The role of glucosamine and chondroitin sulfate in treatment and prevention of osteoarthritis in animals

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Joint disease, in particular osteoarthritis, is an important cause of lameness and debilitation for humans and other animals. Presently, a number of pharmacologic agents are available for treatment for osteoarthritis, including nutraceuticals containing glucosamine and chondroitin sulfate. Although to date clinical trials in veterinary patients are limited, trials conducted in humans have for the most part provided encouraging results. Results of in vitro studies suggest that these compounds may impede the progression of joint degeneration in osteoarthritis.

The purpose of this review is to provide veterinary practitioners with up-to-date information regarding the mechanism of action, pharmacokinetics, clinical efficacy, and safety of glucosamine and chondroitin sulfate.

Structure of Articular Cartilage and Pathophysiology of Osteoarthritis

Chondrocytes, the cellular component of articular cartilage, are responsible for the synthesis and maintenance of the extracellular matrix in which they are embedded. The extracellular matrix is composed of collagen (predominantly type II collagen) and proteoglycans, with a smaller percentage of glycoproteins (Figure 1). Type II collagen arranged in fibrils is responsible for the tensile strength of articular cartilage.1 Proteoglycans consist of a central protein core to which 1 or more glycosaminoglycan (GAG) side chains are attached. In turn, GAGs are composed of repeating disaccharide units of hexosamine (glucosamine or galactosamine) alternating with another residue of glucuronate, iduronate, or galactose. The largest and most predominant proteoglycan in cartilage is aggrecan.2

Chondrocytes synthesize aggrecan by covalently attaching GAGs (chondroitin sulfate and keratan sulfate) to a central protein core of proteoglycans in an organized manner. This core protein of the proteogly-
can forms aggregates with hyaluronan, a nonsulfated GAG. A separate globular protein termed link protein assists this binding. The precursors of GAGs are amino sugars, such as glucosamine, that are synthesized via the hexosamine biosynthetic pathway from glucose (Figure 2). Much of the compressive resistance of cartilage is attributable to these GAG side chains. Specifically, as GAGs are negatively charged, they attract water and it is the water content that imparts resistance to compression and load dissipation.

Osteoarthritis occurs in previously normal joints that may have been damaged by various factors; most commonly in veterinary patients, the damage is caused by trauma. Although all articular tissues are damaged by this disease, the hallmark of osteoarthritis is the progressive and permanent degeneration of articular cartilage.

Grossly, articular cartilage degeneration is apparent as fibrillation, erosion, and wear lines. Cartilage loss can be estimated via joint space narrowing on radiographs of affected joints obtained during weight bearing. Other radiographic abnormalities are also useful in the evaluation of osteoarthritis, and the disease is typified and classified by radiographic manifestations including osteophyte production, subchondral bone sclerosis, and periosteal proliferation.

Cartilage loss in osteoarthritis occurs as a consequence of enzymatic degradation of the extracellular matrix, resulting in loss of proteoglycans and cleavage of type II collagen. Several enzymes are responsible for the degradation, including the matrix metalloproteinases (MMPs) and aggrecanases. The MMPs are zinc-dependent proteinases involved in the normal physiologic turnover of cartilage. The MMPs have naturally produced inhibitors termed tissue inhibitors of metalloproteinases (TIMPs) that help regulate MMP activity. In osteoarthritis, the production of TIMPs is insufficient to control increased MMP activity.

Matrix metalloproteinases are similar in structure but differ somewhat in their preferred substrates. Specifically, collagens (MMP-1, -8, and -13) cleave the intact triple helix of collagen. These collagen fragments are susceptible to further proteolysis by gelatinases (MMP-2 and -9), enzymes that can also cleave aggrecan. Stromelysins (MMP-3, -10, and -11) are capable of degrading aggrecan, denatured type II collagen, and small proteoglycans of the extracellular matrix.

