

Oral Treatment With a Glucosamine-Chondroitin Sulfate Compound for Degenerative Joint Disease in Horses: 25 Cases

R. Reid Hanson, DVM
 Department of Large Animal
 Surgery and Medicine
 College of Veterinary Medicine
 Auburn University
 Auburn, Alabama 36849-5522

Lowell R. Smalley, DVM
 Equine Veterinary Clinic
 9906 North 132 Street
 Omaha, Nebraska 68142

Gerald K. Huff, DVM
 Equine Medicine and Surgery
 2315 North Decatur Boulevard
 Las Vegas, Nevada 89108

S. White, DVM
 Equine Veterinary Clinic
 9906 North 132 Street
 Omaha, Nebraska 68142

**Tarek A. Hamad, MD, PhD,
 Msc, MS**
 Department of Epidemiology
 University of Maryland School
 of Medicine
 Baltimore, Maryland 21201

Degenerative joint disease (DJD) and its associated joint pathology contributes significantly to musculoskeletal lameness and loss of function in athletic and pleasure horses.^{1,2} Cartilage is made up of collagen fibers, glycosaminoglycans (GAG), and proteoglycans in a predominately water matrix.^{3,4} A decrease in GAG content in osteoarthritic cartilage is associated in direct proportion with the severity of the disease.⁵⁻⁸ With a loss of GAG content the articular cartilage loses its elasticity and ability to bear and transmit forces efficiently, thus resulting in a cascading cycle of more cartilage insults.³ This complex process results in the net loss of cartilage and eventual death of the chondrocytes.³

Traditional treatment of DJD has centered around non steroidal anti-inflammatory drugs (NSAIDs) and steroidal therapies.⁹ The chronic use of many of these agents can decrease or suppress chondrocyte metabolism and cause further degradation of the cartilage matrix by the inhibition of normal collagen and proteoglycans synthesis. Some NSAIDs can cause gastrointestinal ulceration and hemorrhage.^{9,10} The problems and limitations of NSAIDs and steroidal anti-inflammatory agents have recently led to a search for agents that relieve pain and inflammation and limit or reverse cartilage degeneration **without** side effects.¹¹

Chondroprotective agents have been

Twenty-five horses with degenerative joint disease that fit the conditions of the study were treated with a glucosamine-chondroitin sulfate compound (Cosequin®:Nutramax Laboratories, Inc., Baltimore, MD) to evaluate its effectiveness in decreasing lameness. All horses were confirmed to have degenerative joint disease (DJD) by physical examination, diagnostic intra-articular anesthesia, and radiographs or fluoroscopy of the distal interphalangeal, metacarpophalangeal, tarsometatarsal or carpal joints. All horses weighing less than 545 kg were given 9 g of the glucosamine-chondroitin sulfate compound orally twice daily for 6 weeks. Horses weighing more than 545 kg were given 12 g twice daily for 6 weeks. Each 3-g measure included 1,800 mg of glucosamine hydrochloride, 600 mg of purified chondroitin sulfate, 16 mg of manganese, and 104 mg of ascorbate. Lameness grade, flexion test grade and stride length (cm) were measured at an initial examination and re-evaluated at 2, 4, and 6 week follow-up examinations. Repeated measurement analysis was implemented to assess the lameness using SAS computer package (Statistical Analysis System, Cary, NC). Within 2 weeks of the start of administration of the glucosamine-chondroitin sulfate compound, the lameness grade, flexion test, and stride length were significantly ($P < 0.0001$) improved. A further significant improvement in lameness was evident at 4 weeks ($p = 0.04$), while flexion score ($p = 0.2$) and stride length ($P = 1.0$) did not show further improvement. The age of horses was not a significant factor in the improvement of the lameness grade, flexion test, or stride length ($p = 0.2$, $p = 0.07$ and $p = 0.2$, respectively), implying that the achieved results were true irrespective of horse age.

defined as compounds that enhance chondrocyte macromolecular synthesis (glycosaminoglycans, proteoglycans, collagen, proteins, RNA, and DNA); enhance synthesis of hyaluronic acid by synovio-cytes; inhibit enzymes that degrade cartilage macromolecules; and mobilize thrombi, fibrin, lipids, and cholesterol deposits in synovial spaces and blood vessels surrounding joints.¹² At present no known drug is able to accomplish all of these objectives. Macromolecules endogenous to cartilage and their semi-

