

Chondroitin and Glucosamine in the Management of Osteoarthritis: An Update

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Abstract The objective of osteoarthritis (OA) treatment is not only control of symptoms (i.e. reducing pain and improving function) but also to preserve joint structure and maintain quality of life. OA management remains challenging. Glucosamine and chondroitin are two compounds available for treatment of OA patients. Taken alone or in combination, they have a good safety profile and a variety of effects. In-vitro and in-vivo experiments have revealed that both compounds induced key intermediates in the OA pathophysiological process. Clinical trials, although providing conflicting and questionable results, report symptomatic and structure-modifying effects for both pharmaceutical-grade compounds. This review will discuss all these subjects and emphasize the importance of the quality of tested compounds for achieving high quality clinical trials.

Keywords Osteoarthritis · Cartilage · Chondroitin sulfate · Glucosamine · Treatment · Complementary and alternative medicine · Animal studies · Clinical efficacy

Introduction

Osteoarthritis (OA) is one of the most debilitating arthritic diseases, associated with pain and impairment of joint function leading to patient disability. This common and multifactorial disease, which evolves over decades, remains incurable. OA involves all joint tissues [58•, 73], and is associated with degeneration of articular cartilage and of the menisci, and

sclerosis of subchondral bone accompanied by inflammation of the synovial membrane.

OA pathogenesis is complex, and management of OA is challenging. No specific therapy has yet been found to stop disease progression: management of OA mostly involves control of symptoms, i.e. reduction of pain and improvement of joint function, and relies on a combination of non-pharmacological and pharmacological approaches as recommended in recent clinical guidelines [34, 47, 93–96, 97••]. Although important, symptom control is not the only objective of OA treatment. An ideal treatment would preserve articular structures, improve patient quality of life [35], and have a good safety profile. It is of great importance to take into account side effects of OA therapy, as illustrated by the long-term risks associated with non-steroidal anti-inflammatory drugs [90].

Symptomatic slow-acting drugs (SYSADOAs), including chondroitin sulfate (CS) and glucosamine (GlcN) sulfate (S) or hydrochloride (HCl), are part of the symptomatic treatment of OA. Some of these compounds have also been revealed, on the basis of joint-space narrowing measured on plain radiographs, to have disease-modifying (DMOAD) potential. Use of these compounds, and the significance of their clinical efficacy, is debated: they are sold “over the counter” as dietary supplements in North America, whereas they are registered drugs in Europe.

CS and GlcN are recommended by European League Against Rheumatism (EULAR) and Osteoarthritis Research Society International (OARSI) guidelines for treatment of symptomatic knee and hip OA [93, 95, 96, 97••]. However, recent American College of Rheumatology (ACR) guidelines did not recommend these compounds [34] because data supporting their efficacy are equivocal, they are not approved by the Food and Drug Administration (FDA), and they are only available as dietary supplements. Both products have a variety of properties, revealed by in-vivo and in-vitro experiments, and clinical trials of their effects revealed many causes for concern. This review will provide an update on possible

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mechanisms of action of GlcN and CS, and will review and discuss clinical trial results. Finally, the potential benefits of treatment with a combination of these products will be investigated.

Glucosamine

In-vivo and in-vitro experiments, many of which have recently been reviewed [32•], have provided much evidence for possible mechanisms of action leading to structure-modifying effects of glucosamine. This section will update the reader on effects observed in vivo and in vitro on cartilage, subchondral bone, and synovial inflammation. It will also cover the effect of glucosamine on OA symptoms, and its structure-modifying potential observed in clinical trials.

