THE NUTRAMAX/COSEQUIN®
CASE BY CASE
STUDENT COMPETITION
WINNING ENTRY

Treatment with Cosequin® of Bilateral Coxofemoral Osteoarthritis in a Great Dane

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This article represents the second of two winning entries in the Nutramax/Cosequin® Case by Case Student Competition. Dr. Hoffman was a senior student at Oklahoma State University when she wrote this case study. She is currently affiliated with California Eye Clinic for Animals, Tustin, California.

Osteoarthritis (OA), the most common cause of degenerative joint disease (DJD) in dogs, is a chronic, progressive, noninfectious joint disorder that leads to degeneration of articular cartilage and proliferative changes. Damage to articular cartilage may result from abnormal stresses that disrupt the normal articular surface, in turn leading to joint instability. Consequently, the normal wear pattern as well as the turnover of articular matrix are accelerated.[1] This process is also accelerated by cytokines and prostaglandins released by synovial cells into the joint. As a result, the joint capsule thickens and periarticular osteophytes form in an effort to improve joint stability.

OSTEOARTHRITIS TREATMENT

Current therapy for symptomatic treatment of OA in dogs includes the use of antiinflammatory medications; slow-acting, disease-modifying agents; or a combination of both. The most commonly used antiinflammatory agents for treating OA are NSAIDs. Although NSAIDs are effective in reducing pain, these agents can result in unwanted side effects such as gastrointestinal upset, hepatocellular toxicosis, renal disease, and occasionally death.[2–4] In addition, the newer cyclooxygenase-2 inhibitors have been associated with side effects.[3] Dose-dependent, nonsteroidal therapy can also result in a decrease in the glycosaminoglycan content in the cartilage, causing OA to worsen over time.[5–8] The current rationale is not to use NSAIDs continually unless they are needed to control inflammation associated with persistent pain.[9] The shortcomings of NSAIDs have encouraged research efforts toward safe, disease-modifying substances that can be used long term and can possibly alter the progression of OA while providing some symptomatic relief.

The first substance that overcame these shortcomings was Adequan® Canine (Luitpold Pharmaceuticals, Shirley, NY). Adequan®, an injectable polysulfated glycosaminoglycan (PSGAG),[10] has been shown to positively affect the cartilage degradation associated with OA.[10,11] Early research has shown that very young, growing dogs predisposed to hip dysplasia treated with this PSGAG had better hip conformation than did control dogs.[12] The drawback to Adequan® use is that it must be given by injection. Because many owners are unable to comply with this route of administration, research has focused on the use of oral products.

The oral product most commonly used to treat cartilage-related problems in veterinary medicine is Cosequin® (Nutramax

Laboratories, Edgewood, MD). Cosequin® is a patented nutraceutical combination of glucosamine hydrochloride, low-molecular-weight chondroitin sulfate, and manganese ascorbate. Some practitioners recommend combining modalities by starting with PSGAG injections then switching to Cosequin® for long-term therapy.[10]

In my opinion, the use of oral nutraceuticals is gaining in popularity. Much of the early research associated with their use has been subjective (e.g., positive feedback from owners). However, controlled experimental data as well as clinical data on mechanism of action, efficacy, and safety in animals have been reported recently.[1,13–20]

NUTRACEUTICAL COMPONENTS

It is important to remember that the first major biochemical change that occurs in cartilage disease and DJD is the loss of proteoglycans.[10] Therefore, based on their components (e.g., glucosamine–chondroitin sulfate–manganese combinations), nutraceuticals may theoretically have some beneficial effects in small animals. These substrates are the backbone needed for the formation of proteoglycan, which is found in the structural matrix of joints. Glucosamine is not a glycosaminoglycan but an amino sugar that has shown bioavailability in dogs.[21] Its primary biologic role seems to be its ability to stimulate chondrocytes to produce glycosaminoglycans.[14] Glucosamine does not have any effect on inhibition of proteases or their degradatory components to the cartilage matrix. Glucosamine has two main salts, which are available in hydrochloride and sulfate forms. The hydrochloride form seems to deliver more bioavailable glucosamine than does the sulfate form.[22] To date, veterinary research has evaluated only the hydrochloride salt in combination with low-molecular-weight chondroitin sulfate.