Aggrecanases appear to be the principal mediators of aggrecan degradation. Their activity results in the release of core protein and GAG constituents of aggrecan into synovial fluid. The GAG fragments have been used as markers of cartilage loss in osteoarthritis. Aggrecanases, like MMPs, are metalloproteinases and can be inhibited by TIMPs. Osteoarthritis is associated with increased concentrations of other inflammatory mediators such as nitric oxide and prostanoids, particularly prostaglandin E2 (PGE2). Nitric oxide is a cytotoxic free radical, the by-product of oxygenation of L-arginine by nitric oxide synthase. Nitric oxide induces a number of pathophysiologic events characteristic of osteoarthritis, including enhanced MMP synthesis and reduced synthesis of interleukin-1 receptor antagonist (IL-1Ra), proteoglycan, and type II collagen. Prostaglandin E2 is present in increased concentrations in synovial fluid of animals with osteoarthritis. Purported actions of PGE2 in affected joints include vasodilation and cartilage proteoglycan depletion. Furthermore, this mediator enhances pain perception, and synovial fluid PGE2 concentrations are correlated with those of substance P, a neurotransmitter found in high concentration in synovial fluid of patients with osteoarthritis.

Central to the induction of degradative enzyme activity and inflammatory mediator synthesis in osteoarthritis tissues are a number of cytokines, the most important of which is IL-1. Cytokines appear to be first produced by cells of the synovial membrane and later by activated chondrocytes. Interleukin-1 mediates its effects on cells through a cell membrane-associated receptor (IL-1R), the expression of which increases in osteoarthritis, resulting in cells that are more sensitive to stimulation by IL-1. In vitro, the response to stimulation with IL-1 is multifactorial, with effects on degradative enzymes, inflammatory mediators, and extracellular matrix components. In general, IL-1 acts to enhance cartilage degeneration and inhibit efforts at repair (Appendix).
Structure and Pharmacokinetics of Glucosamine and Chondroitin Sulfate

Glucosamine—Glucosamine is an amino monosaccharide (2-amino-2-deoxy-β-D-glucose) that, once modified as N-acetylg glucosamine, is a precursor of the disaccharide units of GAGs such as hyaluronan and keratan sulfate. Isomerisation converts glucosamine to galactosamine, a structural component of chondroitin sulfate and dermatan sulfate. Most glucosamine in the body is in the form of glucosamine-6-phosphate. Glucosamine is commercially available in 3 forms: glucosamine hydrochloride, glucosamine sulfate (sulfate salt), and N-acetyl-D-glucosamine. Glucosamine is a small water-soluble molecule (molecular weight, 179) with a pKa that favors its intestinal absorption and intracellular transportation. Absorption is carrier mediated, whereas absorption of N-acetylg glucosamine occurs via diffusion. Quantitative aspects of glucosamine absorption have been debated. Limitations were evident with early analytical methods used in pharmacokinetic and bioavailability studies, suggesting the need to administer doses far exceeding concentrations considered therapeutic or achievable in animals. However, early methods revealed nearly 90% absorption after oral administration (via glucose transporters), incorporation into plasma proteins, and bio-transformation in the liver. In all species tested, glucosamine was rapidly distributed into tissues, with a tropism for articular cartilage indicated by levels of radioactivity in cartilage that exceed those in plasma. Furthermore, cartilage radioactivity is still detectable for up to 6 days after administration of a single dose of radiolabeled glucosamine, and multiple dosing results in accumulation of glucosamine in cartilage.

The recent development of more sensitive and accurate techniques that eliminate interference by degradation products has enabled determination of plasma concentrations achievable after oral administration in rats and dogs. Results of single-dose pharmacokinetics of glucosamine performed by use of those methods support its absorption, with lower oral bioavailability in horses than in dogs. In horses, doses at presently recommended concentrations result in plasma concentrations that are below the limits of quantification, necessitating the use of doses approximately 3 to 10 times greater, and multiple-dose pharmacokinetics remain to be determined. Application of newer methods will help to clarify the concentrations achieved in plasma, synovial fluid, and perhaps cartilage after oral administration and may prove indispensable in modifying present oral dosing protocols.

Chondroitin sulfate—Chondroitin sulfate is a GAG consisting of alternating disaccharide subunits of glucuronic acid and sulfated N-acetylgalactosamine. Substitution can occur at the C4 or C6 position of the sulfate residue attached to N-acetylgalactosamine to form chondroitin-4-sulfate and chondroitin-6-sulfate, respectively. Chondroitin sulfate is a normal constituent of cartilage; chondroitin-4-sulfate predominates in immature cartilage, and the ratio of chondroitin-6-sulfate to chondroitin-4-sulfate increases with age. It seems clear that exogenously administered chondroitin sulfate is capable of influencing the metabolism of cartilage in health and disease.