In-vitro Effect

GlcN was first believed to affect cartilage by providing building blocks for synthesis of glycosaminoglycans (GAG) by the GLUT receptor, then by competing with glucose [30]. Studies reported that GlcN could have anti-catabolic and anti-inflammatory effects: when GlcN-HCl ($100 \mu\text{g mL}^{-1}$) is applied to chondrocytes and synoviocytes it inhibits inflammatory mediators, prostaglandin (PG) E_2 , nitric oxide (NO), and matrix metalloproteinases (MMPs) [65]. This is the result of its effect on different cell-signaling intermediates: for example, it has been revealed to inhibit cyclooxygenase (COX)-2 and MMP-13 in human skin fibroblasts (10 mmol L^{-1}) by blocking p38 [38]. These results support previously published data obtained from chondrosarcoma cell lines [57] and mouse macrophages (RAW 264.7) [71]. D-GlcN (2 mmol L^{-1}) blocks activation of the signaling intermediates p38 and Akt, thus inhibiting COX-2 expression, PGE_2 production and iNOS expression and synthesis (p38), and MMP-3 inhibition and proteoglycan synthesis (Akt) [57]. Inhibition by GlcN-HCl ($2.5\text{--}10 \text{ mmol L}^{-1}$) of COX-2 and iNOS in mouse macrophages was also found to occur via inhibition of p38 [71]. Finally, a cationic derivative of GlcN ($10\text{--}50 \mu\text{g mL}^{-1}$) was proved to inhibit production of cytokines and MAPK, p38 and JNK in RAW 264.7 [60]. The latest study revealed that GlcN inhibited MMP-2 and MMP-9, and confirmed its effect on nuclear factor-kappa B (NF- κ B) and on AP-1 [61]. It was also revealed that GlcN affected both NF- κ B synthesis and its translocation to the nucleus. The inhibitory effect of GlcN on NF- κ B was first observed in human OA chondrocytes with GlcN-S ($10\text{--}1,000 \mu\text{g mL}^{-1}$) [54]. This effect was recently revealed to occur via an epigenetic mechanism [43]: GlcN prevents demethylation of specific CpG sites in the IL-1 β promoter, consequently preventing expression of IL-1 β .

Inhibition of MMPs could be caused by the increased GAG production observed in synovial cells and chondrocytes with GlcN-HCl ($0.06\text{--}1 \text{ mmol L}^{-1}$) [40]. Another study suggested that the protective effect of GlcN-HCl in rat cartilage was brought about via induction of anabolic mediators, including transforming growth factor (TGF)- β 1 and connective tissue growth factor (CTGF) [2]. Kapoor et al. revealed that GlcN-S ($1\text{--}2 \text{ mmol L}^{-1}$) reduced PGE_2 in human chondrocytes via inhibition of microsomal prostaglandin E synthase 1 (mPGES1) [49]. The same study revealed inhibition of COX-2 and increased levels of an anti-inflammatory transcription factor, peroxisome proliferator-activated receptor (PPAR)- λ .

Chiusaroli et al. revealed that low concentrations of GlcN-S ($0.001\text{--}100 \mu\text{mol L}^{-1}$) inhibited IL-1 β -stimulated IL-6, tumor necrosis factor (TNF)- α , MMP-3 and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-5 in a chondrosarcoma cell line (SW1353), via inhibition of NF- κ B and AP-1 [21•]. The same authors continued the investigation with an in-vivo experiment on the STR/ort mouse (which spontaneously develops OA), and reported that GlcN reduced all OA histology scores.

A recent pharmacoproteomic study by Calamia et al. [12••] revealed that GlcN-S inhibited proteins involved in signal transduction pathways, redox and stress response, and protein synthesis and folding processes. GlcN may also increase levels of chaperone GRP78, suggesting another possible mechanism for GlcN's anti-inflammatory effect.

In addition to cartilage and synovial membrane, it is now well recognized that subchondral bone has an important function in OA pathogenesis. GlcN ($0.1\text{--}1 \text{ mmol L}^{-1}$) induced osteoblast differentiation and blocked differentiation of osteoclasts in mouse cells (MC3T3-E1) [41], limiting the effect on bone resorption and enabling bone deposition. The effect that it produced on the osteoblastic differentiation of MG-63 cells was more than that associated with an anti-inflammatory action [51].

Animal Studies

In animal studies, GlcN had different protective effects. High doses of GlcN (300 mg kg^{-1}) given to rats with adjuvant arthritis (AA) reduced both arthritic score and synovitis [39]. This effect was associated with reduction of PGE_2 and NO concentrations in plasma. Different studies have illustrated the anabolic effect of GlcN. GlcN-HCl (100 mg daily) administered to rabbits after anterior cruciate ligament transection (ACLT) preserved cartilage [78]. The same effect was observed when GlcN-HCl (20 or 100 mg day^{-1}) was administered to rabbits after chymopapain injection [66]. Cartilage preservation was believed to be caused by restoration of GAG content. Loss of GAG in cartilage, and bone erosion and osteophyte formation, were also inhibited by GlcN-HCl ($20 \text{ mg kg}^{-1} \text{ day}^{-1}$)

