



## Chondroitin Sulfates

### Introduction

Chondroitin sulfates (CS), a class of glycosaminoglycans, are required for the formation of proteoglycans found in joint cartilage. It is believed they improve joint function by both enhancing endogenous synthesis and preventing enzymatic degradation of joint glycosaminoglycans. Evidence supports oral administration of chondroitin sulfates for degenerative joint disease, both as an agent to slowly reduce symptoms and to decrease the need for nonsteroidal anti-inflammatory drugs (NSAIDs). CS may also be of benefit in alleviating the symptoms of psoriasis. Animal studies suggest a potential healing benefit for inflammatory bowel disease and prevention of post-surgical adhesions.

### Biochemistry

Chondroitin sulfates are formed in the body from alternating sulfated and/or unsulfated residues of D-glucuronic acid and N-acetylgalactosamine,

thus making a disaccharide. Sequences of these disaccharides are formed into polysaccharide chains. The most abundant disaccharides in joint tissue are chondroitin sulfate A (chondroitin-4-sulfate) and chondroitin sulfate C (chondroitin-6-sulfate).

Because of the potential biochemical variety of the disaccharides (based on the number and position of the sulfate groups and the percentage of similar disaccharides) comprising the primary structure of the polysaccharide chain, chondroitin sulfates are actually a heterogeneous group of compounds with different molecular masses and charge densities. CS were first extracted and purified in the 1960s,<sup>1</sup> and most commercially available supplements are currently derived from shark cartilage or bovine trachea. Proprietary chondroitin sulfate products have been utilized in the majority of research on chondroitin sulfates and osteoarthritis.

### Pharmacokinetics

The majority of an oral dose of chondroitin sulfate is hydrolyzed into monosaccharides during the digestive process. Smaller amounts of di-, oligo-, and polysaccharides survive the digestive processes intact. Because of this natural acid hydrolysis, absorption of intact CS molecules is low following an oral dose, and is estimated to be zero percent for high molecular weight chondroitin sulfate polysaccharide chains and possibly between 8-12 percent for lower molecular weight and highly sulfated chondroitin sulfate polysaccharide chains.<sup>2-4</sup>

Despite low absorption of intact chondroitin sulfate molecules, radio labeling in animals suggests as much as 70 percent of an oral dose of CS is absorbed and subsequently found in urine and tissues.<sup>2</sup> The majority of an absorbed dose is in the form of the monosaccharides D-glucuronic acid and N-acetylgalactosamine. Lesser amounts of di-, oligo-, and polysaccharides, as well as intact chondroitin sulfates, also appear in blood and tissues following an oral dose.<sup>4</sup>

After absorption, the products of CS hydrolysis concentrate in the small intestine, liver, and kidneys (tissues responsible for the absorption, metabolism, degradation, and elimination of the compound). A tropism for joints is also demonstrated, since relatively high amounts of chondroitin sulfate components concentrate in tissues that utilize amino sugars, such as joint cartilage, synovial fluid, and the trachea.<sup>2,4</sup>

Human pharmacokinetic studies of oral chondroitin sulfates from shark cartilage and bovine trachea demonstrate varying rates of absorption and bioavailability in healthy male volunteers. A single oral dose of 4 g CS from bovine trachea was quickly absorbed and plasma levels increased more than 200 percent over baseline levels. Tmax (time from administration until highest plasma concentration is reached) was achieved at 2.4 hours post-administration and plasma concentration remained high for six hours, dropping sharply and returning to baseline 12 hours post-dose.<sup>5</sup>

In the case of chondroitin sulfates from shark cartilage, a single 4 g oral dose was more slowly absorbed and plasma levels increased to 120 percent over baseline. The Tmax for shark cartilage CS was achieved at 8.7 hours and remained elevated until 16 hours post-dose. Baseline levels were not reached until 48 hours after dosing. The significant differences in absorption of these two sources of chondroitin sulfates are attributed to differences in molecular mass and charge density. CS from bovine trachea have a lower molecular weight and therefore would be expected to be absorbed and eliminated more rapidly than higher molecular weight shark cartilage CS. With the higher molecular weight CS, absorption is slower, peak concentration is lower and more sustained, and rate of elimination is slower.<sup>6</sup>

## Mechanisms of Action

The primary mechanism of action of CS is increased joint glycosaminoglycan concentration and a subsequent enhancement of synovial fluid viscosity. Improvement in joint structure and function appears to be due to: (1) increased endogenous synthesis of hyaluronic acid and sulfated glycosaminoglycans from chondroitin sulfates; and (2) reduced breakdown of joint glycosaminoglycans subsequent to decreased collagenolytic activity and inhibition of enzymes, such as phospholipase A2 and N-acetylglucosaminidase, which are capable of degrading existing joint glycosaminoglycans.<sup>4,7-9</sup>

## Clinical Indications

### *Osteoarthritis*

Current findings indicate oral administration of chondroitin sulfates is useful for the treatment of osteoarthritis, both as an agent to reduce symptomology and to decrease the need for NSAIDs.

