clinical applications™

CHONDROITIN SULFATE
NEW INSIGHTS & RECOMMENDATIONS
FOR OSTEOARTHRITIS

NAV C
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Understanding of the role of chondroitin sulfate (CS) in cartilage and subchondral bone has been enhanced by recent research on its efficacy as therapy in osteoarthritis (see REPORT sidebar beginning on page 6). As early as 1966, researchers noted a decrease in CS concentration and chain length in osteoarthritic cartilage.

In healthy cartilage, thousands of CS molecules reside within proteoglycans – the structures that bind water in joint cartilage. When the proteoglycans are entrapped by the much larger collagen fibrils, the resulting meshwork maintains the tension and high osmotic pressure that enables joints to function normally. In healthy cartilage, the proteoglycans release fluid and sweep out metabolic waste when the joint is under pressure, and moisture and nutrients flow back into the cartilage when pressure is removed. An amorphous matrix, cartilage is both produced by and contains chondrocytes, with collagen and elastin fibers acting as a framework that gives it its shape and strength.

Disease occurs when the cartilage begins to thin, wear, and crack. The collagen network loses its elasticity and subchondral bone becomes sclerotic and undermineralized. However, bone sclerosis appears to occur prior to cartilage degradation and loss, suggesting that bone remodeling initiates the cartilage damage in osteoarthritis.

Biochemical adaptations in bone and cartilage may follow, possibly involving abnormal osteoblasts. Chondroitin sulfate stimulates production of protease to affect collagen and matrix turnover and may benefit chondrocytes, thereby improving bone mineralization and cartilage metabolism.

**Osteoarthritis progression**

- **Stage I:** Proteolytic breakdown of cartilage matrix
- **Stage II:** Fibrillation and erosion of cartilage surface; accumulation of breakdown products in synovial fluid
- **Stage III:** Synovial cells ingest breakdown products; production of proteases and proinflammatory cytokines
**Pharmacokinetics of Chondroitin Sulfate**

It had been thought that CS was merely a cartilage building block, but current state-of-the-art research has demonstrated multiple mechanisms of action in vitro. The chondroitin sulfate (TRH122\textsuperscript{®}) discussed in this summary has been shown in published studies to be bioavailable in dogs (see Fig. 1) and in horses.\textsuperscript{1,2} With continued administration, CS accumulates at sufficient levels to produce biochemical response. In vitro studies suggest that the low molecular weight form is absorbed more readily than higher molecular weight products.\textsuperscript{6} It is also likely that in addition to size, the degree of purity, degree of sulfation, the species derivation (bovine, porcine, avian, fish, or shellfish) also affects absorption, as not all CS is bioequivalent.\textsuperscript{7} In fact, some sources such as perna...
Chondroitin Sulfate New Insights & Recommendations

**G + CS mechanisms of action**

**IN VITRO**
- Stimulation of synthesis of collagen in ligament cells, tenocytes, & chondrocytes, promoting cartilage matrix production & supporting accessory joint structures (ligaments & tendons), helping joint stability
- **Synergistic** stimulation of the production of cartilage glycosaminoglycans (proteoglycans)
- Inhibition of IL-1-induced gene expression of proteolytic enzymes, MMP-3, MMP-13, Agg-1, and Agg-2, decreasing cartilage degradation
- Inhibition of IL-1-induced gene expression & production of nitric oxide & prostaglandin E₂, decreasing cartilage degradation
- Role as a biological response modifier under conditions of joint stress
- Protection against adverse effects on cartilage caused by certain NSAIDs

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- Protection against cartilage degradation
- Improvement of cartilage matrix metabolism

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**Chondroitin Sulfate with Glucosamine**

Glucosamine HCl (FCHG49®) has also demonstrated multiple mechanisms of action in vitro and appears to be absorbed efficiently. Radiotracer studies show almost complete absorption of glucosamine (G), probably through the intestinal transporter for glucose. Recent in vitro studies have shown that at physiological doses of glucosamine and chondroitin sulfate can antagonize catabolic effects of IL-1 or fibronectin fragments, thus supporting the claim of chondroprotective action.³,⁵,⁸ The combination has been shown to inhibit gene expression of IL-1-induced proteolytic enzymes (matrix metalloproteinases MMP-3 and MMP-13 and aggrecanases Agg-1 and Agg-2)³ in cartilage degradation as well as IL-1-induced production of inflammatory mediators prostaglandin E₂ (COX-2)³ (see Fig. 3 on p. 3) and nitric oxide⁵ (see Fig. 4 on p. 3).