Like glucosamine, results of an early study suggested that the oral bioavailability of chondroitin sulfate was limited. Limitations in detection methods at the time, such as lack of sensitivity to distinguish between constituent chondroitin sulfate disaccharides, prompted the development of other analytic methods to detect plasma concentrations. Further studies have revealed that oral absorption is rapid, with more than 70% absorption in rats and dogs.

Similar to glucosamine, a tropism for articular cartilage has been detected for chondroitin sulfate, with concentrations also exceeding plasma concentrations for prolonged periods after dosing. Of interest, in rats, cartilage concentrations are greater with oral rather than IM administration, and in dogs, the concentration of chondroitin sulfate in synovial fluid exceeds that in plasma by 66.5%.

Development of techniques with higher specificity and recovery has enabled detection of chondroitin sulfate disaccharides in dog and horse plasma after IV administration, and results of a recent pharmacokinetic study suggest ample oral absorption in horses. Although multiple and long-term dosing studies are presently sparse, results indicate that chondroitin sulfate is absorbed in veterinary patients; however, specific concentrations achieved in various tissues remain to be determined.

In combination, orally administered glucosamine hydrochloride and chondroitin sulfate are rapidly absorbed in dogs. Although single- and multiple-dose pharmacokinetics of glucosamine are similar, chondroitin sulfate disaccharides accumulate in plasma after multiple dosing, indicating a substantial carryover effect that is in agreement with that previously detected in vitro. This accumulation and carryover effect may be responsible for the continued improvement noted in clinical trials after administration has been discontinued and may support the administration of lower doses of chondroitin sulfate in maintenance therapy.

Safety Profile and Product Quality Assurance

Results of clinical trials and pharmacokinetic studies suggest a good safety profile for both products in all
species tested, and the popularity of these products as alternatives to nonsteroidal anti-inflammatory drugs (NSAIDs) has been enhanced because they have comparatively fewer adverse effects. An association between glucosamine and diabetes mellitus in humans does not appear to be well-founded. Oral administration of glucosamine hydrochloride, low-molecular-weight chondroitin sulfate, and manganese ascorbate at doses exceeding the recommended daily dose in cats, dogs, and horses is associated with a good safety profile, with adverse effects limited to gastrointestinal upset and, occasionally, polydipsia-polyuria in dogs. No clinically important alterations in hematologic indices are apparent, and clotting profiles are unaltered in cats, dogs, and horses, suggesting that concerns with coagulation abnormalities also appear to be unfounded. Nonetheless, because of the structural similarity of GAGs and heparin, the concurrent use of these products with other platelet inhibitors, such as phenylbutazone or aspirin, is often cautioned.

Nutraceuticals are classified as dietary supplements by the FDA and, as such, are not subject to stringent regulatory guidelines. Thus, commercially available products vary widely in terms of purity and quality, and studies of efficacy and absorption of most of these formulations are lacking. Although results of 1 study suggest that liquid formulations of chondroitin sulfate have better absorption, compared with capsules, direct comparisons of efficacy of different formulations are lacking.

Results of 1 study indicate that human over-the-counter products vary widely in composition, and > 84% do not meet the label claim. Evaluation of veterinary nutraceuticals is less readily available. An independent laboratory reported that only 50% of products tested met label claims. In another study of equine products, actual composition, compared with the label claim, ranged from 63.6% to 112.2% for 5 glucosamine products and 22.3% to 155.7% for 5 chondroitin sulfate products. For 1 combined product, glucosamine content was 86% and chondroitin sulfate content was 83.3% of the label claim. Although products are often marketed with “guaranteed analysis,” only a small number consistently meet label claims. Studies of in vivo or in vitro efficacy of veterinary products are limited, and claims of efficacy are often made on the basis of subjective methods of assessment, including testimonials by owners or clinical trials that have not been subjected to peer review. Despite these issues, glucosamine and chondroitin sulfate products continue to gain popularity.

