Effects of Oral Glucosamine and Chondroitin Sulfates Supplementation on Frequency of Intra-articular Therapy of the Horse Tarsus

Martha R. Rodgers, VMD

Private Practitioner, Equine Lameness
Lexington KY

KEY WORDS: oral glucosamine, tarsus, intra-articular, alternative therapy, equine, chondroitin sulfate

ABSTRACT

Effects of oral glucosamine/chondroitin (Glu/Chon) sulfates supplementation on the frequency of intra-articular injection of the distal intertarsal joints (distal intertarsal [DIT] and tarsometatarsal [TMT]) were evaluated in 10 horses used as competitive hunter/jumpers. Study duration was 8 years—2 years before supplementation and 6 years of supplementation (10 g active Glu/Chon daily). Clinical lameness evaluations (palpation and flexion tests), radiographs, and intra-articular anesthesia or injections were performed by the same clinician (author). The horses were under the consistent management of a single professional trainer during the study period. The frequency of distal tarsal joint injections decreased from a mean of 1.7 injections per year prior to Glu/Chon supplementation to 0.85 injections per year with Glu/Chon supplementation. There was a notable drop in injection frequency after 5 to 8 months of supplementation. Consistent use of an oral glucosamine/chondroitin supplement resulted in a decreased need for distal tarsal joint injections to maintain soundness in a group of show hunters/jumpers.

INTRODUCTION

The beneficial effects of oral glucosamines and oral chondroitin sulfate (Glu/Chon) supplementation either alone or in combination have been well documented over the past 30 years in medical research. Most of the early in vitro and in vivo work documenting chondrocyte response to Glu/Chon and bioavailability were conducted in rat, rabbit, and dog models of osteoarthritis.[1–11] Subsequent studies expanded to human subjects to document the level of absorption and bioavailability of these compounds in both man and trans species applications.[12–21] Clinical trials that followed evaluated primarily post-operative human patients in comparative treatment group studies (oral glucosamine sulfate versus oral nonsteroidal anti-inflammatory drugs [NSAIDs]).[22–46] More recently, there has been more direct research involving the horse in attempts to clarify Glu/Chon safety, absorption, dosing, and potential benefits.[4,5,10,11,47–60] Favorable outcomes within the body of work has resulted in widespread paternal use of Glu/Chon for the treatment of osteoarthritic conditions as well as prophylactic applications for working horses within the equine populace.

There are 5 main forms of glucosamine, 4 of which are tolerated well orally: glucosamine sodium sulfate, glucosamine

potassium sulfate, glucosamine hydrochloride, and N-acetyl D-glucosamine. Glucosamine is a glycoprotein that is converted in the body to an ester form that is preferentially taken up by chondrocytes and synoviocytes.[1–3,60–63] Glucosamine is a direct precursor for glycosaminoglycan (GAG) synthesis and acts to upregulate GAG production under certain conditions.[1,3,4,8,61,64–68] Most of the equine studies have utilized glucosamine hydrochloride as the Glu type tested while in human-based research, most of the studies have used glucosamine sulfates (Na and/or K) as the main Glu type. Preliminary absorption studies in the horse of glucosamine hydrochloride show a 5.9% absorption rate after a single dose.[69] There is both extensive tissue uptake and first-pass conversion in the liver that may account for the lower serum levels found. To date, there have not been sustained oral dosing studies performed in the horse. In rat, dog, and human studies, glucosamine sulfate was found to have a 95% bioavailability with a special tropism for articular cartilage.[12–14]

Chondroitin sulfate is a polysulfated glycosaminoglycan (PSGAG), a long branching sulfated disaccharide that is the predominant GAG in articular cartilage. It has 2 main exogenous forms: C-6-sulfate and A-4-sulfate. Both forms indicate chondroprotective properties when used in vitro and vivo.[4,5,7,53,70–72] However, only chondroitin sulfate A-4 has been proven to be absorbed through oral applications.[20,56] Chondroitin sulfate (in part because of the sulfation) has the ability to bind and trap water in both proteoglycan and collagen matrices, giving articular cartilage its unique resiliency to concussive force.[73,74] Absorption studies of chondroitin sulfate A-4 in the horse show 22% to 30% bioavailability.[54] The variation in absorption may be dependant upon the molecular weight (the lower molecular weight having the higher intestinal permeability). Chondroitin sulfate also shows a tropism for articular cartilage with synovial fluid levels exceeding plasma concentrations after dosing.[20,43]