administered to collagen-induced-arthritis (CIA) mice [44]. Reduced soluble receptor activator of nuclear factor-kappa B ligand (RANKL) and interleukin (IL)-6, and increased IL-10, were believed to cause this protective effect. For rats, GlcN-HCl also reduced macroscopic changes induced by ACLT, and inhibited degradation and enhanced synthesis of type II collagen [64]. For guinea pigs spontaneously developing OA, GlcN-HCl (200 mg kg⁻¹) reduced Mankin histology scores for OA via inhibition of MMP-3 mRNA [75]. For ACLT rabbits with early stage OA, GlcN-HCl (100 mg day⁻¹) preserved joint structure, possibly by attenuating bone changes [87]. Finally, GlcN-S (250 mg kg⁻¹ day⁻¹) affected rat nociception, protected cartilage and reduced synovitis, via inhibition of mitogen-activated protein kinases (MAPK), p38, and JNK, and increasing extra-cellular Erk1/2 [89]. It is noted that most experimental data concern GlcN-HCl.

Clinical Efficacy

Whether GlcN should be regarded as a SYSADOA and whether it has a structure-modifying effect remain controversial. However, numerous published clinical trials document a symptomatic effect, i.e. reduced pain and improved joint function. There have been several meta-analyses (MAs) of data from these trials [8, 59, 70, 79, 82].

The DMOAD effect of GlcN was analyzed by two MAs [55•, 86]. On the basis of an effect size (ES) for joint pain of -0.17 (-0.28 to -0.05) and for joint space width (JSW) of -0.16 (-0.25 to 0.00), Wandel et al. reported no clinically meaningful effect [86]. However, this MA had several limitations [29] and several OA experts have questioned the validity of the conclusions. Disadvantages of this MA were addressed in part by the report from the British Medical Journal post-publication review meeting, which states that the study data did not directly support the strong negative conclusion (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; accessed July 21, 2013).

A second MA reported a small-to-moderate protective effect on the minimum JSN after three years. However, it included only two trials [55•]. The GAIT study, the largest randomized controlled trial (RCT), did not report any significant effect of GlcN-HCl for knee OA patients [24], and no effect of GlcN-S was observed for hip OA [72]. However, a recent trial suggested GlcN-S could prevent total knee replacement (TKR) [9].

When analyzing the symptomatic and structure-modifying effects of GlcN, it is important to consider the RCT analysis provided in OARSI's recommendations. OARSI guidelines committee members analyzed 19 RCTs (16 of GlcN-S and three of GlcN-HCl) [97••]. They reported an ES for pain of 0.46 (0.23 to 0.69), which was reduced in size compared with

the previous analysis (0.61 (0.28 to 0.95)) but still equivalent to a moderate effect on symptoms [96]. Data analysis continues to emphasize the difference between different preparations of glucosamine: the ES for pain of GlcN-S is 0.58 (0.30 to 0.87), whereas that of GlcN-HCl ES is -0.02 (-0.15 to 0.11). In addition, the ES for pain of GlcN-S tended to decrease when only high-quality clinical trials were included in analysis (0.29 (0.003 to 0.57)). This analysis also reported a reduction of joint space narrowing (JSN) ES for GlcN-S of 0.24 (0.04 to 0.43) for knee OA, but no effect on hip OA.

Chondroitin Sulfate

As for GlcN, understanding of the mechanisms of action of CS is incomplete. Several extensive reviews [26, 31, 85] have detailed the effectiveness of CS *in vivo* and *in vitro*. This section will summarize available information and discuss use of CS as a symptomatic and structure-modifying OA treatment. Just as there is controversy about which glucosamine formulation has the greatest effect, different authors favor different chondroitin formulas. Different CS formulations produce different effects *in vitro*. C4S from shark cartilage and C6S from porcine cartilage had different efficacy profiles for chondrocytes and synoviocytes [42], and in a pharmacoproteomic study [10•] on chondrocytes, reported by Tat et al. [76], different results were obtained with three different CS formulations. Hence, because CS is extracted and purified from animal sources, different properties and effects are observed [83, 84].

