The Role of Glucosamine Sulfate and Chondroitin Sulfates in the Treatment of Degenerative Joint Disease

Gregory S. Kelly, N.D.

Abstract
Successful treatment of osteoarthritis must effectively control pain, and should slow down or reverse progression of the disease. Biochemical and pharmacological data combined with animal and human studies demonstrate glucosamine sulfate is capable of satisfying these criteria. Glucosamine sulfate’s primary biological role in halting or reversing joint degeneration appears to be directly due to its ability to act as an essential substrate for, and to stimulate the biosynthesis of, the glycosaminoglycans and the hyaluronic acid backbone needed for the formation of proteoglycans found in the structural matrix of joints. Chondroitin sulfates, whether they are absorbed intact or broken into their constituent components, similarly provide additional substrates for the formation of a healthy joint matrix. Evidence also supports the oral administration of chondroitin sulfates for joint disease, both as an agent to slowly reduce symptoms and to reduce the need for non-steroidal anti-inflammatory drugs. The combined use of glucosamine sulfate and chondroitin sulfates in the treatment of degenerative joint disease has become an extremely popular supplementation protocol in arthritic conditions of the joints. Although glucosamine sulfate and chondroitin sulfates are often administered together, there is no information available to demonstrate the combination produces better results than glucosamine sulfate alone. (Alt Med Rev 1998;3(1):27-39)

Introduction
The combined use of glucosamine sulfate (GS) and chondroitin sulfates (CS) in the treatment of degenerative joint disease has become an extremely popular supplementation protocol. Both GS and CS have been available as supplements for many years, and appear to positively impact symptoms in osteoarthritis; however, their ability to work as a synergistic combination remains open to debate.

Glucosamine, which is formed in the body as glucosamine 6-phosphate (G6-P), is the most fundamental building block required for the biosynthesis of the classes of compounds, such as glycolipids, glycoproteins, glycosaminoglycans (formerly called mucopolysaccharides), hyaluronate and proteoglycans, requiring amino sugars. Because it is a component of all these
compounds, it is an essential component of cell membranes and cell surface proteins as well as interstitial structural molecules that hold cells together. Directly or indirectly, glucosamine plays a role in the formation of articular surfaces, tendons, ligaments, synovial fluid, skin, bone, nails, heart valves, blood vessels, and mucus secretions of the digestive, respiratory, and urinary tracts.

Connective tissue is comprised primarily of collagen and proteoglycans. Proteoglycans provide the framework for collagen and hold water, enhancing the flexibility and resistance to compression needed to counteract physical stress. The building blocks for collagen are amino acids such as proline, glycine, and leucine; however, the building blocks for all proteoglycans are amino sugars. G6-P is the building block needed as the precursor for all subsequent amino sugar synthesis. The formation of galactosamine, N-acetylglucosamine (NAG), and CS all require G6-P. Hyaluronic acid, the backbone of proteoglycans, also requires G6-P for its synthesis.

Joint cartilage consists of cells embedded in a matrix of fibrous collagen within a concentrated water-proteoglycan gel. The integrity of this matrix is crucial for the biomechanical properties of the joint cartilage. The proteoglycans are large macromolecules consisting of a protein core to which are attached multiple chains of glycosaminoglycans and oligosaccharides. CS are a critical class of glycosaminoglycans required for the formation of proteoglycans found in joint cartilage.

GS’s primary biological role in halting or reversing joint degeneration appears to be directly due to its ability to act as an essential substrate for, and to stimulate the biosynthesis of, the glycosaminoglycans and the hyaluronic acid backbone used in the formation of the proteoglycans found in the structural matrix of joints. CS, whether they are absorbed intact or broken into their constituent components, similarly provide additional substrates for the formation of a healthy joint matrix.
Biochemistry of Glucosamine

Glucosamine (2-amino-2-deoxy-alpha-D-glucose) is one of the two hexosamine sugars (6 carbon amino sugars) common in animal cells (the other being galactosamine). Structurally, glucosamine is modified glucose with a \( \text{NH}_3 \) group replacing the \( \text{OH} \) group found on carbon two \( (C-2) \). G6-P is an aminomonomosaccharide (amino sugar) produced in the body by the combination of glutamine with fructose, through the enzymatic action of glucosamine synthetase.