In Vitro Studies of Mechanism of Action

Glucosamine—Initially, beneficial effects of glucosamine supplementation were attributed to the provision of raw materials required for components of cartilage. When an exogenous form of glucosamine is available, the rate-limiting steps in the hexosamine biosynthetic pathway are bypassed (Figure 2); exogenous glucosamine is preferentially used in the synthesis of GAGs when cells are cultured without glucose. The preferential incorporation of glucosamine into galactosamine moieties of chondroitin sulfate in articular cartilage explants supports the use of glucosamine as a source of cartilage matrix components; however, this mode of action has been debated.

Glucosamine has numerous in vitro effects and influences the expression or activity of many mediators of osteoarthritis (Appendix). Actions include a reduction in proteoglycan degradation and inhibition of the synthesis and activity of degradative enzymes and inflammatory mediators such as aggrecanases, MMPs, nitric oxide, and PGE₂, (Figure 3). Anabolic effects are limited to stimulation of GAG and proteoglycan production, including aggrecan, with no effect on type II collagen.

The form of glucosamine appears to influence its activity, with glucosamine hydrochloride and glucosamine sulfate appearing to inhibit cartilage degener-
and chondroitin sulfate decreases nitric oxide produc-

tion and proteoglycan degradation and inhibits MMP-9 and -13 but not MMP-2, which is suggestive of a syn-
ergistic effect. Under conditions simulating in vivo joint stress in bovine cartilage, the combination protects against stress-induced reduction of proteoglycan syn-
thesis. Of interest, although cartilage from aged animals is more responsive to stress, it is also more responsive to supplementation. In vitro, combination doses are lower than those that are effective when each com-

High doses of glucosamine may have a detrimental effect on chondrocyte viability in vitro, however, other studies using similar doses failed to reveal similar effects on cell viability, although a protective action against cytokine-induced catabolic effects was maintained. Furthermore, no detrimental effect on chondrocyte metabolism was observed with long-term exposure to glucosamine.

Results of recent studies indicate that glu-

Glucosamine and chondroitin sulfate in combina-

tion—Because many commercially available products contain both glucosamine and chondroitin sulfate, effects of the combination in vitro have been investigat-
ed and results add support to the chondroprotective effect reported in clinical trials. In equine cartilage in vitro, the combination of glucosamine hydrochloride and chondroitin sulfate decreases nitric oxide produc-

In Vivo Clinical Trials of Efficacy

Humans—Several clinical trials have been per-

Glucosamine and chondroitin sulfate versus

NSAIDs—Part of the attraction of glucosamine and chondroitin sulfate is their potential use as an alter-

ative to other drugs presently used in the treatment of osteoarthritis, in particular NSAIDs, for which adverse
effects have long been a concern. Compared with ibuprofen, glucosamine has greater influence in terms of pain reduction in patients with temporomandibular joint osteoarthritis. In another study, NSAID administration resulted in prompt reduction of clinical signs; however, signs reappeared after cessation of treatment, compared with patients treated with chondroitin sulfate who had a delayed onset but greater duration of benefit (3 months) after cessation of treatment. Despite shortcomings of glucosamine-chondroitin sulfate, results in human clinical trials suggest that relief from clinical signs is comparable between glucosamine-chondroitin sulfate and NSAIDs, and trials in which substantial preservation of joint space was detected suggest that both may actually slow the progression of cartilage loss.

The combination of NSAIDs and nutraceutical therapy has been proposed for the treatment of osteoarthritis. Such treatment has the potential to reduce the dose requirement of NSAIDs and therefore their associated adverse effects; however, such an approach may raise concerns with respect to coagulation problems. Although it appears that NSAIDs and nutraceuticals induce their effects through different pathways, nutraceuticals are also capable of cyclooxygenase inhibition and potentially have further widespread beneficial effects (Appendix). Nevertheless, a program of maintenance supplementation with nutraceuticals combined with supplementation with NSAIDs when needed is often permitted in human clinical trials and could perhaps become the mainstay of treatment programs for other animals with osteoarthritis in the future.