In-vitro Effect

Recent *in-vitro* studies have investigated the mechanism of action of CS to explain its variety of properties. Its anti-inflammatory effects have been widely reviewed [26, 32•, 85]. In addition to an anabolic effect, CS has anti-inflammatory, anti-catabolic, anti-apoptotic, and anti-oxidant effects (Fig. 1) on articular tissue. Its anti-catabolic effects have been studied in human chondrocytes and synovial fibroblasts [42]. CS (1 – 10 $\mu\text{g mL}^{-1}$) inhibited IL-1 β -induced expression of ADAMTS-4 and ADAMTS-5 genes in both cell types, and increased levels of tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-3 in synoviocytes. CS also had an anabolic effect, characterized by increased type II collagen and proteoglycan synthesis in human articular chondrocytes [4, 88] and increased GAG, with concentrations in the range 1 – $1,000$ $\mu\text{g mL}^{-1}$, in bovine chondrocytes [56]. The anti-catabolic effect in chondrocytes occurred at doses in the range 1 – $1,000$ $\mu\text{g mL}^{-1}$, via inhibition of MMP-1, MMP-3, and MMP-13, and via ADAMTS-4 and ADAMTS-5 expression [56, 63, 74]. Another mechanism of action is induction of

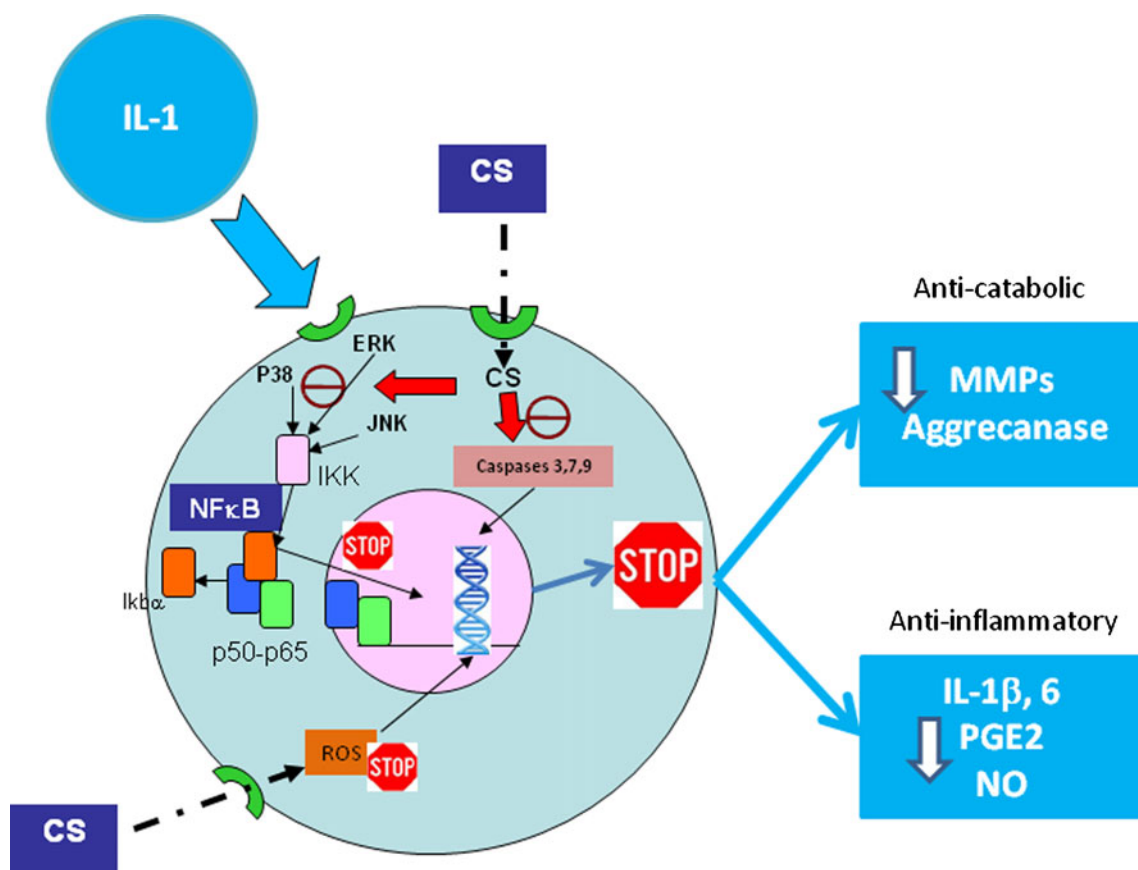


Fig. 1 Schematic representation of the cellular mechanisms of action of chondroitin sulfate (CS). *ERK*, extracellular signal-regulated kinases; *JNK*, c-Jun N-terminal kinases; *IKK*, I κ B kinase; *NF κ B*, nuclear factor