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synthetic or synthetic analogs have been shown to accomplish some but not all of these objectives.¹³⁻¹⁶ Because the roles and functions of endogenous macromolecules are integral to cartilage metabolism, they alone appear able from a pharmacological perspective to accomplish multiple objectives.^{13,17,18} Combining the use of anti-inflammatory or analgesic drugs with macromolecules have exhibited some but not all of the objectives.¹⁸⁻²⁰ However, adverse side effects of these drugs reduces therapeutic benefits of the combinations.^{19,20}

Glucosamine and chondroitin sulfate are considered chondroprotective and appear to enhance or increase chondrocyte macromolecular synthesis by different mechanisms.^{4,13-15,21} Glucosamine is a direct precursor as well as stimulatory agent for chondrocyte and connective tissue glycosaminoglycan synthesis.²²⁻²⁵ Exogenous glucosamine salts significantly enhance chondrocyte synthesis of glycosaminoglycans, collagen and DNA and ameliorate the clinical signs of DJD in humans.^{17,18,22-25} The physio-chemical properties of glucosamine account for a favorable pharmacokinetic profile including oral bio-availability and specific cartilage tropism, as was shown in animals and humans using radio-labeled compounds.^{26,27} Excretion of glucosamine is primarily via urine and feces with 87% of orally administered glucosamine being absorbed.²⁷

Chondroitin sulfate is a long chain polymer of a repeating disaccharide unit: galactosamine sulfate and glucuronic acid. It is the predominant GAG found in articular cartilage and is a natural component of several other tissues (i.e., tendons, bone, vertebral discs, heart and cornea) found in the body.²⁸ Differing from glucosamine, chondroitin sulfates stimulate glycosaminoglycan and proteoglycans synthesis by extracellular as well as intracellular mechanisms. Chondroitin sulfate, by virtue of long chain lengths, competitively inhibits degradative enzymes of proteoglycans in cartilage and synovial fluid.^{16,29,30,31} Bioavailability has been well documented with 70% absorption following oral administration in experimental animals and in humans.³¹⁻³³ Chondroitin sulfate's affinity for synovial fluid and articular cartilage has also been demonstrated.³³

A synergistic rather than an additive effect would be expected by combining glucosamine and chondroitin sulfate, since both agents are endogenous to chondrocytes. In addition chondroitin sulfates possess extracellular properties not found with glucosamine. Both of these connective tissue compounds have been

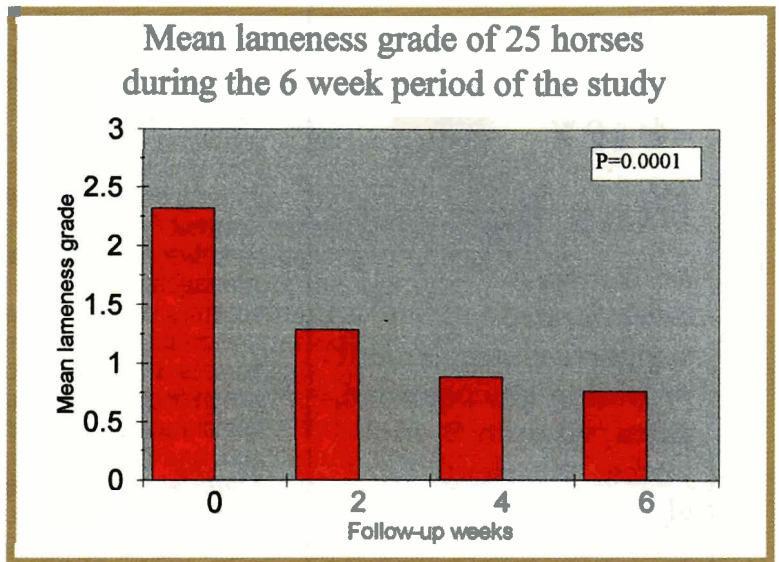


FIG. 1 – Mean lameness grade of 25 horses during the 6-week period of the study.