**Companion animals**—Recently, several clinical trials and experimental models that used a combination of glucosamine hydrochloride and chondroitin sulfate were conducted in companion animals. Results of such trials suggest a cartilage-sparing or chondroprotective effect via a reduction in histologic severity of osteoarthritis lesions. The combination of glucosamine hydrochloride and chondroitin sulfate results in a greater chondroprotective effect in rabbits than either compound alone, which suggests a synergistic effect; however, comparisons were not made to responses to increased individual doses, and the synergistic mechanism is unknown. In dogs, results of 2 studies indicate both preventative and therapeutic effects in experimental models of osteoarthritis. Clinical signs as well as synovial fluid variables, serum GAG content, and articular cartilage metabolism improved, which suggests a more normal synovial environment.

**Horses**—To date, clinical trials in horses are limited and results are variable. Similar to the findings in companion animals, the efficacy of these compounds appears to be supported by results of some studies. Flaws in study design and assessment of outcome have increased skepticism regarding the value of these compounds in pleasure and performance horses. Administration of a product containing glucosamine hydrochloride, low-molecular-weight chondroitin sulfate, and manganese ascorbate to horses with osteoarthritis in the distal interphalangeal, metacarpophalangeal, tarsometatarsal, or carpal joints resulted in improvement in lameness grade, flexion test grade, and stride length within 2 weeks; however, no further improvement in lameness grade and no significant changes in other variables were seen after 4 weeks. Although the lack of continued improvement may be attributable to the return of most of the horses in the study to exercise and competition after the initial 2 weeks of treatment, return to previously attainable performance levels and continuation in a competitive career would appear to be a necessity and expectation for owners of affected horses.

Results of other studies using this combination have varied; no beneficial effects were evident in a chemically induced model of osteoarthritis, whereas in another trial, force plate measures of lameness improved. In a study of horses with osteoarthritis of the distal intertarsal or tarsometatarsal joints, administration of another commercially available product containing glucosamine, glutamic acid, glycine, and glucuronic acid resulted in improvement in vertical ground reaction force and reduction in gait asymmetry. Similarly, in an experimentally induced model of osteoarthritis, chondroitin sulfate (administered IM and PO) was associated with improved joint function and reduced lameness scores. Maximum level of improvement was comparable for both routes of administration; however, time of onset of clinical improvement was slower with oral administration. Results of clinical trials of glucosamine and chondroitin sulfate in horses suggest possible improvement in clinical signs; however, rigorously designed long-term trials are needed.

**Correlation Between Concentrations Used In Vitro and Those Achievable After Oral Administration**

Concentrations of glucosamine and chondroitin sulfate that have a substantial in vitro effect vary depending on the species, method of analysis, and the measured effect. Combining these compounds has revealed significant effects, often at doses lower than that of either product alone. For instance, in equine cartilage, glucosamine concentration as low as 250 µg/mL decreases PGE2 production, MMP activity, and proteoglycan release, although higher concentrations are required to decrease nitric oxide production or to affect MMP mRNA expression. Plasma concentrations have been measured in dogs after single dosing, with concentrations from 7.1 to 12.1 µg/mL for glucosamine and 19.0 to 21.5 µg/mL for chondroitin sulfate. Multiple dosing did not alter glucosamine concentrations, although chondroitin sulfate did accumulate in plasma (after 2 weeks, concentration was 208 µg/mL). As would be expected, IV administration results in higher plasma concentrations of glucosamine and chondroitin sulfate in dogs and horses. In horses, single oral-dose administration results in maximum plasma concentrations of 10.6 and 36.5 µg/mL for glucosamine and chondroitin sulfate, respectively, < 2 hours after administration. Thus, the cumulative concentration of chondroitin sulfate in vivo (208 µg/mL) is similar to the concentration that inhibits cartilage degradation in vitro (250 µg/mL), whereas glucosamine concentration does not appear to have a similar correlation; however, glucosamine may accumulate in cartilage.
It appears likely that these compounds achieve concentrations compatible with at least some of their reported chondroprotective effects at presently recommended oral doses (22 mg/kg [10.0 mg/lb] for glucosamine HCl and 8.8 mg/kg [4.0 mg/lb] for low-molecular-weight chondroitin sulfate). Although concentrations presently used in vitro exceed measured plasma concentrations, a number of factors suggest that studies are using more representative concentrations that are achievable with oral administration. In vitro studies have largely involved simultaneous administration of these compounds as the osteoarthritis process is stimulated. Effective concentrations of glucosamine and chondroitin sulfate in vitro may in fact be lower if these compounds are used prior to the induction of osteoarthritis, and it is not known whether their in vivo chondroprotective effects may occur at concentrations lower than those required in vitro. Furthermore, the fact that these compounds accumulate in cartilage and synovial fluid suggests that therapeutic concentrations may be lower than those measured in plasma. Determination of the minimal effective concentration of these compounds, alone and in combination, requires further investigation.