It is found in many tissues and secretions in the body, and is the primary amino sugar substrate for the biosynthesis of the macromolecules, such as CS and hyaluronic acid, which provide the framework for collagen formation. It is believed that glucosamine’s role is potentiated by the presence of sulfate, which is also an essential component of proteoglycans.

The synthesis of G6-P begins with the structural rearrangement of glucose 6-phosphate to fructose 6-phosphate to facilitate interaction with the amino acid glutamine. The enzyme glucosamine synthetase facilitates the transfer of an amide group \( (\text{NH}_3) \) from glutamine to fructose 6-phosphate. The enzyme simultaneously isomerizes this compound to form G6-P (note: isomerization indicates an intramolecular rearrangement of a compound without any net change of the components of the compound). The resulting G6-P molecule is the precursor to all hexosamines and hexosamine derivatives. This first biotransformation of glutamine and fructose 6-phosphate to G6-P is considered the rate limiting step in amino sugar biosynthesis, and is an essential step in the glycosylation of all proteins. G6-P is then acetylated by coenzyme A, resulting in the formation of NAG.

NAG can subsequently be converted into either N-acetylglactosamine or N-acetylmannosamine. An additional three carbon atoms can be added to N-acetylmannosamine to form N-acetylnuraminic acid (also called sialic acid). G6-P and its sugar derivatives can then be incorporated into all of the macromolecules requiring amino sugars. (See Figure 1)

Biochemistry of Chondroitin Sulfates

CS, along with dermatan sulfate, keratan sulfate, and heparan sulfate and heparan, are compounds classified as glycosaminoglycans. CS are formed primarily from combining alternating residues of differently sulfated and/or unsulfated residues of glucuronic acid and N-acetylglactosamine into a polysaccharide chain. Although the chondroitin sulfates are often referred to as if they were a homogenous substance, their polysaccharide chains are comprised of several unique but structurally similar disaccharides, the most abundant of which are typically CS A (chondroitin-4-sulfate) and CS C (chondroitin-6-sulfate). The difference between these two compounds corresponds to the location of the sulfate molecule \( (\text{SO}_3^-) \). CS A is a disaccharide consisting of glucuronic acid and N-acetylglactosamine, which has the sulfate molecule attached to the R group on carbon four \( (C-4) \) of N-acetylglactosamine; whereas, CS C has the sulfate group attached to the R group on carbon six \( (C-6) \) of N-acetylglactosamine. Within a CS chain it is also possible to have disaccharide residues of glucuronic acid and N-acetylglactosamine with no sulfate groups, with a sulfate group as the R group on carbon two \( (C-2) \) of glucuronic acid, and with any combination of sulfate groups attached as the R group on C-2, C-4, and C-6 of either component of the disaccharide. Because of the 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, CS are a heterogeneous group of compounds having different molecular masses and charge densities. This capability to have a similar structure, but variable primary structure, allows CS to have specialized biological functions within a living organism. (See Figure 2.)

CS function as a component of proteoglycans. Proteoglycans are macromolecules (giant molecular complexes) containing many molecules of glycosaminoglycans (some of which are CS) attached to a long strand of hyaluronic acid (hyaluronate). In order to attach the glycosaminoglycans to the hyaluronic acid backbone, glycosaminoglycans are anchored to an amino acid (either serine, threonine, or asparagine). Table 1 provides a summary of the different types of macromolecules dependent on amino sugars.

Metabolism of Glucosamine Sulfate

The glucosamine component of GS is quickly and almost completely absorbed from the gastrointestinal tract following an oral dose; however, it is unclear whether the entire GS molecule is absorbed intact or to what extent it might be degraded prior to and after absorption.