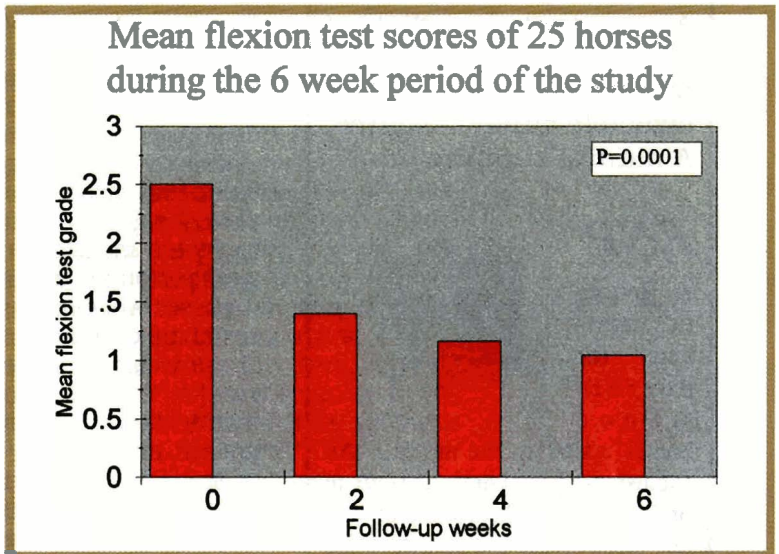


FIG. 2 – Mean flexion test scores of 25 horses during the 6-week period of the study.

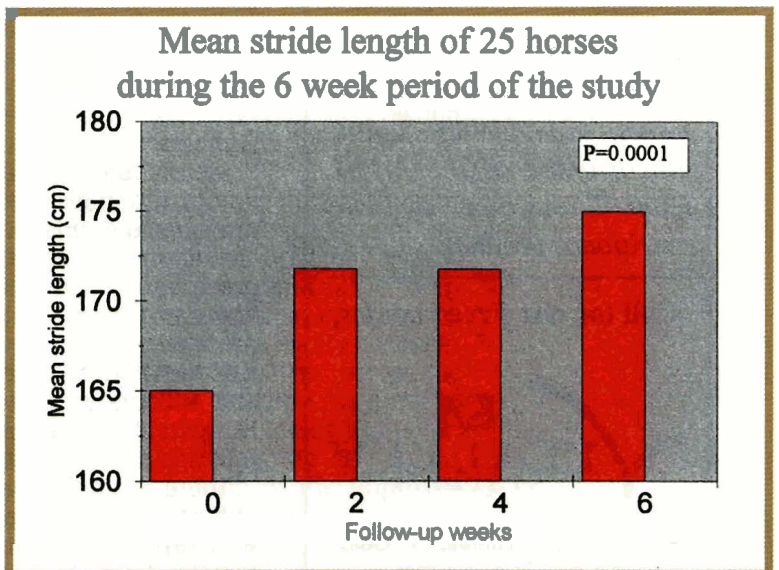


FIG. 3 – Mean stride length of 25 horses during the 6-week period of the study.

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purified to homogeneity, and are available for use as oral or injectable agents. The compound evaluated in this study contains glucosamine hydrochloride, chondroitin sulfate, ascorbate and manganese. These agents have been reported to work synergistically in forming GAGs, inhibiting degradative enzymes, and stimulating cartilage metabolism and matrix production.^{34,35} Manganese is used as an essential cofactor in proteoglycans synthesis and is necessary for normal cartilage development.^{35,36}

Although this combination is being routinely used in the clinical management of DJD in small animals where safety and efficacy were recently confirmed, studies demonstrating the success of oral administration of these agents in equine patients are lacking.³⁷⁻³⁹ The objective of this study was to evaluate the clinical effectiveness of a glucosamine-chondroitin sulfate compound under field conditions of veterinary practice in horses with clinical evidence of DJD.