G + CS has also been shown to provide protection against proteoglycan depletion in the cartilage matrix by acting synergistically to stimulate production of glycosaminoglycans (GAGs) (see Fig. 2 on p. 3). Researchers have suggested that G + CS with manganese ascorbate (GAG cofactor) may stimulate cartilage matrix production by acting as signaling molecules for up-regulation of aggrecan and collagen II encoding genes.⁹ G + CS significantly stimulates collagen synthesis in the ligament cells, tenocytes, and chondrocytes, which promotes cartilage matrix production and supports ligaments and tendons (the accessory structures for joint stability).¹⁰ A study in dogs showed benefit in healing the cranial cruciate ligament in a transection/repair model.¹¹ In an in vitro study, G + CS showed activity as a biological response modifier (a compound that increases a tissue’s own protective mechanisms under adverse conditions) on aged and young cartilage under simulated conditions of joint stress.¹²

**Structure Modifying Effects of G + CS**

In an in vivo placebo-controlled trial of the effects of G + CS using a rat model of collagen-induced autoimmune cartilage degradation, G + CS significantly reduced the incidence and severity of
cartilage degradation. In an instability model in rabbits, G + CS was noted to maintain the cartilage (see photos), whereas lesions were seen in each of the single-agent and placebo groups. A dog study suggested that these compounds might act to improve cartilage matrix metabolism in vivo.

**Treatment Recommendations**

Intervention is key. Different breeds age at different rates and regular checkups can identify candidates for early G + CS supplementation. Oral G + CS has been shown to maintain cartilage structure while slowing the enzymes that cause the destruction of cartilage. Because G + CS is a nutritional supplement, it may take a little while to see improvement in an arthritic patient. An initial starting dose is recommended every day for the first 4 to 6 weeks or until improvement is seen, and then a reduction to a maintenance dose (see Cosequin DS dosing chart). The G + CS levels in pet food do not reach dosage levels found in supplements; so additional amounts should be given even when pet foods are labeled to contain G + CS.

**Safety**

In safety studies with Cosequin in dogs, cats, and horses, no clinically significant changes were noted in glucose levels or any biochemical, hematologic, or hemostatic parameters. Studies evaluating oral supplementation have not noted any adverse effects on glucose metabolism. In a study of rats sensitive to development of insulin resistance, neither glucosamine alone, chondroitin sulfate alone, nor the combination given orally led to development of insulin resistance. Studies have also been conducted to evaluate the use of glycosaminoglycans and their effect on blood coagulation. It is believed that the coagulation effect is determined by the degree of sulfation – the more sulfates present, the more effect. Studies with monosulfated CS, such as found in Cosequin, did not show any clinical effect on coagulation. Some dogs may experience a mild gastrointestinal upset such as when switching foods when the supplement is first administered. In this case, Cosequin should be given with food.

**Objectives of OA therapy**

- Control pain
- Increase joint mobility
- Decrease progression of disease

**Therapeutic options**

- Physical therapy
- Surgical therapy
- Drug therapy
- Nutritional supplementation

**Important groups**

- Obese and at risk
- Younger animals with OA
- Early OA (minimal cartilage loss)
- Geriatric animals

<table>
<thead>
<tr>
<th>Weight (lb)</th>
<th>Initial dosage ~4 to 6 wk (scored tablets)</th>
<th>Maintenance dose† (scored tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to 24*</td>
<td>1 daily *(under 10 lb ½ daily)</td>
<td>½ daily</td>
</tr>
<tr>
<td>25 to 49</td>
<td>2 daily</td>
<td>1 daily</td>
</tr>
<tr>
<td>50 to 100</td>
<td>3 daily</td>
<td>1-2 daily</td>
</tr>
</tbody>
</table>

†Once consistent improvement is seen, dose may be reduced to every other day. Maintenance level can also be used long-term on normal dogs to keep joints healthy.
Chondroitin sulfate: Mechanisms of action and clinical response in osteoarthritis

■ Novel mechanisms of action of chondroitin sulfate

Patrick du Souich, MD, PhD, Professor & Chair, Department of Pharmacology, University of Montreal Medical School

- Increases the synthesis of cartilage matrix components
- Reduces the degradation of cartilage matrix components
- Elicits antiinflammatory effect

■ Pharmacokinetics of chondroitin sulfate

Nicola Volpi, BSc Biol, Associate Professor of Biochemistry, Department of Animal Biology, University of Modena & Reggio Emilia, Modena, Italy

- Several studies have demonstrated that after oral absorption of exogenous low molecular weight CS, mean plasma levels peak between 2.4 and 5.0 hr.
- The structure and properties of polysaccharides strongly influence absorption and bioavailability.
- The extent of absorption depends on the kind of CS.

■ Structure modifying effects of chondroitin sulfate in knee osteoarthritis

Beat A. Michel, MD, Director, Clinic of Rheumatology & Physical Medicine, University Hospital, Zurich, Switzerland

- Joint space width (JSW) measurements were used to evaluate therapy over a period of 2 years.
- Mean JSW did not decrease in the patients given CS, but significantly decreased in the control patients.