Glucosamine is a small molecule (m.w. = 179) and is very soluble in water. Because of its small molecular weight and its pKa, it is well absorbed in the intestine. Based on the fecal excretions of radioactively labeled molecules, gastrointestinal absorption of glucosamine is about 87% in the dog. In humans, about 90% of glucosamine, administered as an oral dose of GS, is absorbed. Evidence indicates absorption of glucosamine by intestinal cells is carrier mediated resulting in the active transport of glucosamine into these cells. Its acetylated derivative NAG appears to be absorbed without deacetylation of the molecule; however, this process occurs by diffusion.

Glucosamine is rapidly incorporated into articular cartilage following oral administration. In fact, articular cartilage concentrates glucosamine to a greater extent than any other structural tissue. Elimination
of glucosamine is primarily in the urine, with a small amount of glucosamine or its derivatives eliminated in the feces.\textsuperscript{1,4}

**Metabolism of Chondroitin Sulfates**

The metabolic fate of orally administered CS is equivocal and characterized by some disagreement in the available literature. Adding to the complexity of the issue is the fact that CS exist in a wide range of molecular weight, chain length, electrical charge distribution, locations of sulfate groups, and percentage of similar disaccharide (glucuronic acid and N-acetylgalactosamine) residues. A further complication occurs because low molecular mass derivatives of CS have also been pharmacologically created and utilized in some of the pharmacokinetic and therapeutic studies and trials. It is quite possible the contrasting metabolic results subsequent to oral administration of CS are a direct reflection of this dissimilarity in the actual primary structure and physical properties found within the general CS category.

Baici et al investigated the ability of an oral dose of CS to impact the concentration of glycosaminoglycans in humans. CS were administered to six healthy volunteers, six patients with rheumatoid arthritis, and six patients with osteoarthritis. They reported the concentration of glycosaminoglycans in serum was unchanged following ingestion of CS in all subjects studied. These researchers concluded that “...chondroprotection by orally administered chondroitin sulfate is a biologically and pharmacologically unfounded theory.” Although they did not rule out the possibility that oral administration of CS might benefit patients with osteoarthritis, they suggested that any benefit “...after ingestion of chondroitin sulfate should be sought at the gastrointestinal rather than at the plasmatic or articular cartilage level.”\textsuperscript{5} Morrison indicated the intact absorption of CS was extremely low. He estimated the absorption rate to be between 0-8\%.\textsuperscript{5}

### Table 1. Macromolecules Containing Amino Sugars

<table>
<thead>
<tr>
<th>Macromolecule</th>
<th>Description and Composition</th>
</tr>
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<tbody>
<tr>
<td>Glycoprotein</td>
<td>Proteins with attached carbohydrates; however, the carbohydrates are short, branching chains, not polymers of repeating units of sugar residues.</td>
</tr>
<tr>
<td>Glycolipid</td>
<td>Lipids with a chain of one or more amino sugar residue derivatives.</td>
</tr>
<tr>
<td>Glycosaminoglycans</td>
<td>Carbohydrate chains made primarily of alternating residues of either NAG or N-acetylgalactosamine plus glucuronic acid or its epimer iduronic acid. This category includes chondroitin, dermatan, keratan, and heparan, almost always with sulfate groups attached.</td>
</tr>
<tr>
<td>Hyaluronate</td>
<td>This is the backbone of all proteoglycans. It is a chain of alternating residues of NAG and glucuronic acid.</td>
</tr>
<tr>
<td>Proteoglycans</td>
<td>Giant molecules with many glycosaminoglycans attached to a long strand of hyaluronate by a core protein (either serine, threonine or asparagine).</td>
</tr>
</tbody>
</table>
The pharmacokinetic properties of a proprietary CS (Condrosulf) were investigated by Conte et al. Significant extraction procedures were utilized to generate a low molecular mass product which could be characterized for structure, physiochemical properties, and purity. Only the fraction with a relative molecular mass of about 14,250 Daltons was used for their experiments. This fraction had a sulfate-to-carboxyl ratio of 0.95 due to the high percentage of monosulfated disaccharides (55% chondroitin sulfate A and 38% chondroitin sulfate C), and a low amount of disulfated disaccharides (1.1%) inside the polysaccharide chains. The purity of the preparation was greater than 97% CS.