Materials and Methods

Twenty-five horses with lameness confirmed to be due to degenerative joint disease by physical examination, diagnostic anesthesia and radiographs or fluoroscopy were included in the study. Horses were between 6 to 20 years old (mean, 12.3 +/- 4.3 years). There were 17 geldings, 1 stallion, and 7 mares. Primary location of the lameness was the distal interphalangeal (n = 4), metacarpophalangeal joint (n = 12), carpus (n = 2), or tarsometatarsal joint (n = 7). Most of the horses were performance horses. None had received corticosteroids or NSAIDs for 3 weeks prior to nor during the study. All were graded for lameness and flexion using the American Association of Equine Practitioner's classification.⁴⁰ An average of 3 full stride lengths of the affected limb from toe-to-toe impression at a walk were measured (Table 1). Horses with at least a grade of 1 in lameness evaluation and a grade of 2 in flexion test were included in the study. The lameness grading evaluations were performed at the initial examination and 2, 4, and 6 weeks later.

Horses weighing less than 545 kilograms were given 9 g of the glucosamine-chondroitin sulfate compound orally twice daily for 6 weeks. Those weighing more than 545 kg were given 12 g twice daily for 6 weeks. Each 3-g measure included 1800 mg of glucosamine hydrochloride, 600 mg of purified chondroitin sulfate, 16 mg manganese, and 104 mg of ascorbate. There was no restriction of exercise or activity except when deemed necessary by the investigator.

Repeated measurement analysis was implemented to assess the response of the lameness to the treatment. The procedure MIXED of the SAS computer package (Statistical Analysis System, Cary, NC) was used to conduct this analysis. The null hypothesis tested was that the baseline measurement and the following repeat examinations were the same. The effects of age, affected joint and use of the horse were tested. Differences were considered significant if the p value was equal to or less than 0.05.

Results

Means and standard deviations of various outcomes (lameness grade, flexion test grade and stride length) measured at baseline examination and during the 6 week evaluation period, are shown in Table 1. There was an overall significant difference between the lameness grade at baseline and subsequent measurements ($p < 0.0001$) (Fig. 1). There was a rapid improvement during the first 2 weeks. Improvement continued at a lower rate through the remainder of the study. The differences between measurements at baseline and 2 weeks, and at 2 and 4 weeks were significant ($p = 0.0001$ and $p = 0.04$, respectively). However, the difference between measurements at 4 and 6 weeks ($p = 0.5$) was not significant.

There was an overall significant difference between the flexion score at baseline and subsequent measurements ($p = 0.0001$) (Fig. 2). There was rapid improvement during the first 2 weeks. Improvement remained almost level through the remainder of the study. The difference between flexion scores at baseline and 2 weeks was significant ($p = 0.0001$). However, the differences between scores at 2 and 4 weeks

($p = 0.2$) and at 4 and 6 weeks ($p = 0.5$) were not significant.

There was an overall significant difference between the stride length at baseline and subsequent measurements ($p < 0.0001$) (Fig. 3). There was a rapid improvement during the first 2 weeks, which remained almost level through the remainder of the study. The difference between stride length measurements at baseline and 2 weeks was significant ($p = 0.001$). However, the differences between the measurements at 2 and 4 weeks ($p = 1.0$) and at 4 and 6 weeks ($p = 0.1$) were not significant.

The age of horses was not a significant factor in the improvement of lameness grade, flexion test, or stride length ($p = 0.2$, $p = 0.07$, and $p = 0.2$, respectively). Most horses were able to return to exercise and competition after the initial two weeks of therapy.

Discussion

A significant improvement of the horses treated with the tested glucosamine-chondroitin sulfate compound in this study was observed irrespective of age, joint affected or use of the horse. All of the outcomes measured showed a trend of improvement of clear clinical importance, which was statistically significant. It is important to note that in most cases the exercise and activity of the horses was increased, while some horses returned to competition after the second week of therapy. This increased activity and workload may explain leveling of the response after 2 weeks.

The study lacked a placebo group. This limits the interpretation of the magnitude of the improvement of the horses. There was no blinding of the examiners to the treatment. Examiner bias could play a role in the assessment of the outcomes measured. However, the results for both the objective (stride length) and subjective outcomes (lameness and flexion test) were consistent, tending to allay the concern about this potential bias. It is possible that the owners who volunteered to participate were more health conscious and thus, would take better care of their horses and subject them to less than normal physical effort during the treatment period. This would reflect a better treatment effect than would be found in other populations of horses with DJD. However, this bias was not found in this study since most of the horses returned to exercise and even to competition after the initial 2 weeks of therapy.