kappa-light-chain-enhancer of activated B cell; *ROS*, reactive oxygen species; *MMP*, matrix metalloproteases; *IL*, interleukin; *PGE2*, prostaglandin E2; *NO*, nitric oxide

some cell signaling intermediates, including Akt and Erk1/2, and inhibition of some others, including p38 and JNK. In human synoviocytes, CS ($100 \mu\text{g mL}^{-1}$) brought about activation of hyaluronic acid (HA) synthase and HA production [25]. The investigators interpreted their results as indicating that CS had an anti-inflammatory effect, and that it maintained viscosity within the joint. A joint-lubricating effect was also suggested in bovine cartilage explants [50]. Other signaling mediators are also affected by CS: p38 and Erk1/2 activation were inhibited by CS ($25 \mu\text{g mL}^{-1}$) in human articular chondrocytes stimulated by lipopolysaccharide (LPS), reducing levels of MMP-13 [37].

CS ($0.5\text{--}1.0 \text{ mg mL}^{-1}$) had anti-apoptotic effects on mouse chondrocytes stimulated with LPS [17], and CS ($30\text{--}120 \text{ mg kg}^{-1}$) inhibited caspase-3 and caspase-9 and NF- κ B in mouse CIA [16].

Inhibition of NF- κ B by CS could be an important mechanism for both its chondroprotective and its anti-inflammatory effect. CS inhibits both p38 and Erk1/2 activation, and inhibits NF- κ B translocation in rabbit chondrocytes (CS, $200 \mu\text{g mL}^{-1}$) [46]. A potent anti-inflammatory effect of CS ($25\text{--}50 \mu\text{g mL}^{-1}$) was observed in mouse chondrocytes. In this model, inhibition by CS of the signaling pathway involving MyD88, TRAF-6

and NF- κ B activation [18] caused down-regulation of inflammatory cytokines and iNOS. This evidence supports the theory that CS has a function in cell survival and anti-inflammatory action [81], resulting in its chondroprotective effect.

Another potentially important aspect of the effect of CS on OA is its anti-oxidant effect. CS provided protection against hydrogen peroxide and superoxide anions, limited cell death by reducing DNA fragmentation and protein oxidation, reduced generation of free radicals, and acted as a scavenger. It reduced lipid peroxidation, and supported anti-oxidative defense by restoring endogenous anti-oxidants, including glutathione and superoxide dismutase (GSH and SOD) [14, 15]. Interestingly, CS had anti-angiogenic potential in an innovative model of culture of human OA synoviocytes [53]: CS ($10\text{--}200 \mu\text{g mL}^{-1}$) reversed the inhibitory effect of IL-1 on the anti-angiogenic factors VEGF and TSP-1. This mechanism could explain the protective and anti-inflammatory effect of CS in the synovial membrane. Finally, CS ($200 \mu\text{g mL}^{-1}$) preserved subchondral bone in human OA osteoblasts, reducing bone resorption while increasing osteoprotegerin (OPG) and reducing RANKL, then modulating the OPG/RANKL ratio to favor bone formation [77]. A recent study of primary calvaria mouse osteoblasts confirmed and detailed the CS

mechanism of action [69•]: CS ($100 \mu\text{g mL}^{-1}$) reduced PGE₂ and MMP-3 and MMP-13 in an inflammatory context, and inhibited COX-2, mPGES1, and RANKL. Furthermore, the previously mentioned pharmacoproteomic study on articular chondrocytes [12••], revealed that CS blocked proteins involved in energy production (31 %) and metabolic pathways (15 %). An additional investigation of the chondrocyte secretome [11••] also provided evidence of potential anti-inflammatory, anti-angiogenic, and anti-catabolic properties of CS. CS inhibited several complement components (CFAB, C1S, CO3, and C1R) and increased TNF- α -induced protein (TSG6), which is responsible for reduction of pro-MMP activation.