Chondroitin sulfate is statistically superior to placebo for minimum joint space stabilization and mean joint space width stabilization.
Preliminary results from the Glucosamine/chondroitin Arthritis Intervention Trial (NIH GAIT)††

Daniel O. Clegg, MD, Stevenson Professor of Internal Medicine & Chief, Division of Rheumatology, University of Utah School of Medicine

- 1258 patients completed the study
- Treatment groups
  - P = placebo
  - CE = celecoxib (200 mg)
  - G = glucosamine HCl (1500 mg)
  - CS = chondroitin sulfate (1200 mg)
  - G + CS = glucosamine + chondroitin sulfate (above doses)

Findings
- All patients – Celecoxib response rate was statistically significant (p = 0.008). G + CS response rate showed a trend toward treatment effect (p = 0.09).
- Moderate to severe pain group – Response rate to G + CS was statistically significant (p = 0.002). Celecoxib response rate showed a trend toward treatment effect (p = 0.06).
- Mild pain group – Celecoxib response rate was statistically significant (p = 0.04). G + CS response rate was not significant.
- Individual nutraceuticals not effective in any group.
- All study agents were well tolerated.

Response rates by treatment group and pain stratum

<table>
<thead>
<tr>
<th>Agents</th>
<th>All patients</th>
<th>WOMAC++ Pain 301 to 400mm</th>
<th>WOMAC++ Pain 125 to 300mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>P (placebo)</td>
<td>60.1%</td>
<td>54.3%</td>
<td>61.7%</td>
</tr>
<tr>
<td>CE (celecoxib)</td>
<td>70.1%**</td>
<td>69.4%†</td>
<td>70.3%*</td>
</tr>
<tr>
<td>G (glucosamine)</td>
<td>64.0%</td>
<td>65.7%</td>
<td>63.6%</td>
</tr>
<tr>
<td>CS (chondroitin sulfate)</td>
<td>65.4%</td>
<td>61.4%</td>
<td>66.5%</td>
</tr>
<tr>
<td>G + CS (glucosamine plus chondroitin sulfate)</td>
<td>66.6%†</td>
<td>79.2%*</td>
<td>62.9%</td>
</tr>
</tbody>
</table>

** p = 0.008 CE vs. P
† p = 0.09 G + CS vs. P
¶ p = 0.06 CE vs. P
* p = 0.04 CE vs. P

++ WOMAC = Western Ontario and McMaster Osteoarthritis Index
Source: NIH

†† Abstract results from the Glucosamine/chondroitin Arthritis Intervention Trial; also published as an abstract in Arthritis & Rheumatism 52(9):S256, 2005.

* Presentation by Slack, Inc. with an unrestricted grant by Bioiberica, Barcelona, Spain. Further details and references to be published by Slack, Inc. @ www.slackinc.com, spring 2006.
Commentary

Recent studies show that chondroitin sulfate is absorbed and bioavailable, and that it works synergistically with glucosamine to produce measurable results. This is great news for chronic OA patients: long-term improvement and maintenance is possible. As part of multifaceted OA management, slow-acting and disease-modifying agents like G + CS can improve the environment for damaged tissues in the joint and help ameliorate pain. Management of OA should also include a weight reduction program, physical rehabilitation, controlled exercise, and antiinflammatory medications. For obese patients, body fat should be reduced to 20% to 25% of body weight and be maintained for life. G + CS supplementation should be added for optimal response and continued for the patient’s lifetime. Patients with slight to mild clinical signs should begin low-impact exercise. In moderate to severe OA, other strategies include environmental alterations in addition to physical rehabilitation (stretching, aquatic exercises, and walking), tailored to patient and owner capabilities. Finding the most effective NSAID is worthwhile and I find that G + CS can help improve the clinical response while using the lowest effective dose of an NSAID. G + CS supplementation also may be useful in young, very active animals to improve the joint environment and possibly reduce the risk of OA. — Darryl L. Millis, MS, DVM, DACVS, GCRP, University of Tennessee, Knoxville

REFERENCES


Cosequin® product highlights

- Synergistic combination of exclusive, low molecular weight chondroitin sulfate and glucosamine hydrochloride® with manganese ascorbate
- #1 joint health supplement brand** recommended by veterinarians
- The only glucosamine/chondroitin sulfate brand shown safe, effective, and bioavailable in peer-reviewed, published, controlled, U.S. veterinary studies
- The only veterinary brand containing the same bioactive chondroitin sulfate used in the National Institutes of Health GAIT study
- Analyzed using validated assay methods and documented in scientific publications to meet label claims
- Economical long-term maintenance

* Cosequin® contains TRH122® sodium chondroitin sulfate and FCHG49® glucosamine HCl, Nutramax Laboratories® exclusive veterinary research specifications
** Surveys of veterinarians who recommended oral joint health supplements (small animal 2001 & 2004; equine 2002 & 2004)

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