Chondroitin sulfate (whether absorbed intact or broken into constituents) may also provide for the formation of a healthy joint matrix. Chondroitin sulfate is the most common glycosaminoglycan found in cartilage and has also shown bioavailability in dogs when given in a pure form.[23] The molecular weight of the chondroitin sulfate has an effect on its bioavailability.[24] The primary role of chondroitin sulfate is to inhibit degradatory enzymes that lead to cartilage breakdown. Low-molecular-weight chondroitin sulfate has been shown to be efficacious in treating OA in humans.[25] Human trials using low-molecular-weight chondroitin sulfate show a carryover effect of up to 3 months after cessation of therapy.[26] This is important because it may take up to 3 months for signs to return when therapy is stopped or medication changed. In two human trials,[26,27] chondroitin sulfate was shown to slow the progression of OA. Chondroitin sulfate also has an antiinflammatory action similar to that of NSAIDs, possibly because of its mechanism of action.[27]

Glucosamine and chondroitin sulfate have different mechanisms of action, which are evident when comparative studies are evaluated.[28,29] The combination of glucosamine and chondroitin sulfate used in the study presented here was thought to protect the cartilage matrix as well as slow the progression of arthritic changes, as shown in an animal instability model of DJD.[14] Because of its glucosamine, chondroitin sulfate, and manganese ascorbate components, Cosequin® is believed to provide the raw materials essential for synovial fluid synthesis and the

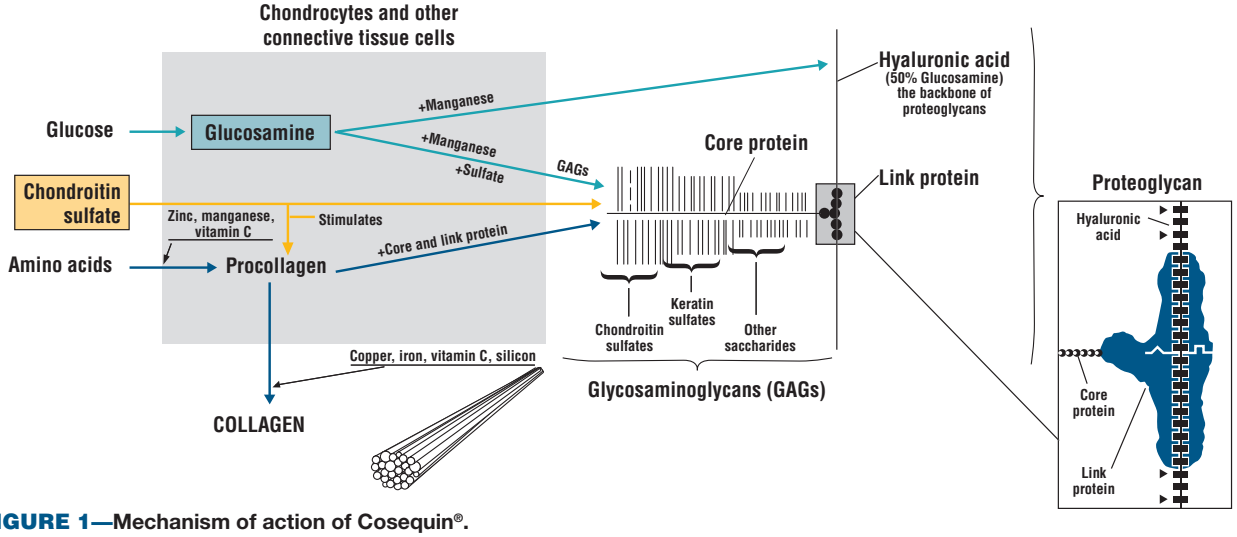

FIGURE 1—Mechanism of action of Cosequin®.

complete cartilage matrix, including collagen, hyaluronic acid, and glycosaminoglycans (Figure 1).