This preparation was radioactively labeled and administered by oral route in the rat and dog. Although more than 70% of the radioactivity was absorbed and was subsequently found in urine and tissues, the radioactivity associated with an intact molecule of CS corresponding to the molecular mass of the administered dose was relatively small (approximately 8.5%), and decreased rapidly over time. The majority of the radioactivity absorbed was actually associated with molecules with a molecular mass of less than or equal size to N-acetylgalactosamine (one of the two constituent monosaccharides comprising the polysaccharide chain). This radioactivity increased over time and remained elevated. Radioactivity after 24 hours was highest in the small intestine, liver, and kidneys (tissues responsible for the absorption, metabolism, degradation, and elimination of the compound); however, relatively high amounts of radioactivity were also found in tissues which utilize amino sugars; such as joint cartilage, synovial fluid, and trachea.

Conte et al also administered CS (Condrosulf) orally to healthy volunteers in either a single daily dose of 0.8 g or in two daily doses of 0.4 g. Although both dosing schedules increased plasma concentration of exogenous molecules associated with CS, results indicated oral administration of one dose of 0.8 g CS was the more effective dosing regimen. They also measured some biochemical parameters (hyaluronic acid and sulfated glycosaminoglycans) associated with glycosaminoglycans in order to demonstrate whether orally administered exogenous CS impact synovial fluid in subjects with osteoarthritis. Their results indicate treatment could modify these parameters. Concentrations of hyaluronic acid increased and, although the overall concentration of sulfated glycosaminoglycans was unchanged, a shift toward sulfated glycosaminoglycans with a lower molecular mass was observed. Based on these results, the authors suggested that, “...at least a part of the low molecular mass material present in joint synovial fluid after 5 days of treatment is exogenous chondroitin sulfate....”

The intact absorption of CS subsequent to an oral dose is a controversial subject. Physiology textbooks routinely teach that molecules with a high molecular mass and charge density cannot pass through gastric and intestinal mucosa intact. Available data seems to partially refute this belief since some findings indicate as much as 8.5% of an oral dose can be absorbed intact under some circumstances. However, the majority of physiological benefits subsequent to administration of CS appear to be a direct result of increased availability of the monosaccharide building blocks (glucuronic acid and N-acetylglactosamine) created by the hydrolysis of CS into smaller molecules during digestion and absorption.

**Mechanism of Action**

One of the primary physiological roles of GS is stimulation of the synthesis of substances required for proper joint function. It is capable of stimulating proteoglycan synthesis, inhibiting the degradation of proteoglycans, and stimulating the
regeneration of cartilage after experimentally induced damage. GS also might promote incorporation of sulfur into cartilage.

GS appears to be ineffective at inhibiting both cyclooxygenase and the proteolytic enzymes involved in inflammation. Although GS protects against carrageenan, dextran, and formalin induced edema in an experimental model, it was not effective in counteracting edema provoked by specific mediators of inflammation, such as bradykinin, serotonin, or histamine. Unlike NSAIDs, which act through the inhibition of cyclooxygenase and modification of prostaglandin synthesis, the mechanism of action of GS appears to be linked to its ability to stimulate synthesis of the proteoglycans needed to stabilize cell membranes and increase intracellular ground substance.

Since the anti-inflammatory ability of GS is different than that of NSAIDs, it is possible the two might have a synergistic effect in alleviating some types of inflammation. Evidence indicates a combined treatment utilizing glucosamine with either voltaren, indomethacin, or piroxicam can decrease the amount of NSAID required to produce an antiinflammatory result by a factor of about 2-2.7 times with preservation of activity.

The mechanism of action of CS is probably similar in nature to GS, since it can also provide substrates for proteoglycan synthesis. Bassleer et al demonstrated, in vitro, both GS and CS have a stimulatory effect on the production of proteoglycans by cultured differentiated human articular chondrocytes. Karzel and Lee also reported both glucosamine derivatives and CS could influence the in vitro growth and metabolism of glycosaminoglycans. Glucosamine hydrochloride, glucosamine hydroiodide, and GS promoted a significant increase in the glycosaminoglycans in the extracellular cartilage matrix and induced an increase in the secretion of glycosaminoglycans from the surface of the bone cells into the culture medium. Although CS were also capable of positively influencing the metabolism of glycosaminoglycans, their effect was not significant in this experiment.