Glucosamine and chondroitin likely fall into the category of a slow-acting disease-modifying osteoarthritic drug. Therefore, repetitive oral dosing at appropriate intervals (q12h) would be critical for accurate assessment of Glu/Chon in long-term efficacy studies. Single oral dosing, although necessary for studies to evaluate absorption, is unlikely to reflect or approximate the biokinetics of longer-term use.

Both glucosamines and chondroitin sulfate inhibit proteoglycan degradation primarily by the inhibition of MMPs and the IL-1 pathway. Glycosaminoglycan production is stimulated by both glucosamine and chondroitin under specific conditions.[17,74,75] Glucosamine sulfate may also further increase GAG synthesis by presenting higher levels of sulfur to cartilage that is necessary for production. Glucosamine also inhibits the negative effects of nitrous oxide and PGE2 while chondroitin has variable effects on those mediators.[66,76] Chondroitin sulfate and glucosamine in combination have a strong stimulatory effect on hyaluronan production, thereby increasing synovial fluid viscosity.[77]

There are numerous studies in the horse that suggest a synergistic action between glucosamine and chondroitin that, when given together, the beneficial effects are greater than when each is used independently. The objective of this study was to determine if consistent long-term oral Glu/Chon supplementation would decrease the necessity and frequency of intra-articular therapeutic injections of the distal tarsal joints in working show hunters and jumpers.

MATERIAL AND METHODS

Ten horses were included in this study and were followed from 1997 to 2004. The horses ranged in age from 4 years to 16 years (average age, 8.8 years) at the start of the study period and from 11 years to 23 years (average age, 15.8 years) at the conclusion of the study period. The breed distribution was 6 Thoroughbreds, 2 Irish Sport Horses, and 2 Quarter Horses. Of the horses includ-

ed in the study, 9 were geldings and 1 was a mare. Breed, sex, and age distributions were all representative of horses used for show purposes within the practice population. These horses performed as show hunters/jumpers or event horses and maintained consistent work levels throughout the study period. The 2 oldest horses (Horses 3 and 7) that began in the study (age 11 and 16 respectively) were already receiving oral methylsulfonylmethane (MSM) prior to the start of Glu/Chon supplementation and continued to take it during the study period. The first 2 years of the study (1997-1998) were before any Glu/Chon supplementation. During the first year of supplementation (1999), some horses began on the supplement in April (Horses 1, 6, and 7) and the remaining horses began in August. Including the first year of supplementation (1999-variable start) and the following 5 years (2000-2004) of the study, the Glu/Chon supplement was administered daily. The oral Glu/Chon supplement used in the study provided active ingredients of 1200 mg glucosamine sodium sulfate, 1200 mg glucosamine potassium sulfate, 1200 mg glucosamine hydrochloride, 300 mg N-acetyl D-glucosamine, and 1200 mg chondroitin sulfate per dose (5.1 g scoop). The supplement also contained 300 mg ascorbate and 100 mg manganese per dose for theoretical catalytic activity of the Glu/Chon. The total daily dose (by weight) of 11 g was divided into BID dosing (5.5 g AM and PM). No other intramuscular, intravenous, or topical therapies directed at joint pain were administered during this time.

All the horses were ridden by and under the daily management of the same trainer, and lameness evaluations were performed by the same veterinarian (author) over the course of the study. Distal tarsal pain/tarsitis was diagnosed by a combination of at least 2 of the following: gait evaluation, flexion/palpation test results, radiographic changes, and/or intra-articular anesthesia. Veterinary clinical evaluation of each horse was usually initiated by the trainer or owners' complaint of soreness, improper gait transitions, or change in jumping impulsion. The horses were all examined at least once annually for lameness if a complaint had not necessitated an exam that year. Intra-articular therapy (hyaluronan and steroid injection) was performed if distal tarsal pain was confirmed by the above-mentioned criteria.