Studies show oral administration of CS is superior to placebo in osteoarthritis of the knees and hands. An average 50-percent improvement in assessed parameters, such as pain, walking time, pain medication use, and joint mobility has been consistently reported. Significant changes have been produced after a minimum of 1-2 months of supplementation and appear to be both dose- and time-dependent, with better results often demonstrated when supplementation periods were extended over greater time periods.<sup>10-18</sup>

Three randomized, double-blind, placebo-controlled clinical trials each enlisted over 100 patients and had study durations of three months to one year. Dosages ranged from 800-1,200 mg CS daily, and the main outcome measure in each was joint function as measured by Lequesne's Index, a standardized and validated tool used to evaluate pain and impaired function in knee and hip osteoarthritis patients. All three trials demonstrated significant improvements (up to 50 percent in one study)<sup>16</sup> in Lequesne's Index. Significant improvement in pain with activity was also observed in the treatment group. Patients in the CS groups also reported a longer duration of symptom improvement than those in the placebo groups.<sup>13,16,18</sup>

Co-administration of chondroitin sulfates with NSAIDs is reported to result in a significant reduction in the use of NSAIDs over time.<sup>11,12,19,20</sup> This was demonstrated by Morreale et al in a multicenter, double-blind, placebo-controlled clinical trial of 146 patients with osteoarthritis of the knee. Study duration was six months and patients were randomized to two groups. For the first four months of the study, one group received either 1,200 mg CS daily or placebo and the other group received the NSAID diclofenac sodium at 150 mg daily. Both groups received placebo for the last two months of the trial. Therapeutic response occurred later in the CS group than in the NSAID group, but lasted three months after the treatment was discontinued. In contrast, the NSAID group experienced an exacerbation of symptoms immediately upon treatment cessation.<sup>11</sup> A second trial involving 120 patients demonstrated chondroitin sulfates administration over three months, with a two-month non-treatment phase, resulted in a significant reduction in NSAID use compared to patients in the placebo group.<sup>12</sup> Another study reported a 72-percent reduction in the effective dose of NSAIDs required to relieve pain.<sup>19</sup>

In a controlled clinical trial, 24 patients with symptomatic osteoarthritis of the hands were randomly assigned to receive either 500 mg naproxen daily (placebo group, n=12) or 500 mg naproxen plus 800 mg oral CS daily (treatment group, n=12) for 24 months. Radiographic assessment of the hands was conducted at baseline and 12 and 24 months. The total number of joints with erosion increased in both groups, but at 24 months progression of erosion was lower in patients taking CS, i.e., fewer joints demonstrated erosion compared to placebo.<sup>20</sup>

Two large, long-term, randomized, controlled trials demonstrated similar results in patients with osteoarthritis of the knee. In 2004, Uebelhart et al demonstrated that 800 mg oral CS daily (n=60) for two three-month periods over one year resulted in a 36-percent decrease in Luquesne's Index compared to a 23-percent decrease in the placebo group (n=60). Patients in the treatment group also experienced less joint pain, improved walking time on a flat track, and improved global judgment scores evaluated by patient and physician. In addition, radiologic progression at 12 months revealed significantly decreased

joint space in the placebo group with no additional degeneration in the CS group.<sup>21</sup>

In a second, larger trial, 300 patients were randomized to receive either 800 mg oral CS (n=150) or placebo (n=150) once daily for two years. The main outcome was joint space loss over 24 months as determined by radiographic assessment of the knee. In the placebo group, all patients had progressive narrowing of the joint with a mean joint space loss of  $0.14 \pm 0.61$  mm over two years. Conversely, there was no change in mean joint space width in the CS treatment group over two years. Although symptomatic improvement did not reach statistical significance for either group, the results demonstrate CS may slow progression of osteoarthritis of the knee compared to placebo.<sup>22</sup>