Several studies indicate low molecular weight polysulfated glycosaminoglycans (GAGPS) (note: some CS preparations depending on their processing would be considered low molecular weight and all chondroitin sulfates are polysulfated glycosaminoglycans) have antiarthritic activity. Kalbhen reported intraarticular or intramuscular applications of GAGPS can significantly reduce the intensity and progression of joint degeneration. Glade reported GAGPS could stimulate net collagen and glycosaminoglycans synthesis by normal and arthritic equine cartilage tissues. In his experiments arthritic tissues were more sensitive to GAGPS stimulation. Injection of 250 mg of GAGPS also inhibited the rate of collagen and glycosaminoglycan degradation in cell culture.

Some evidence suggests a component of the activity of GS and CS is related to the sulfate residues found in these compounds. Sulfur is an essential nutrient for the stabilization of the connective tissue matrix. Because of this, it has been proposed that the sulfate molecules of GS and CS contribute to the therapeutic benefits of these compounds in degenerative joint diseases. If this speculation is true, it would lend support to the proposition that GS, as opposed to NAG or glucosamine hydrochloride, is the best form of glucosamine supplementation for patients with arthritis. It would also give added importance to the sulfate-to-carboxyl ratio of CS.

van der Kraan et al studied the effect of low sulfate concentrations on glycosaminoglycan synthesis in rat patellar cartilage in vivo as well as in vitro. Sulfate depletion resulted in a decrease of glycosaminoglycan synthesis in patellar cartilage. These same authors subsequently reported the rate of sulfated glycosaminoglycan synthesis in human articular
cartilage is sensitive to small changes in physiological sulfate concentrations. A reduction in the sulfate concentration from 0.3 mM (physiological) to 0.2 mM resulted in a 33% reduction in glycosaminoglycan synthesis.18

Animal experiments indicate arthritic tissue has an increased demand for and uptake of total glycosaminoglycans and monosulfated, highly-sulfated, and non-sulfated glycosaminoglycans.19 Animal experiments have also indicated an increased incorporation of radioactive sulfate in specimens of bone and cartilage during the process of induced arthritis.20 Lending additional support to the argument that sulfur is an important mineral for halting degeneration of joints is an article written in 1934, in which Senturia reported the benefits of colloidal sulfur administration in arthritis and rheumatoid conditions.21

**Glucosamine Sulfate and Chondroitin Sulfates: Research on Osteoarthritis**

The primary therapeutic use of GS and CS is in the treatment of degenerative diseases of the joints. Several trials have demonstrated the therapeutic efficacy of oral GS administration in the treatment of osteoarthritis. Although many of these have compared GS to placebo, in the trials where GS has been compared to NSAIDs, long-term reductions in pain are greater in patients receiving GS. As discussed under the section covering mechanisms of action, GS has very little direct anti-inflammatory effect and no demonstrated ability to directly act as an analgesic or pain relieving agent. Instead, GS appears to directly halt the progression of and probably promote the regeneration of the joint matrix by stimulating production of proteoglycans.

Reichelt et al have demonstrated the efficacy of intramuscular injections of GS in a placebo-controlled, double-blind trial conducted with 155 out-patients diagnosed with osteoarthritis of the knee. Intramuscular injections of GS (400 mg) were given twice a week for six weeks. A favorable response rate to therapy was reported in 55% of patients given IM GS and 33% of patients receiving placebo.22 During a 12-month study period, GS had a chondroprotective activity, which was significant after the first 3 months of therapy.23 Hehne et al treated 68 patients with mild or moderate degeneration of the knee joint by injecting either GS or GAGPS intraarticularly for six weeks. Two-thirds of the patients responded favorably to the therapy. “Loading” pain was eliminated or improved in about 80%, “getting-going” pain in about 64%, and signs of synovialitis in about 66%. The authors noted that GS had a superior effect overall, particularly in individuals with mild arthritis, achieving an improvement of pain in 90% of patients; however, administration of GAGPS was judged to be more successful in advanced cases of degeneration.24