RESULTS

In the 2 years before supplementation (1997-1998), the mean number of injections per year was 1.7 and the mean injection interval was 6.8 months. During the 6 years of supplementation (1999-2004), the mean number of injections per year was 0.85 and the mean injection interval was 9.98 months. Because of the variable starting month in 1999 for supplementation (April or August), consistent response to the Glu/Chon supplement may not be reflected in this time period's data as well as in the following years (2000-2004). If 1999 data is not included, the mean number of injections per year falls to 0.7 with the mean injection interval extending to 10.82 months. Even with the data from 1999 included, the fewer number of injections required to maintain soundness and the longer injection interval are significant.

DISCUSSION

The data collected from this study show that with sustained oral supplementation of Glu/Chon, the overall number and frequency of intra-articular distal tarsal injections drops dramatically. Horses that had required 2 to 3 distal intertarsal joint injections per year to maintain performance prior to the oral therapy were able to perform well with one injection or less per year while taking oral Glu/Chon supplementation. Of the 10 horses, 3 horses (Horses 2, 4, and 9) actually had a slight increase in their mean number of injections and a slight decrease in the injection interval, but this difference was not significant (Table 1). All 3 horses had required on average 1 injection or less per annum prior to supplementation while the

Table 1. Average Number of Injections and Intervals.

Year	Average Injections per Year	Average Interval, Months
1997	1.5	7.7
1998	1.9	5.9
1999	1.7	5.8
2000	1.2	9.5
2001	0.7	10.6
2002	0.5	11.5
2003	0.6	10.9
2004	0.4	11.6

Presupplement averages: 1.7 injections per year with a 6.8-month interval (1997-1998).
Supplement averages: 0.85 injections per year with a 9.98-month interval (1999-2004).

other 7 horses in the study had required on average 2 injections or more per annum to maintain initial soundness. Therefore, it seems that horses that are experiencing more noticeable distal tarsal joint pain respond more significantly to the Glu/Chon supplement, at least by the parameters reviewed in this study. It also would be expected that with increasing age and the continued demands of show horse performance, all the horses would be more likely to develop more pronounced distal tarsal pain. Because distal tarsitis is a progressive disease (until functional fusion occurs, the timing of which is highly variable), it would therefore most often require more therapy, not less. In light of this, the overall drop in number of injections required and the decrease in injection frequency over the 8-year study period can be viewed as an even more convincing argument for the beneficial effects of long-term oral Glu/Chon supplementation.

Due to the invasive nature of joint injections and their possible negative sequelae (infection, post-injection synovitis, periarticular fibrosis, etc), oral or other parenteral therapies have been sought after over the last 20 years. The findings of this study confirm that long-term oral Glu/Chon supplementation provides a viable treatment option that can reduce the required frequency of joint injections. Concurrent use of intramuscular PSGAG or intravenous hyaluronan with oral Glu/Chon has not been evaluated but in theory should result in even further alleviation of joint pain. Because of the different modes of anti-inflammatory action directed at different target tissues within the joint, a synergistic relationship would most likely be a result of combining oral Glu/Chon use and intramuscular PSGAG or intravenous hyaluronan. With many horses traveling to shows or events, often at great distances from their primary veterinarians, the decrease in frequency of necessary veterinary intervention would also be desirable. Most owners and trainers would prefer to have the veterinarian who would perform more invasive procedures be one in whom they have confidence and a regular working relationship. Fewer joint injections done while on the road in sometimes less than ideal surroundings and with an unfamiliar staff should hopefully result also in fewer potentially adverse complications.

