluded that GlcN-H was ineffective for pain reduction in patients with knee OA. GlcN-S may have function-modifying effects in patients with knee OA when administered for more than 6 months. However, it showed no pain-reduction benefits after 6 months of therapy.

Finally, it is also important to consider the analysis of the RCTs provided by the Osteoarthritis Research Society International (OARSI) in its recommendations to interpret both the symptomatic and structure-modifying effect of GlcN. It analyzed 19 RCTs (16 of them with GlcN-S and 3 with GlcN-HCl) [8]. It reported an ES for pain of  $0.46$  ( $0.23$ – $0.69$ ), translating a moderate symptomatic effect even if it decreased since the last analysis ( $0.61$  ( $0.28$ – $0.95$ )) [6]. However, it revealed a strict difference between GlcN-S (ES for pain  $0.58$  ( $0.30$ – $0.87$ )) and GlcN-HCl ( $-0.02$  ( $-0.15$  to  $0.11$ )). In addition, ES of GlcN-S for pain tended to decrease when considering only high quality clinical trials ( $0.29$  ( $0.003$ – $0.57$ )). It also reported an ES on the reduction of joint space narrowing (JSN) of  $0.24$  ( $0.04$ – $0.43$ ) for GlcN-S on knee OA but no effect on hip OA.

#### 2.1.2. Chondroitin sulfate (CS)

As with GlcN, CS has also been evaluated in different clinical trials to document both its symptomatic potential and its structure-modifying effect. The symptomatic efficacy of CS in knee OA has been proven [16]. In addition, a highly purified CS formulation (800 mg/day) produced symptomatic effect in hand OA [20]. A recent study [21] demonstrated a similar efficacy of CS on symptoms (pain on VAS and LI for function) when administered as a single daily dose of 1200 mg or three times a day at 400 mg. The authors concluded at an efficient and safe intervention. Interestingly, CS produced a significant reduction in joint swelling and effusion during the GAIT study [18].

A significant DMOAD effect for CS has been reported in RCTs. It was shown to produce a reduction of JSN [22], a significant difference in mean and minimal JSW [23] and a significant difference in joint space surface and mean JSW [24]. The MA by Hochberg et al. [25] and its update including studies of 2-year duration [26] demonstrated a modest but significant effect of CS (800 mg/kg) on the rate of decline of the minimum JSW. The MA by Lee et al. concluded at a delay of disease progression by CS [14]. A recent clinical trial, not yet included in MAs reported a symptomatic effect of CS (800 mg/day) combined with a reduction of the cartilage volume loss, bone marrow lesions and synovitis in knee OA patients [27].

The analysis provided in the OARSI guidelines [8] determined an ES of  $0.75$  ( $0.50$ – $0.99$ ) on pain and of  $0.26$  ( $0.16$ – $0.36$ ) for JSN but mentioned the industry bias that could exist and the heterogeneity of the results. If all studies are considered, the ES on pain of CS ( $0.75$  ( $0.50$ – $1.01$ )) was higher than those reported for GS ( $0.58$  ( $0.30$ – $0.87$ )) and especially for NSAIDs ( $0.29$  ( $0.22$ – $0.39$ )). This last consideration is important since we know the severe adverse effect induced by the long-term use of NSAIDs in OA patients. Clearly, the

risks/benefits balance seems to be in favor of CS. This should be considered at the time of therapeutic decision in the daily practice.

### 2.1.3. *GlcN and CS in combination*

While administered alone, neither GlcN-H nor CS produced any clinical effect during the GAIT study. However, the combination (GlcN-HCl 500 mg–CS 400 mg; three times a day) was shown to be efficient for pain relief and function improvement in OA patients with moderate to severe knee pain [18]. This finding suggests that a combination of GlcN and CS could be more efficient than CS or GlcN administered alone. Recently, the effects of GlcN/CS combination on progression of structural changes in knee OA was evidenced in a sample of the National Institutes of Health Osteoarthritis Initiative (OAI) longitudinal cohort. In participants taking a combination of GlcN and CS, the loss of cartilage volume over 24 months was reduced in some subregions when the assessment was made with quantitative magnetic resonance imaging (qMRI), arguing for a disease-modifying effect of GlcN and CS combined [28]. Finally, a double randomized placebo-controlled clinical trial with 2-year follow-up of 605 patients with knee OA, demonstrated that after adjusting for factors associated with structural disease progression (gender, body mass index, baseline structural disease severity and Heberden's nodes), dietary supplement combination of GlcN and CS resulted in a statistically significant reduction of joint space narrowing compared to placebo while CS or GlcN alone were without effect [29].

### 2.2. *GlcN and CS in guidelines*

The European League Against Rheumatism (EULAR) and the 2010 OARSI guidelines for the treatment of symptomatic knee OA recommend CS and GS [5–8]. In contrast, the UK's National Institute for Health and Care Excellence (NICE) has recommended that these products should not be used, mainly for economical reasons, while the American College of Rheumatology (ACR) recommended GS and CS under certain conditions [4]. Recently, OARSI has released new guidelines based on previous OA guidelines, an update of the 2010 OARSI systematic review and a consensus of 13 experts from relevant medical disciplines using the RAND/UCLA Appropriateness method and Delphi voting process for consensus [30]. The experts' vote resulted in an uncertain appropriateness for CS and GS despite a good quality of evidence, a very low risk score, a moderate to high effect size (up to 0.75 for CS) and a high benefit score.