CASE PRESENTATION

A 1-year-old, 51-kg, spayed Great Dane was presented to the Boren Veterinary Medical Teaching Hospital at Oklahoma State University on October 20, 1998, with a shortened limb stride bilaterally, quadriceps fibrosis, an intermittent "bunny-hop" gait, and hyperextension of the tarsi. The patient demonstrated severe loss of hip range of motion and became aggressive on palpation of the coxofemoral joints. No other abnormalities were observed on history, physical examination, complete blood count, or biochemical analysis. Radiography revealed good joint congruity, bilateral periarticular osteophytosis, and a mild degree of bilateral subchondral sclerosis (Figure 2).

TREATMENT AND CLINICAL COURSE

A twofold hypothesis was made. First, it was thought that the combination of glucosamine, chondroitin sulfate, and manganese ascorbate would slow the progression of DJD. Secondly, it was hypothesized that treatment with a nutraceutical would show objective evidence of weight transfer from the forelimbs to the hindlimbs, indicating improved coxofemoral joint function as demonstrated by force-plate analysis.

The patient was started on Cosequin® DS at a dose of two capsules in the morning and one in the evening. Each tablet contains glucosamine (500 mg), sodium chondroitin sulfate (400 mg), ascorbate (66 mg), and manganese (10 mg). The dog required several reevaluations over time; therefore, a quantitative and qualitative method was designed to evaluate the patient during treatment with the nutraceutical. This approach could then be used as a standard by which other patients with DJD could be evaluated, whether untreated or treated with a nutraceutical or pharmaceutical.

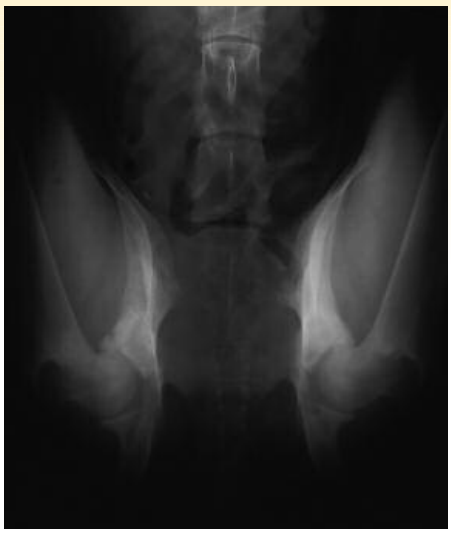

FIGURE 2—Ventrodorsal radiograph of the pelvis obtained during the initial patient evaluation revealed good congruity of both coxofemoral joints, a mild degree of periarticular osteophytosis along the cranial borders of both acetabula, and underlying subchondral sclerosis. The femoral heads have no such osteophytosis or subchondral sclerosis.

Qualitative evaluations at 3 weeks, 4 months, and 6 months after the initial examination included lameness scores, hindlimb goniometry using range-of-motion exercises, and measurements of thigh circumference. Quantitative evaluations included state-of-the-art force-plate technology (piezoelectric quartz-crystal type) to determine if there was improved joint function and analyze how these data correlated with the qualitative data.

During the 6-month evaluation period, there was a decrease in the dog's lameness scores (Table 1). Initial lameness scores were established using the following criteria:

- **Grade I**—Subtle and inconsistent lameness not apparent at a walk and not consistently identified at a trot
- **Grade II**—Consistent and mild lameness at a trot
- **Grade III**—Consistent moderate lameness at a walk
- **Grade IV**—Severe, non–weight-bearing lameness

TABLE 1. Lameness Scores During the Treatment Period

Time Period	*Grade*
Initial evaluation	III
3-week follow-up	III
4-month follow-up	II
6-month follow-up	I/II