Animal Studies

The effect of CS observed in animal models provided insight into the potential of CS for use as an anti-inflammatory agent able to preserve articular structures. It has been known for a long time that CS can reduce synovitis ($1,000 \text{ mg kg}^{-1}$) [67] and inhibit IL-6 ($1,200 \text{ mg kg}^{-1}$) [22] in mouse CIA. In addition, when administered as a food supplement ($1.2 \text{ g kg}^{-1} \text{ day}^{-1}$) CS halted IL-1 β effects in rat adjuvant arthritis (AA) [23], inhibited plasma TNF- α and myeloperoxidase, and limited destruction of articular structures in rat CIA [13]. More recently, CS ($300\text{--}900 \text{ mg kg}^{-1}$) reduced severity of arthritis and inhibited oxidative stress in rat AA [5]. The authors reported that the treatment reduced C-reactive protein (CRP), phagocytic activity and the intra-cellular oxidative burst of neutrophils. As also observed for GlcN-HCl, when tested on guinea pigs spontaneously developing OA, CS (200 mg kg^{-1}) protected cartilage by inhibition of MMP-3 mRNA [75].

Clinical Efficacy

Clinical trials have evaluated the symptomatic potential and structure-modifying effect of CS. There is much evidence of the symptomatic efficacy of CS for knee OA [9], and a highly purified CS formulation (800 mg day^{-1}) reduced symptoms of hand OA [27••]. A recent study [92] observed a similar efficacy of CS for symptoms (pain on VAS and LI for function) when administered as a single daily dose of $1,200 \text{ mg}$ or three times a day at 400 mg . The authors concluded that CS was an effective and safe intervention. One of the few positive findings of the GAIT study was that CS significantly reduced joint swelling and effusion [24].

A significant DMOAD effect of CS has been reported by RCTs. It was observed to produce a reduction of JSN [48], a significant difference in mean and minimum JSW [62], and a significant difference in joint space surface and mean JSW

[80]. The MA by Hochberg et al. [36] and its update [33], including studies of two years' duration, concluded that CS (800 mg kg^{-1}) had a modest but significant effect on decline of minimum JSW. A second MA by Lee et al. concluded that both CS and GlcN could delay disease progression [55•]. A recent trial, not yet included in published MAs, reported a symptomatic effect of CS (800 mg day^{-1}) combined with reduction of cartilage volume loss, bone marrow lesion, and synovitis for knee OA patients [91].

The analysis in the OARSI guidelines [97••] determined an ES of 0.75 (0.50–0.99) for pain and of 0.26 (0.16–0.36) for JSN, but mentioned that industry bias could exist and that results were heterogeneous. If all studies are considered, the ES for pain of CS (0.75 (0.50–1.01)) was higher than those reported for GS (0.58 (0.30–0.87)) and, interestingly, for NSAIDs (0.29 (0.22–0.39)). Therefore, some investigators suggest that the risk/benefit balance seems to be in favor of CS and that this should be considered when making therapeutic decisions in daily practice.

Glucosamine and Chondroitin Combination

GlcN and CS have also been tested for efficacy when administered in combination, to determine whether concomitant administration of GlcN and CS could provide additional benefit over either agent alone.

In-vitro Effect

Some evidence for combined effects of GlcN and CS comes from in-vitro experiments. A combination of $5 \mu\text{g mL}^{-1}$ GlcN-HCl and $20 \mu\text{g mL}^{-1}$ CS had complementary anti-catabolic and anti-inflammatory effects in bovine cartilage explants stimulated by IL-1 β [19, 20]. The combination reversed the catabolic effect of IL-1 β by inhibiting the proteolytic enzymes MMP-3, MMP-13, ADAMTS-4, and ADAMTS-5, and by increasing the expression of TIMP-1 and TIMP-3. This effect resulted in increased expression of GAG and increased type II collagen. Under the same experimental conditions the anti-inflammatory mediators mPGES1, COX-2, PGE₂, and NO were inhibited by the GlcN–CS combination, rather than by CS alone.

Another study ([12••], previously mentioned) observed that not only could both compounds affect different pathways, but that they could also induce combined inhibition of superoxide dismutase (SOD)-2. This further supports the theory that, at least in combination, these two agents have an anti-oxidant effect.

The anti-resorptive effect observed with CS alone was confirmed for the combination of GlcN ($200 \mu\text{g mL}^{-1}$) and CS ($200 \mu\text{g mL}^{-1}$) in OA osteoblasts [77]. On the basis of this

study, the combination might be more effective against bone resorption than either compound alone.

