

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

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## 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.<sup>1-11</sup> Subsequent studies expanded to human subjects to document the level of absorption and bioavailability of these compounds in both man and trans species applications.<sup>12-21</sup> Clinical trials that followed evaluated primarily post-operative human patients in comparative treatment group studies (oral glucosamine sulfate versus oral non-steroidal anti-inflammatory drugs [NSAIDs]).<sup>22-46</sup> More recently, there has been more direct research involving the horse in attempts to clarify Glu/Chon safety, absorption, dosing, and potential benefits.<sup>4,5,10,11,47-60</sup> 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.<sup>1-3,60-63</sup> Glucosamine is a direct precursor for glycosaminoglycan (GAG) synthesis and acts to upregulate GAG production under certain conditions.<sup>1,3,4,8,61,64-68</sup> 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.<sup>69</sup> 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.<sup>12-14</sup>

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.<sup>4,5,7,53,70-72</sup> However, only chondroitin sulfate A-4 has been proven to be absorbed through oral applications.<sup>20,56</sup> 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.<sup>73,74</sup> Absorption studies of chondroitin sulfate A-4 in the horse show 22% to 30% bioavailability.<sup>54</sup> 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.<sup>20,43</sup>

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.<sup>17,74,75</sup> 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.<sup>66,76</sup> Chondroitin sulfate and glucosamine in combination have a strong stimulatory effect on hyaluronan production, thereby increasing synovial fluid viscosity.<sup>77</sup>

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 own-

ers' 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.<sup>52,53</sup> 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 ( $\geq 8$  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.

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