The oral supplement used here was a Glu/Chon combination that delivered 3.9 g glucosamine/1.2 g chondroitin (active ingredients) per dose given BID. This gives a total daily dose of 10.2 gm of active Glu/Chon for a typical 1000-lb horse; this dose was extrapolated from in vivo canine and human studies (20 mg/kg) that showed positive study results. Most of the equine studies that have utilized oral Glu/Chon products in their study design used a minimum dose of 9 g up to 12 g of active Glu/Chon compound for 6 to 8 weeks of treatment in order to show any efficacy.[52,53] It appears then that a daily dose of 9 g of active Glu/Chon for a period of 6 to 8 weeks is the lowest amount that has resulted in measurable clinical relief of joint pain.

A recent non-published study evaluated the oral absorption rate of glucosamine hydrochloride in horses and found it to be 5.9% for a single dose of 10 g of glucosamine hydrochloride. This same study also collected joint fluid and analyzed it for the presence of glucosamine. Although the

level within the synovial fluid after single oral dosing was lower than that used in in vitro studies to show glucosamine effects on cartilage, its presence was still detectable at 12 hours after dosing. To truly evaluate the serum and joint levels attainable with oral glucosamine supplementation, a longer-term study would be required to elucidate any cumulative effects that sustained (≥8 weeks) BID dosing of glucosamine may provide in the horse. There is also some question on whether another form of glucosamine—glucosamine sulfate (Na and K), which has been the main form studied in radio-marker testing as well as human research—may have better absorption. Administration of glucosamine sulfate results in higher serum and synovial fluid sulfate levels that lead to increases in sulfate incorporation into cartilage and the sulfation process of GAGs. Low sulfate concentrations have been shown in vivo and in vitro to slow the rate of GAG synthesis. Therefore, using the sulfated form of glucosamine would make more physiologic sense to maximize any potential benefits of increasing sulfur levels.

The oral absorption rate for chondroitin sulfate in the horse has been documented at 22% for a single dose of 3 g of a higher molecular weight compound and 32% for a single dose of 3 g of a lower molecular weight compound. Although the study mentioned above did not evaluate synovial fluid levels, it has been shown in dogs that there was a 66.5% higher level in synovial fluid than in plasma after dosing of chondroitin sulfate. Again, sustained oral dosing of chondroitin sulfate may result in significantly higher measurable joint levels that would in turn correlate with the beneficial effects on cartilage seen in the in vitro studies. Again, using a product that utilizes the lower molecular weight chondroitin as its component will yield a higher level absorbed and ultimately utilized by the horse.

In this study, consistent twice-daily administration of 10 g of a Glu/Chon supplement resulted in favorable results of longer duration of soundness and fewer required joint injections in regard to the lower hock joints. The joint supplementation data showed that 6 to 8 months of consistent use was necessary before those favorable results were evident. When helping to outline a joint health program for clients (especially those who are on the road or circuit), veterinarians can now more accurately advise their clients on the daily dose required and the duration of treatment needed if an oral Glu/Chon joint supplement product will be included in the overall program.