Two groups of patients with chronic degenerative articular disorders received either 400 mg of GS or a piperazine/chlorbutanol (P/C) combination either IV or IM daily for seven days. After completion of the injections, the group who had been receiving GS was given 500 mg of GS orally three times daily for two weeks, while the other group of patients was placed on placebo. Symptoms improved in both groups during parenteral treatment; however, a faster and greater improvement in symptoms was reported for the individuals receiving GS (58% decrease in symptoms as opposed to 31% for P/C group). An additional reduction in the symptom score (13%) was reported by individuals receiving follow-up oral GS, while individuals on placebo had a reversal of symptom scores, with their symptoms returning to approximately pretreatment levels.25 Crolle and D’Este, utilizing a similar protocol, reported the same favorable outcome in terms of symptom improvement.
Additionally, they observed a significant functional improvement, as measured in walking speed over 20 meters, with the GS group improving their speed by 72%.\textsuperscript{26}

An open study on the effectiveness of GS for arthritis was conducted by 252 doctors on 1183 patients. Patients were given 500 mg of GS orally three times per day for a period of 50.3 +/-14.4 (range 13-99) days. The treatment was judged “effective” by doctors in 58.7% of the patients and as “sufficient” in an additional 36% of the patients (a total of almost 95% positive response to GS). Based on the objective criteria the doctors were using, only 5.3% of patients were judged as having an “insufficient” response to GS. Results indicate that pain produced by active and passive movement was reduced, and symptoms of pain at rest, standing, and during exercise improved steadily throughout the treatment period. Tapadinhas et al noted that patients with arthritis of the shoulder or elbow responded the best (about 75% judged as “good” and only 1% judged as “insufficient”), while polyarticular arthritis and arthritis of the hip had the poorest response rate (43% and 49%, respectively) and might require longer treatment duration. Improvements remained 6-12 weeks following cessation of treatment regimen.\textsuperscript{27}

Twenty-four patients with osteoarthritis of the knee were randomly assigned to a treatment group (500 mg GS three times per day orally) or placebo group for 6-8 weeks. A significant alleviation of self-assessed degree of articular pain, joint tenderness, and swelling was reported by the group receiving GS. Results were confirmed by physician assessment of efficacy with the outcome rated as “excellent” in all 10 patients receiving GS and “fair” to “poor” in patients receiving placebo.\textsuperscript{28}

Forty-one patients with a diagnosis of unilateral osteoarthritis of the knee were randomly assigned to either a GS group (500 mg GS three times per day) or an ibuprofen group (400 mg ibuprofen three times per day) for eight weeks of treatment. Self-assessed pain scores decreased in both treatment groups. The ibuprofen-treated patients experienced a more dramatic reduction in pain during the initial two weeks of treatment; however, pain scores stabilized at this point and no further reductions were reported. While reduction in pain was not as rapid for individuals being treated with GS, after four weeks of treatment, reduction in pain was greater in GS-treated patients than in ibuprofen-treated patients. In contrast to individuals treated with ibuprofen, continued administration of GS also resulted in a continued decrease in individual pain scores throughout the eight weeks of therapy.\textsuperscript{29} Rovati similarly reported that administration of GS was more effective than placebo and comparable in effect to ibuprofen for treatment of osteoarthritis of the knee.\textsuperscript{30}

CS have been investigated in the treatment of arthritis; however, typically, proprietary CS products are utilized. The most commonly investigated products are referred to in the literature as glycosaminoglycan polysulfate (Arteparon), galactosaminoglycuronoglycan sulfate (Matrix), CS (Condrosulf), and CS (Structum). These preparations appear to produce a favorable outcome when administered to individuals with arthritis; however, many of the trials to date have used either intraarticular or intramuscular routes of administration. In trials which have given these substances orally, improvement in symptoms has been noted. Based on the metabolic data on CS, this effect is probably primarily a result of the degradation products of CS (glucuronic acid and N-acetylgalactosamine) since, at best, only about 8% of a low molecular weight preparation of CS is absorbed intact.