A combination of chondroitin sulfate, glucosamine HCl, and manganese ascorbate demonstrated efficacy in osteoarthritis in two randomized, placebo-controlled studies.<sup>23,24</sup> In one six-month study, 93 patients with osteoarthritis of the knee were assigned to Cosamin DS<sup>®</sup> (1,000 mg glucosamine HCl, 800 mg low-molecular weight CS, and 152 mg manganese ascorbate) or placebo twice daily. Using Lesquene's Index to gauge outcomes, a 52-percent response rate was observed in the treatment group, compared to a 28-percent response in the placebo group; only subjects with mild-to-moderate arthritis improved.<sup>23</sup>

In a second four-week study on a similar combination, 34 men with chronic pain and degenerative joint disease of the knee or lower back were randomly assigned to receive glucosamine HCl (1,500 mg), CS (1,200 mg), and manganese ascorbate (228 mg) or placebo daily. Symptom scores for osteoarthritis of the knee improved significantly, although there was no significant benefit for spinal degeneration.<sup>24</sup>

In a case report, a combination protocol utilizing 500 mg glucosamine HCl, 400 mg low-molecular weight CS, and 66 mg manganese ascorbate per capsule (three capsules daily for nine months, followed by two capsules daily for 15 months), demonstrated therapeutic benefit in a 56-year-old man with lumbar disc degeneration. At the end of the two-year period, the patient reported less pain (beginning at about six months) and gradual improvement in range of motion and back function. Magnetic resonance imaging revealed an improvement in the structural quality of

the disc cartilage and decreased disc protrusion over the two-year period.<sup>25</sup> Although anecdotal, this case is included to demonstrate more significant effects may occur when the subject is evaluated after taking the supplement for a longer duration.

### *Psoriatic Arthritis*

Chondroitin sulfates are present in high amounts in normal papillary dermis and to a lesser extent in reticular dermis. Versican is the primary CS found in skin and is associated with skin elasticity, cellular proliferation, and tissue remodeling.<sup>26</sup> Chondroitin sulfate alterations have been observed in the skin of individuals with psoriasis,<sup>27</sup> and urinary excretion of dermatan sulfate and chondroitin sulfate is elevated in psoriatic individuals, indicating increased turnover of these components.<sup>28</sup>

A small study of 11 patients with osteoarthritis of the knee and concomitant moderate-to-severe psoriasis revealed 800 mg oral CS daily not only improved the symptoms of arthritis but also dramatically improved psoriatic lesions. Skin biopsies were taken before and after treatment and demonstrated a reduction in swelling, redness, itching, and flaking compared to baseline observations. Histopathological assessment showed a statistically significant decrease in epidermal thickness, decreased thickness between the basale and granulosum layers, and a significant improvement in psoriasis activity as assessed by the patients' physicians.<sup>29</sup>

### *Inflammatory Bowel Disease*

Oral administration of CS decreased incidence of bloody stools and erosions, and enhanced certain aspects of immunity in dextran sulfate sodium-induced colitis in rats. The therapeutic effect was hypothesized to be secondary to protecting the integrity of the lining of the intestinal mucosa.<sup>30</sup> No evidence currently exists documenting efficacy in inflammatory conditions of the digestive tract in humans.

### *Surgery*

A single intraperitoneal administration of chondroitin sulfate solution to rats was shown to be effective in preventing post-operative adhesion formation following abdominal surgery. Both deposition of fibrin and collagen type I was significantly reduced.<sup>31</sup>

### *Side Effects and Toxicity*

Chondroitin sulfates are well tolerated following an oral dose, and no signs or symptoms of systemic toxicity have been reported.<sup>2</sup> Long-term tolerance after one year of treatment resulted in no side effects in more than 90 percent of subjects.<sup>16</sup> The most commonly occurring side effects of CS administration are slight dyspepsia or nausea, which occur in about three percent of subjects.<sup>32</sup>

### *Dosage*

The therapeutic oral dosage of chondroitin sulfates is 800-1,200 mg per day. A single daily dose appears to be as effective as two or three smaller doses.<sup>2,18</sup> Results obtained from administration of CS are not permanent, so either chronic supplementation or repeated cycles of administration appear to be needed to produce optimal results.

### *Comment*

The processing (degree of fractionation, range of particle size, and molecular mass), location and percentage of sulfation, and purity of chondroitin sulfate polysaccharides (based on the amount of other glycosaminoglycans such as keratan sulfate, dermatan sulfate, etc.) present in the preparation might dramatically alter the metabolic fate and therapeutic results following oral or parenteral administration.

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