TABLE 2. Thigh Circumference Measurements During the Treatment Period

Time Period	*Right (inches)*	*Left (inches)*
Initial evaluation	15.75	16
3-week follow-up	15.75	16
4-month follow-up	16.75	17.25
6-month follow-up	17	17.5
Total increase	1.25	1.5

TABLE 3. Hindlimb Goniometry Evaluation

Time Period	*Right Extension*	*Right Abduction*	*Left Extension*	*Left Abduction*
Initial evaluation	90°	40°	70°	60°
3-week follow-up	90°	40°	80°	60°
4-month follow-up	120°	50°	90°	70°
6-month follow-up	130°	90°	110°	75°
Net increase	40°	50°	40°	15°

The patient initially presented with grade III lameness. On the final evaluation, the dog tested at lameness grade I/II.

Thigh circumference was also assessed. With the dog in a standing position, thigh circumference was measured high in the flank region at the level of the ischiatic tuberosity. The measuring tape was kept parallel to the ground. There was a 1.25-inch increase in right thigh circumference and a 1.5-inch increase in left thigh circumference during the treatment period (Table 2).

Hindlimb goniometry using range-of-motion exercises was performed during the testing period. During the final evaluation, goniometry revealed a 40° increase for both the right and left hindlimb extensions. Increases for right and left hindlimb abduction were 50° and 15°, respectively (Table 3).

Evaluation of Cosequin® efficacy also involved trotting the patient across a force plate. Four trials for the right and left forelimbs and hindlimbs were conducted during the four evaluations, generating 64 graphs (Figure 3). Data generated by the graphs indicated an upward slope, demonstrating an overall increase in hindlimb loading by a 44-N average or an 11-lb difference for the treatment period (Figure 4). A significant increase was detected using the r^2 analysis (coefficient of determination) with a P value of less than .001.

Radiographs obtained 6 months after the initial evaluation revealed that the OA was still present, as were periarticular osteophytes and subchondral sclerosis (Figure 5).

DISCUSSION

This is the first known published clinical evaluation regarding the use of an oral nutraceutical in a young animal with radiographically evident hip dysplasia and using the defined parameters for qualitative-quantitative analysis. Traditionally, these compounds have been used in older animals with established disease or as a preventive measure in predisposed dogs.[10] In a retrospective survey, 3000 veterinarians who evaluated thousands of dogs (96% of which were older than 5 years of age) concluded that Cosequin® alleviated the pain and discomfort of OA with less than 2% of the animals showing side effects.[30]

The study presented here evaluated a young Great Dane with radiographic and clinical signs of hip dysplasia with secondary OA changes. Although the patient still had radiographic OA changes at the 6-month follow-up, the dog showed pronounced clinical improvement with Cosequin® treatment over the 6-month period with no side effects. This improvement was assessed qualitatively by a decrease in lameness score, a bilateral increase in thigh circumference, and a bilateral goniometric increase. Final analysis of the force-plate graphs revealed an increase in the vertical force applied

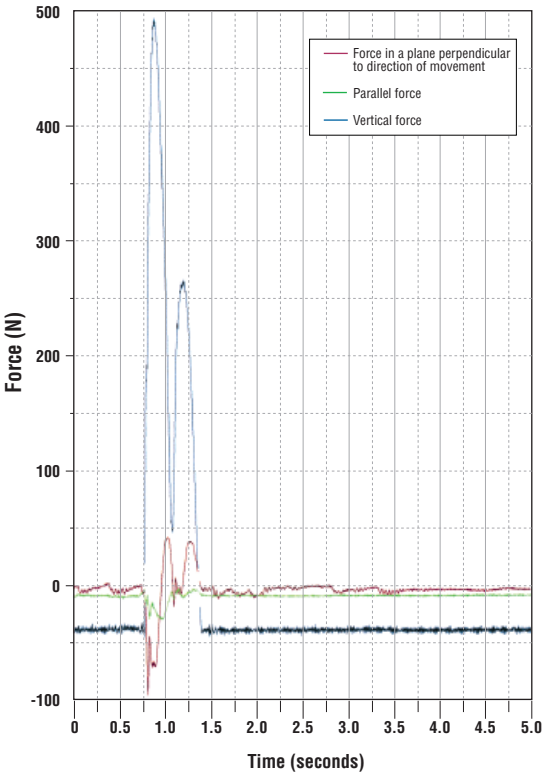

FIGURE 3—Standard force-plate graph. The hindlimb vertical force detected by the force plate is shown as the second spike on the graph.