REFERENCES

1. Bassleer C, Rovati L, Franchimont P: Stimulation of proteoglycan production by glucosamine sulfate in chondrocytes isolated from human osteoarthritic articular cartilage in vitro. *Osteoarthritis Cartilage* 1998;6:427-434.
2. Raiss R: Effect of D-glucosamine sulfate on experimentally injured articular cartilage. Comparative morphometry of the ultrastructure of chondrocytes. *Fortschr Med* 1985;103(24):658-662.
3. Anderson CC, Cook JL, Kneeger JM, Tomlinson JL, Wagner-Mann CC: In vitro effects of glucosamine and acetylsalicylate on canine chondrocytes in three-dimensional culture. *Am J Vet Res* 1999;60:1546-1551.
4. Glade MJ: Polysulfated glycosaminoglycans accelerate net synthesis of collagen and glycosaminoglycans by arthritic equine cartilage tissues and chondrocytes. *Am J Vet Res* 1990;51:779-785.
5. Caron JP, Eberhart SW, Nachreiner R: Influence of polysulfated glycosaminoglycans on equine articular cartilage in explant culture. *Am J Vet Res* 1991;52:1622-1625.
6. Caron JP, Toppin DS, Block JA: Effect of polysulfated glycosaminoglycan on osteoarthritic equine articular cartilage in explant culture. *Am J Vet Res* 1993;54:1116-1121.
7. Bassleer C, Malaise M: Chondroitin sulfate, its in vitro effect on human articular chondrocytes cultivated in clusters. *Osteoarthritis Cartilage* 1997;5(SupplA):69.
8. Lippiello L, Idouraine A, McNamara PS, Marr SC, McLaughlin RM: Cartilage stimulatory and antiproteolytic activity is present in sera of dogs treated with a chondroprotective agent. *Canine Pract* 1999;24:1.
9. Bassleer C, Henrotin Y, Franchimont P: In-vitro evaluation of drugs proposed as chondroprotective agents. *Int J Tissue React* 1992;14:231-241.
10. Orth MS, Peters TL, Hawkins JN: Glucosamine HCl and chondroitin sulfate inhibit the catabolic response of articular cartilage explants cultured with lipopolysaccharide. *Osteoarthritis Cartilage* 2001;9(Suppl B):S54.