Arteparon has been used in veterinary medicine in Europe for over two decades for treatment of degenerative joint disease. The drug is administered directly into the diseased
Table 2. Reported Side-effects of Glucosamine Sulfate

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% of patients complaining</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric pain/tenderness</td>
<td>3.48</td>
</tr>
<tr>
<td>Heartburn</td>
<td>2.73</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2.48</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.16</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0.99</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.83</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0.83</td>
</tr>
<tr>
<td>Constipation</td>
<td>0.66</td>
</tr>
<tr>
<td>Gastric Heaviness</td>
<td>0.50</td>
</tr>
<tr>
<td>Skin Reactions</td>
<td>0.33</td>
</tr>
<tr>
<td>Headaches</td>
<td>0.33</td>
</tr>
<tr>
<td>Anorexia</td>
<td>0.25</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>0.25</td>
</tr>
<tr>
<td>Meteorism</td>
<td>0.17</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0.17</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.08</td>
</tr>
<tr>
<td>Edema</td>
<td>0.08</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0.08</td>
</tr>
</tbody>
</table>

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joint to improve functional properties of the cartilage and to stimulate cartilage metabolism. The effect of Arteparon administered intraarticularly or intramuscularly has also been investigated in humans with osteoarthritis of hip-joints. Patients received either six injections with 125 mg/0.5 ml intraarticularly or 10 injections with 125 mg/0.5 ml IM. Reduction of pain, and improved function and motility of the treated hip-joints was observed, and results were similar irrespective of the method of administration.31

Matrix has also produced improvements in arthritic symptoms regardless of the manner of administration. Matrix was given orally (800 mg/day) for two years to patients with osteoarthritis of the hands. The results indicated treatment was capable of having a positive influence on joint pain.32 A double-blind, placebo-controlled trial of Matrix was conducted on 40 patients with tibiofibular arthritis of the knee. Patients received 50 intramuscular injections (one injection twice a week) for 25 weeks. The following symptoms were evaluated: spontaneous pain, pain on loading, on passive movement, and on pressure. Analysis of results indicated a statistically significant therapeutic effect by Matrix on all symptoms taken into consideration.33

Oliviero et al also reported favorable effects both in reduction in pain and improvement in motility when Matrix is given (either intraarticularly or orally) to elderly patients with joint degeneration.34

Condrosulf was given orally to 61 patients with osteoarthritis of the hip, knee and/or finger joints, in an open, multicenter, phase IV trial for 3 months. NSAIDs were used concurrently throughout the trial period. Co-administration of Condrosulf resulted in a 72% reduction in the effective dose of NSAIDs required to relieve pain.35

Morreale et al conducted a randomized, multicenter, double-blind clinical trial to assess the efficacy of CS administered orally in comparison with diclofenac sodium (an NSAID) in patients with osteoarthritis of the knee. During the first month, patients in the NSAID group were treated with 50 mg diclofenac sodium and 400 mg placebo tid. From month 2 to month 3, these patients were given only 400 mg of placebo tid. In the CS group, patients were treated with 50 mg placebo (for diclofenac) and 400 mg of CS tid during the first month. From month 2 to month 3, these patients received only 400 mg of CS tid. The patients treated with the NSAID (diclofenac sodium) showed a prompt reduction of clinical symptoms; however, symptoms reappeared quickly after the discontinuation...
of treatment. Patients treated with CS had a slower response to treatment, although the favorable response remained up to three months after discontinuation of treatment.36

Mazieres et al conducted a randomized, placebo-controlled, double-blind trial designed to evaluate the effectiveness of Structum on 120 patients with osteoarthritis of the knees and hips. Patients received 200 mg Structum orally qid for three months. The treatment phase was followed by a two-month treatment-free phase to allow evaluation of carry-over effects. At the completion of the three-month treatment phase, patients taking Structum were using significantly less NSAIDs and overall patient and physician assessments indicated an improvement in symptoms.37