Animal Studies

In vivo, the combination of GlcN-S ($1,000 \text{ mg kg}^{-1}$) and CS (800 mg kg^{-1}) was chondroprotective for rabbit OA generated through partial meniscectomy [52]. The combination of $1.5 \text{ g kg}^{-1} \text{ day}^{-1}$ GlcN-S + $1.2 \text{ g kg}^{-1} \text{ day}^{-1}$ CS, given via a food bar, was observed to have a better effect than CS alone on mouse CIA, inhibiting IL-1 β and MMP-9. A combination of GlcN (750 mg) and CS (750 mg) administered intramuscularly also had a positive effect on horses with OA, measured via a flexion test of the tarsocrural and metacarpophalangeal joints [3]. A significant symptomatic effect of the combination (1.8 g day^{-1} GlcN + 5.4 g day^{-1} CS) was also reported by an in-vivo investigation on global pain of horses [28].

Finally, a combination of GlcN-HCl (500 mg) and CS (400 mg) seemed to enable rabbits to remodel tendon [68]. It is important to consider the effect of potential OA treatment on soft periarticular tissues, because these also affect pathogenesis of OA.

Clinical Efficacy

Only very limited data are available regarding the effect of combined GlcN and CS on humans. When administered alone, neither GlcN-HCl nor CS had any clinical effect during the GAIT study. However, the combination (GlcN-HCl 500 mg + CS 400 mg; three times a day) brought about pain relief and function improvement for OA patients with moderate to severe knee pain [24]. The limitations of the GAIT trial are well known, and make it difficult to determine whether this result is clinically meaningful.

Discussion

Glucosamine and chondroitin sulfate have a variety of in-vitro anti-inflammatory and anti-catabolic effects, although these have been obtained by using higher concentrations than those reached in humans [6, 7, 31, 32]. These effects have led to the generation of hypotheses regarding potential mechanisms by which GS and CS might bring about symptom control and structure modification for OA patients.

The actions of these products involve multiple signaling intermediates: for example, they bring about their anti-inflammatory and anti-catabolic effect via inhibition of P38, AKT, and NF- κ B. CS and GS also stimulate synthesis of proteoglycans, via a “building block” process. Interestingly, these

compounds act on the three main articular tissues involved in OA pathophysiology, i.e. cartilage, subchondral bone, and synovial membrane. CS and GS may counteract the deleterious crosstalk between these tissues and break the vicious circle that perpetuates OA.

These in-vitro data contribute to explaining the symptomatic and structural effects of GS and CS. Some meta-analyses have supported these beneficial effects, and the compounds are now recommended by EULAR and OARSI, two international organizations for scientists and health care professionals focused on the prevention and treatment of OA. These organizations also emphasized the importance of using pharmaceutical grade products: quality control requirements for prescribed drugs and OTC dietary supplements are not the same. Interestingly, most of the positive results were obtained from sponsored studies, but these were also the ones using pharmaceutical-grade products. In addition, doses and formulations should be adjusted to achieve sufficient concentration of treatment in plasma [1]. A recent pharmacokinetic study of both compounds (GlcN-HCl 500 mg three times a day, CS 400 mg three times a day), alone or in combination, for knee OA patients reported the compounds had low circulating levels after oral administration [45]. It could be worth testing an improved formulation.

Conclusions

GlcN and CS have promising in-vitro properties and effects. The extent to which formulation of the products affects efficacy in vitro remains the subject of debate. Although symptomatic effect is well documented, the structure-modifying effect suggested by animal and human clinical trials should be confirmed by additional studies to establish their clinical efficacy beyond doubt. In addition, it might be worth further investigating use of GlcN and CS in combination. Finally, standardization of the outcome measures of clinical trials would assist data interpretation and enable rigorous comparisons.

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Compliance with ethics guidelines

Conflict of interest Yves Henrotin has served as a consultant for Tilman; has received grant support from Biolberica, Royal Canin, and Nestle; has received honoraria from IBSA, Artialis, and Synolyne; has held stock/stock options in Artialis and Synolyne; has received speaker fees from IBS and Biolberica; and has had travel/accommodation expenses covered/reimbursed by IBSA, Expanscience, and Biolberica.

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Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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