11. DeChant JE, Baxter GM, Frisbie DD, Trotter GW, Mcllwraith CW: Effects of glucosamine and chondroitin sulfate alone and in combination, on normal and interleukin-1 conditioned equine articular cartilage explants in vitro. Proceedings of ACVS Veterinary Symposium, Chicago IL; October 11-14(5), 2001.
12. Setnikar I, Giacchetti C, Zanolo G: Absorption, distribution and excretion of radioactivity after a single intravenous or oral administration of c14 glucosamine sulfate to the rat. *Pharmacotherapuetica* 1984;3:538-550.
13. Setnikar I, Giacchetti C, Zanolo G: Pharmacokinetics of radio labeled glucosamine in dog and in man. *Arzneimittelforschung* 1986;36:729-734.
14. Setnikar I, Palumbo R, Canali S, Zanolo G: Pharmacokinetics of glucosamine in man. *Arzneimittelforschung* 1993;43:1109-1113.
15. Tesoriere G, Dones F, Magistro D, Castagnetta L: Intestinal absorption of glucosamine and N-acetylglucosamine. *Experientia* 1972;3:538-550.
16. Conte A, Volpi N, Palmiera L, Bahous I, Ronca G: Biochemical and pharmacokinetic aspects of oral treatment with chondroitin sulfate. *Drug Res* 1995;45:918-925.
17. Baici A, Horler D, Moster B, et al: Analysis of glycosaminoglycans in human serum after oral administration of chondroitin sulfate. *Rheumatol Int* 1992;12:81-1288.
18. Huang Y, Toyoda H, Toida T, et al: Determination of chondroitin sulfates in human whole blood, plasma and blood cells by high performance chromatography. *Biomed Chrom* 1995;9:102-105.
19. Okazaki J, Kamada A, Matsukawa F, et al: Disaccharide analysis of chondroitin sulfate in human gingival crevicular fluid using high-performance liquid chromatography. *Arch Oral Biol* 1995;40:777-779.
20. Conte A, De Bernardi M, Palmieri L, et al: Metabolic fate of exogenous chondroitin sulfate in man. *Arzneimittelforschung* 1991;41:768-772.
21. Gross D: Pharmacokinetic study on oral chondroitin sulfate. Rheumatology and rehabilitation. *Therapiewoche* 1983;33:4238-4244.
22. Crolle G, D'Estel E: Glucosamine sulfate for the management of arthrosis: a controlled clinical investigation. *Curr Med Res Opin* 1980;7:104-109.
23. Reginster JY, Deroisy R, Rovati LC, et al: Long-term effects of glucosamine sulfate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001;357:251-256.
24. Pavelka K, Gatterova J, Olejarova M, et al: Glucosamine sulfate decreases progression of knee osteoarthritis in a long-term, randomized, placebo-controlled, independent, confirmatory trial. Presented at the American College of Rheumatology 2000 Annual Meeting. *Arthritis Rheum* 2000;49(Suppl):1908.
25. Drovanti A, Bingnamini AA, Rovati AL: Therapeutic activity of oral glucosamine sulfate in osteoarthritis: a placebo controlled double blind investigation. *Clin Ther* 1980;3:260-272.
26. Giacovelli G, Rovati LC: Clinical efficacy and safety of glucosamine sulfate in osteoarthritis of the spine. a placebo-controlled, randomized, double-blind study. *Rev Esp Rheumatol* 1993;20:96.
27. Muller-Fabbender H, Bach GL, Haase W, et al: Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. *Osteoarthritis Cartilage* 1994;2:61-69.
28. Vas AL: Double-blind clinical evaluation of the relative efficacy of ibuprofen and glucosamine sulfate in the management of osteoarthrosis of the knee in outpatients. *Curr Med Res Opin* 1982;8:145-149.
29. Qiu GX, Gao SN, Giacovelli G, Rovati L, Setnikar I: Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. *Arzneimittelforschung* 1998;48(5):469-474.
30. Rovati LC: Clinical research in osteoarthritis; design and results of short and long-term trials with disease-modifying drugs. *Int J Tissue React* 1992;14:243-251.
31. Pujalte JM, Liavore EP, Ylescupidez FR: Double blind clinical evaluation of oral glucosamine sulfate in the basic treatment of osteoarthritis. *Curr Med Res Opin* 1980;7:110-114.
32. Zupanets IA, Drogovoz SM, Bezdetko NV, et al: The influence of glucosamine on the antiexudiative effect of nonsteroidal anti-inflammatory agents. *Farmakol Toksikol* 1991;54:61-63.
33. Giordano N, Nardi P, Senesi M, et al: The efficacy and safety of glucosamine sulfate in the treatment of gonarthritis. *Clin Ther* 1996;147:99-105.
34. Hehne HJ, Blasius K, Ernst HU: Therapy of gonarthritis using chondroprotective substances. prospective comparative study of glucosamine sulfate and glycosaminoglycan polysulfate. *Fortschr Med* 1984;102:676-682.
35. Hughes RA, Carr AJ: A randomized, double-blind, placebo-controlled trial of glucosamine to control pain in osteoarthritis of the knee. *Arthritis Rheum* 2000;43:1903.
36. D'Ambrosia ED, Casa B, Bompasi R, et al: Glucosamine sulfate: a controlled clinical investigation in arthrosis. *Pharmatherapeutica* 1981;2:504-508.
37. DaCamara CC, Dowless GV: Glucosamine sulfate for osteoarthritis. *Ann Pharmacol* 1998;32:580-587.
38. Mazieres B, Loyau G, Menkes CJ, et al: Chondroitin sulfate in the treatment of gonarthrosis and coxarthrosis. 5-months result of a multicenter double-blind controlled prospective study using placebo. *Rev Rhum Mal Osteoartic*. 1992;59(7-8):466-472.
39. Morreal P, Manopulo R, Galati M, Boccanera L, Saponati G, Bocchi L: Comparison of the antiinflamatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. *J Rheumatol* 1996;23(8):1385-1391.
40. Verbruggen G, Goemaere S, Veyes EM: Chondroitin sulfate as a structure/disease modifying anti-arthritis drug in the treatment of finger joint osteoarthritis. *Osteoarthritis Cartilage* 1998;6(Suppl A):37-38.