Toxicity and Dosage

No LD$_{50}$ is established for GS or glucosamine, since even at very high levels (5000 mg/kg oral, 3000 mg/kg IM, and 1500 mg/kg IV) there is no mortality in mice or rats.38 Tapadinhas et al evaluated the tolerability of GS treatment in 1208 patients; 1062 (88%) of the individuals reported no side-effects. Table 2 lists the reported side-effects and their frequency. Most of the reported complaints were mild in character and all complaints were reversed when treatment with GS was discontinued.27

GS has been administered safely to patients with a variety of disease conditions, including circulatory disease, liver disorders, diabetes, lung disorders, and depression, with no observed interference with either the course of the illness or pharmacological treatment for the conditions.26

The typical dosage routine for GS is 500 mg three times daily orally for a minimum of six weeks. Most individuals will benefit from repetitive courses of administration, since improvements from GS only appear to be retained for an average of 6-12 weeks following cessation of a six-week period of treatment. Since it is safe for long-term administration, continuous administration is also appropriate.

Obesity has been associated with a below average response to GS.27 It has not been determined whether a higher dose of GS would result in a better clinical outcome in these individuals; however, this strategy is safe and might result in improved clinical outcomes. Evidence also indicates individuals with active peptic ulcers and those taking diuretics have a below average response to GS and tend to have an increased incidence of side-effects.27

CS are well tolerated following an oral dose and no signs or symptoms of toxicity have been reported.7 About 3% of individuals report slight dyspeptic symptoms or nausea following oral administration of CS.34 Similar to GS, results obtained from administration of CS are not permanent, so repeated cycles of administration are needed to produce best results. The typical oral dosage is 400 mg twice daily; however, a single dose of 800 mg per day appears to be equally effective based on pharmacokinetic data.

The source of CS is usually bovine trachea (while GS is derived from the chitin of crab shells); however, the processing (degree of fractionation, range of particle size, and range of molecular mass), location and percentage of sulfation, and purity of CS (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 the therapeutic results following oral or parenteral administration. It is important to recognize that most of the proprietary products utilized in the studies are extracted and purified to contain a high degree of CS (up to 97%). It is quite likely that some available products actually have a significantly lower percentage of CS, which could dramatically influence the dosage required for therapeutic efficacy. The molecular
mass of CS might also have an impact on clinical results. The most significant absorption of intact CS appears to occur with a low molecular mass product.

Although information is limited on the combined oral administration of GS and CS, there is currently no reason to suspect this combination would increase the incidence of side-effects. There is also no information currently available in the literature which would indicate what the optimal dose would be of each substance if they are taken together.

**Conclusion**

G6-P is the starting point in the synthesis of many important macromolecules including, glycoproteins, glycolipids, glycosaminoglycans, and hyaluronate. As a supplemental form of G6-P, GS has a role in the synthesis of structural proteins (cell membrane lining, collagen, osteoid, bone matrix), lubricants and protective agents (mucin, mucous secretions), transport molecules, immunological molecules (immunoglobulins, interferon), hormones (gonadotropin, TSH, TRF), enzymes (proteases, nucleases, etc.), and lectins.

Treatment with GS is thought to normalize biosynthesis of the substrates required to restore the functional ability of a joint. Successful treatment of osteoarthritis must effectively control pain and should slow down or reverse the progression of the disease. Biochemical and pharmacological data combined with animal and human studies demonstrate that GS is capable of satisfying both criteria. While treatment with GS does not produce the initial dramatic reductions in pain normally associated with NSAIDs, its ability to reduce pain is consistent and progressive throughout the course of its administration, resulting in a long-term improvement in the condition.

CS are an integral component of proteoglycans. As such, they are essential for the structural and functional integrity of joints. Current findings indicate oral administration of CS are useful for treatment of osteoarthritis, both as an agent to slowly reduce symptoms and to reduce the need for NSAIDs. Since only a small percentage of even low molecular weight CS is absorbed intact, a great deal of the clinical effect appears to be a result of the digestion to and absorption of the constituent alternating residues of glucuronic acid and N-acetylglalactosamine which comprise the polysaccharide chain of CS. Although GS and CS are often administered together, currently there is no information available to demonstrate the combination produces better results than GS alone.

**References**