The findings of the current study are in concordance with previous reports about the efficacy of the studied agents in management of DJD in horses and in small

animals.^{37,41} They are further in agreement with human randomized double-blinded controlled clinical trials that used preparations of glucosamine salts and have verified its efficacy in the management of osteoarthritis and lack of side effects.⁴²⁻⁵⁰ Electron microscopic examination of cartilage samples revealed healthier and less degenerated cartilage in the treatment group versus the placebo group.⁴² Moreover, administration of chondroitin sulfates was associated with reduction of osteoarthritis symptoms together, being very well tolerated without local or systemic side effects, in many clinical studies and randomized double-blind controlled clinical trials.^{19,51-56} A reduction in the use of concomitant NSAIDs and a favorable carryover effect after termination of the treatment has also been reported.⁶²

The findings are also in agreement with previous reports about the synergistic effects of the studied agents in forming GAGs, inhibiting degradative enzymes, and enhancing cartilage metabolism and matrix production.^{34,35} Glucosamine is probably the key compound necessary for cartilage matrix synthesis as it enhances chondrocyte synthesis of glycosaminoglycans, collagen and DNA.^{22-25,57} Glucosamine has been shown to possess anti-inflammatory activity, although mild, in different animal models without inhibiting the synthesis of prostaglandin.^{23,24} Furthermore, it has been hypothesized to enhance synthesis of synovial fluid hyaluron.⁵⁸ On the other hand, chondroitin sulfates have exhibited the ability to enhance chondrocyte macromolecular synthesis in cultures.⁷ The proposed mechanisms of chondroitin sulfate chondroprotection are: contribution to the pool of GAGs in cartilaginous tissue; competitively inhibit degradative enzymes of proteoglycans in cartilage and synovial fluid hyaluronic acid; and prevention of fibrin, thrombi, and plaque formation in the synovium and /or subchondral blood vessels.^{22,58}

It is important to note that most commercially available complex sugars are only for parenteral use. Certainly an oral dosage form that has clinically proven chondroprotective effects on arthritic cartilage in horses would be highly desirable in the treatment of DJD. The therapeutic potential of the studied agents is extremely promising in horses. However, controlled clinical trials are needed to assess the magnitude of the improvement in horses with DJD. 🐾

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TABLE 1
Comparison of Lameness Score, Flexion Test Score, and Stride Length in 25 Horses with a Diagnosis of Degenerative Joint Disease Receiving a Glucosamine-Chondroitin Sulfate Compound During a 6-Week Period

	Lameness Score*		Flexion Test Score*		Stride Length (cm)*	
	Mean	SD	Mean	SD	Mean	SD
Initial Exam	2.32	0.99	2.44	0.59	165.0	14.6
2 Weeks	1.28	1.24	1.40	0.65	171.8	15.2
4 Weeks	0.88	1.13	1.16	0.85	171.8	16.3
6 Weeks	0.76	1.13	1.04	0.79	175.0	16.7

*Lameness score: grade 0 = sound; grade 1 = difficult to observe; not consistently apparent regardless of circumstances (i.e., weight-carrying, circling, inclines, hard surfaces, etc.); grade 2 = difficult to observe at a walk or trotting in a straight line; consistently apparent under certain circumstances (i.e., weight-carrying, circling, inclines, hard surfaces, etc.); grade 3 = consistently observable at a trot under all circumstances; grade 4 = obvious lameness, marked bobbing, hitching or shortened stride; grade 5 = minimal weight-bearing in motion and/or at rest, inability to move.

*Flexion test score: grade 0 = sound, no response to flexion; grade 1 = a few lame steps that diminish and then travel sound; grade 2 = consistent lameness after flexion that does not improve; grade 3 = exaggerated lameness that does not improve or improves slowly; grade 4 = after flexion a resulting non supporting leg lameness.

*Definition: Average toe-to-toe measurement of three full strides of the affected limb at a walk.

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