41. Uebelhart D, Thonar EJMA, Delmus PD, Chantraine A, Vignon E: Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study. *Osteoarthritis Cartilage* 1998;6(Suppl A):39-46.
42. Ronca F, Palmieri L, Panucucci P, Ronca G: Anti-inflammatory activity of chondroitin sulfate. *Osteoarthritis Cartilage* 1998;6(Suppl A):14-21.
43. Fleisch AM, Merlin C, Imahoff A, Hodler J, Kissling R: A one year randomized, double-blind, placebo-controlled study with oral chondroitin sulfate in patients with knee arthritis. *Osteoarthritis Cartilage* 1997;5(Suppl A):6.
44. Michel B, Vignon E, De Vathaire F, et al: Oral chondroitin sulphate in knee OA: radiographic outcome of a 2-year study. Evaluation of the efficacy of chondroitin sulfate as a potential disease modifying drug in knee osteoarthritis by assessing femorotibial joint space narrowing using quantitative radiology. *Osteoarthritis Cartilage* 2001;9(Suppl B):S68.
45. Leffler CT, Philipi AF, Leffloer SG, Mosure JC, Kim PD: Glucosamine, chondroitin and manganese ascorbate for degenerative joint disease of the knee and low back: a randomized double-blind placebo-controlled pilot study. *Mil Med* 1999;164(2):85-91.
46. Das AK, Eitel J, Hammad T: Efficacy of a new class of glucosamine hydrochloride, sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis: a randomized double-blind placebo-controlled clinical trial. American Association of Hip and Knee Surgery 8th Annual Meeting, November 1998.
47. Wright IM. Oral supplements in the treatment and prevention of joint diseases: a review of their potential application to the horse. *Equine Veterinary Education:* AE 2001;179-183.
48. Jaeschke G, Steinbach W: Specific treatment of arthrosis deformations in horses with glucosamine sulfate. *Dtsch Tierarztl Wochenschr* 1982;89:288-293.
49. Hanson RR: DJD Medications; Chondroprotective Agents; Oral Chondroprotectives. Will Medicine Keep Your Horse Sound. Reprinted in *The Horse* 1996;38-42.
50. Eddington ND, Du J, White N: Evidence of the oral absorption of chondroitin sulfate as determined by total disaccharide content after oral and intravenous administration to horses. *AAEP Proceedings* 2001;47:326-328.
51. Gustafson SB, McIlawraith CW, Jones RI: Comparison of the effect of polysulfated glycosaminoglycan, corticosteroids, and sodium hyaluronate in the potentiation of a subinfective dose of *Staphlococcus aureus* in the midcarpal joint of horses. *Am J Vet Res* 1989;50(12):2014-2017.
52. Hanson RR, Smalley LR, Huff GK, White S, Hamad TA: Oral treatment with a glucosamine-chondroitin sulfate compound for degenerative joint disease in horses: 25 cases. *Equine Pract* 1997;19(9):16-22.
53. Hanson RR, Brawner WR, Blaik MA, Hammad TA, Kincaid SA, Pugh DG: Oral treatment with a nutriceutical (Cosequin) for ameliorating signs of navicular syndrome in horses. *Vet Ther* 2001;2(2):148-159.
54. Hanson RR, Hammad TA, Brawner WR: Evaluation of the clinical efficacy of cosequin in the treatment of navicular syndrome, a double-blind, placebo-controlled randomized clinical trial. Proceedings of the Veterinary Orthopedic Society's 25th Annual Conference. February 1998; Abstract 63.
55. Turner T, Stone WC, Herthel D, Weinberg C, Leitch M, Markell R: Current management of equine degenerative joint diseases. *Equine Practice-Roundtable*. 1997;19;7-8.
56. White N, Benner E, Grant B, Hanson RR, McNitt D, Mitchell R: Roundtable on equine degenerative joint disease. *Equine Pract* 1995;17:6.
57. Hanson RR: Oral glycosaminoglycans in the treatment of degenerative joint disease in horses. *Equine Pract* 1996;18(10):18-22.
58. Kirker-Head CA, Kirker-Head RP: Safety of oral chondroprotective agent in horses. Tufts University School of Veterinary Medicine, Department of Clinical Sciences. *Vet Ther* 2001;2(4):345-353.
59. Fenton JI, Chlebek-Brown KA, Peters TL, CaronJP, Orth MW: Glucosamine HCL reduces equine articular cartilage degeneration in explant culture. *Osteoarthritis Cartilage* 2000;8:258-265.
60. Davenport DF, Blackford J, Bishop MR, Sommardahl CS, Martin EJ: Equine therapeutic nutrition i & ii, nutritional supplement ingredients, the good, the bad and the useless. *Proceedings WWVC* 2002;(i):707-720.
61. Kelly GS: The role of glucosamine sulfate and chondroitin sulfates in the treatment of degenerative joint disease. *Altern Med Rev* 1998;3(1):27-39.
62. McCarty MF: Enhanced synovial production of hyaluronic acid may explain rapid clinical response to high-dose glucosamine in osteoarthritis. *Med Hypotheses* 1998;50(6):507-510.
63. Rovati LC: The clinical profile of glucosamine sulfate as a selective symptom modifying drug in osteoarthritis: current data and prospective. *Osteoarthritis Cartilage* 1997;5(Suppl A):72.
64. Karzel K, Lee KJ: Effect of hexosamine derivatives on mesenchymal metabolic process of in vitro cultured fetal bone explants. *Z Rheumatol* 1982;41:212-218.
65. Russell AL, Glucosamine in osteoarthritis and gastrointestinal disorders: an exemplar of the need for a paradigm shift. *Med Hypotheses* 1998;51(4):347-349.
66. McCarty MF. The neglect of glucosamine sulfate as a treatment for osteoarthritis. *Med Hypotheses* 1994;42(5):323-327.
67. Van der Kraan PM, Vitters EL, De Vries BJ, Van Den Berg WB: High susceptibility of human articular cartilage glycosaminoglycan synthesis to changes in inorganic sulfate availability. *J Orthop Res* 1990;8:565-571.