## 3. Discussion and conclusions

There is significant evidence in the published literature as reviewed here to support the promising DMOAD potencies of both GlcN and CS. Some MAs have evidenced these beneficial effects and these compounds are currently recommended by EULAR. In contrast, these products were not recommended by the recent OARSI 2014, ACR 2013 and NICE 2013 guidelines. In most European countries, these drugs are prescribed whereas in US, they are delivered over-the-counter and they are not of pharmaceutical grade. In 2008, OARSI published evidence and expert consensus-based recommendations for the management of hip and knee osteoarthritis (OA) Treatment with GlcN-S and/or CS was recommended for knee OA with the proviso that it should be discontinued if no response is apparent within 6 months, although both may have long-term structure-modifying effects as shown in previous clinical trials [31,32] and confirmed in later study [22]. In 2010, Zhang et al. [8] published an update of the evidence available for therapies used in the treatment of hip and knee OA. The highest level of evidence (1a) was available for CS, GlcN-S while glucosamine

hydrochloride (GlcN-H) received a lower level (1b). The effect size (ES; 95% CI), which measures the strength of efficacy comparing to placebo was 0.58 (0.30, 0.87) for GlcN-S and 0.75 (0.50, 1.01) for CS. These ES were considered as moderate and they were smaller in more recent and higher quality trials, but they were still clinically relevant and at least comparable to those of NSAIDs and superior to acetaminophen (paracetamol). Recently, OARSI has released new guidelines based on previous OA guidelines, an update of the 2010 OARSI systematic review and a consensus of 13 experts from relevant medical disciplines [30]. Treatments were recommended as appropriate, uncertain, or not appropriate for each subphenotype. Appropriate pharmacological treatments for specific clinical subphenotypes included acetaminophen (paracetamol), capsaicin, duloxetine, oral NSAIDs (COX-2 selective and non-selective) and topical NSAIDs. Treatments of uncertain appropriateness for specific subphenotypes included Avocado/Soybean unsaponifiables, CS, GlcN, diacerein, opioids and rosetip. Only riserodronate was considered as inappropriate. The experts' vote resulted in an uncertain appropriateness for GlcN and CS despite a good quality of evidence, a very low risk score, a moderate to high effect size (up to 0.75 for CS) and a high risk/benefit score. Oral NSAIDs, well known to possibly induce adverse events especially in older patients and in patients with digestive, cardiovascular, or renal comorbidities, were appropriate for individuals without comorbidities despite a high risk score and a benefit score in the same order of magnitude of SYSADOAs. Therefore, why this reluctance for GlcN and CS? Several hypotheses can be formulated: (1) non-European experts were not familiar with prescription SYSADOA and were faced with products sold over-the-counter with heterogeneous and non-pharmaceutical grade quality; (2) favorable results from clinical trials of the prescription products have been mixed and confused with those obtained in poorer quality studies and/or performed with over-the-counter lower quality products, causing high study heterogeneity; (3) there may be a gap between results from clinical trials performed on a subset of well-characterized OA patients and the effects observed by practitioners on a general population in the real life; (4) a lack of confidence of the experts for industry sponsored clinical trials (although this should apply to all drugs, since they are all developed by the industry). Therefore, the term "uncertain" associated to GlcN and CS must be well explained to practitioners. The OARSI experts themselves did not consider the term "uncertain" as a negative recommendation which could preclude the use of GlcN and CS. Rather, it requires a role for physician–patient interaction in determining whether such treatments may have merit in the context of their risk-benefit profile and the individual characteristics, co-morbidities and preference of the individual patient. In this context, CS and GS which show a favorable risk/benefit ratio should be considered especially for the treatment of older OA patients with co-morbidities limiting the long-term and/or recurrent administration of drugs like oral NSAIDs and paracetamol, that were considered appropriate but have a lower risks/benefits ratio. Recent MAs [33] and clinical trials [22,34–37] have suggested that GlcN-S, GlcN-H and CS may contribute to reduce the intake of NSAIDs or paracetamol. Exclusion of GlcN and CS from the therapeutic arsenal of OA patients carries the risk to increase iatrogenic damages due to the overuse of NSAIDs and analgesics that in some countries are delivered over-the-counter without medical control. It is the responsibility of practitioners to treat OA patients by integrating within their individual level analysis, the risks and benefits for each treatment, the individual's co-morbidities, the efficacy of the therapy (continuous assessment of the symptoms) and the patient's personal preference.

Therefore, the used of CS and GS is an individual patient/physician informed decision by scientific, medical and economical evidence.

Most of the authors of the literature cited recommend the use of pharmaceutical grade products rather than food supplements. They insist on the importance of the formulation and quality of GlcN [38,39] and CS [40,41]. In the same way of thinking, one may consider the use of GlcN and CS as a combination therapy. Moreover, much evidence has been gathered here that document the potential that both compounds could exert on joint tissues during OA. One may therefore foresee additional benefits if not merely a synergistic potency.

### Contributors

YH has written the paper. MM and AM have reviewed it and checked the literature.

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