Conclusions
The beneficial effects of glucosamine and chondroitin sulfate, alone and in combination, have been established in vitro in several species. Although concentrations used in recent studies more closely resemble concentrations achievable in vivo after oral administration, cartilage and synovial fluid concentrations have not been determined. As the use of products containing these compounds continues to gain popularity, studies to further elucidate the mechanism of action and pharmacokinetics are needed. These compounds have promise in terms of protection of articular cartilage and provision of relief of clinical signs of osteoarthritis. Extrapolation of results of human trials to veterinary patients suggests that the use of these compounds is likely to be of greater benefit in patients with mild to moderate osteoarthritis than those with more severe or chronic lesions. Furthermore, use of these compounds may reduce the requirement for other anti-inflammatory drugs and analgesics such as NSAIDs. Glucosamine and chondroitin sulfate-containing nutraceuticals may become a mainstay of preventative maintenance programs that provide support for aging animals and may aid in extending competitive careers of athletes, particularly horses. The duration of their effect and possible beneficial effects in slowing the progression of osteoarthritis or even preventing its onset warrant further investigation.

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### Appendix

Influence of interleukin-1 (IL-1) on articular cartilage matrix components, inflammatory mediators, and degradative enzymes.

<table>
<thead>
<tr>
<th>Mediator/matrix molecule</th>
<th>IL-1 effect on chondrocyte biosynthesis</th>
<th>Blocked by glucosamine*&lt;sup&gt;13,40,41&lt;/sup&gt;</th>
<th>Blocked by chondroitin sulfate*&lt;sup&gt;30,35&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>COX-2/PGE₂, iNOS/NO, MMPs</td>
<td>Stimulates synthesis, induces synthesis, activity, and secretion</td>
<td>√&lt;sup&gt;30,35&lt;/sup&gt;</td>
<td>√&lt;sup&gt;30,35&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aggrecanases/aggrecan</td>
<td>Increased synthesis and activity</td>
<td>√&lt;sup&gt;34,36&lt;/sup&gt;</td>
<td>X&lt;sup&gt;34,36&lt;/sup&gt;</td>
</tr>
<tr>
<td>PGs/GAGs</td>
<td>Decreased synthesis, increased degradation</td>
<td>X&lt;sup&gt;38&lt;/sup&gt;</td>
<td>√&lt;sup&gt;38,40,46&lt;/sup&gt;</td>
</tr>
<tr>
<td>Type II collagen</td>
<td>Inhibits synthesis</td>
<td>X&lt;sup&gt;38&lt;/sup&gt;</td>
<td>X&lt;sup&gt;38&lt;/sup&gt;</td>
</tr>
<tr>
<td>Transcription factors (NFκB, AP 1)</td>
<td>Stimulates increased mRNA expression and activity</td>
<td>√&lt;sup&gt;(NFκB, AP 1)&lt;/sup&gt;</td>
<td>√&lt;sup&gt;(NFκB, AP 1)&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*The ability (check marks) or lack of ability (X's) of glucosamine or chondroitin sulfate to inhibit effects induced by IL-1 as reported in various studies is indicated. Superscript numerals indicate reference numbers. COX-2 = Cyclooxygenase-2. PGE₂ = Prostaglandin E₂. iNOS = Inducible nitric oxide synthase. NO = Nitric oxide. MMPs = Matrix metalloproteinases. PGs = Proteoglycans. GAGs = Glycosaminoglycans. NFκB = Nuclear factor kappa B. AP 1 = Activator protein 1.*