68. Woodward JS, Lippiello L, Karpman RR: Beneficial effect of dietary chondroprotective agents in a rabbit instability model of osteoarthritis. Presented at the American Academy of Orthopedic Surgeons 1999 Annual Meeting; Paper No: 048.
69. Laverty S, Sandy JD, Celeste C, Vachon P, Marier JF, Plaas AH: Synovial fluid levels and serum pharmacokinetics in a large animal model following treatment with oral glucosamine at clinically relevant doses. *Arthritis Rheum* 2005;52(1):181-191.
70. Todhunter RJ, Lust G: Polysulfated glycosaminoglycans in the treatment of osteoarthritis. *J Am Vet Med Assoc* 1994;204:1245-1251.
71. Paroli E, Antonilli L, Biffoni M: A pharmacological approach to glycosaminoglycans. *Drugs Exp Clin Res* 1991;17(1):9-19.
72. Uebelhart D, Thonar EJ, Zahang J, Williams JM: Protective effect of chondroitin sulfate 4 and 6 in the accute degeneration of articular cartilage in the rabbit. *Osteoarthritis Cartilage* 1998;6(Suppl A):6-13.
73. Nerucci F, Fioravanti A, Bisogno S, Spinelli G, Marcolongo R: Evaluation of the chondroitin sulfate on chondrocytes cultures placed in a pressurization system. Third International Congress of the Osteoarthritis Research Society. *Osteoarthr Focus* 1997;5(Suppl A):69.
74. Bollet AJ, Nance JL: Biochemical findings in normal and osteoarthritic articular cartilage ii: chondroitin sulfate concentration and chain length, water and ash contents. *J Clin Invest* 1966;45:1170-1175.
75. Adebowale AO, Cox DS, Linang I, et al: Analysis of glucosamine and chondroitin sulfate content in marketed products and CACO-2 permeability of chondroitin sulfate raw materials. *J Am Nutraceuticals Assoc* 2003;3:37-44.
76. Byron CR, Orth MW, Venta PJ, et al: Influence of glucosamine on matrix metalloproteinase expression and activity in lipopolysaccharde-stimulated equine chondrocytes. *Am J Vet Res* 2003;64:666-671.
77. Davis WM: The role of glucosamine and chondroitin sulfate in the management of arthritis. *Drug Topics* 2000;Supplement:3S-13S.