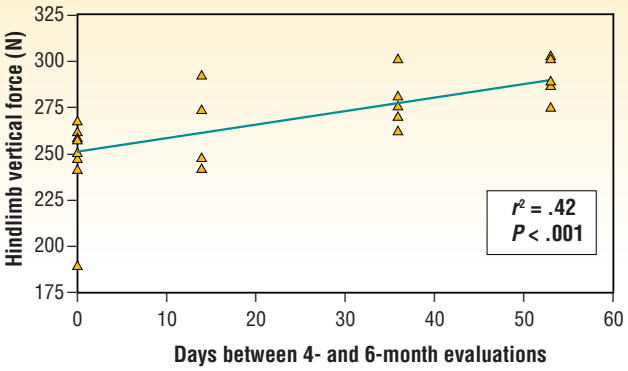

FIGURE 4—Analysis of force plate measurements yields a 44-N average increase in hindlimb loading during the treatment period.

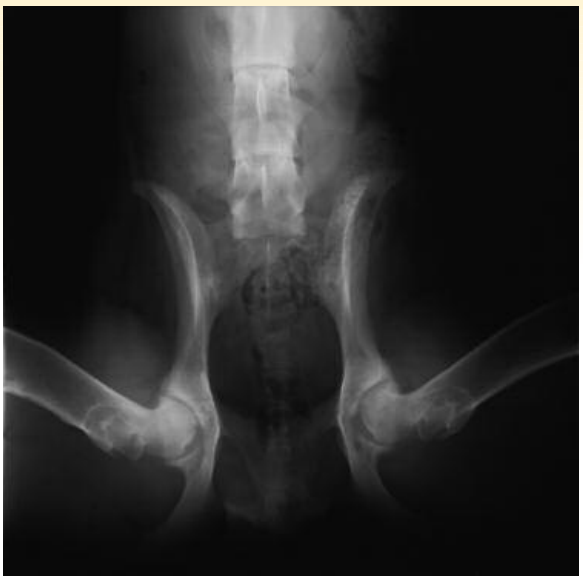

FIGURE 5—Ventrodorsal radiograph of the pelvis obtained at the 6-month follow-up evaluation. Periarticular osteophytosis and subchondral sclerosis were still evident with significant remodeling.

to the hindlimbs that was in fact transferred from the forelimbs, suggesting improved joint function.

Veterinarians often prescribe oral nutraceuticals alone or in combination with NSAIDs. When given this combined therapy, patients receive the benefits of quick pain relief and minimal side effects from the NSAID as well as the safe, long-term, disease-modifying potential provided by the nutraceutical. Human trials using the equivalent of the test agent showed a decreased dependence on NSAIDs.[31] This case study reported the efficacy of an agent that has been used with good clinical results in both veterinary and human medicine.[13,19,20,31,32] The same agent has also recently been shown to palliate joint inflammation and protect cartilage when given prior to cartilage insult.[13,33] This may result in the further use of oral disease-modifying agents as preventive agents.

Because oral nutraceuticals are not drug compounds, their purity, molecular size, and efficacy can vary greatly. Some compounds promoted as disease-modifying agents (e.g., Perna mussel supplements) cannot be substantiated.[34,35] Products that make such claims (e.g., cures arthritis, regenerates and rebuilds cartilage) should be considered as questionable. Some manufacturers promote topical or liquid products as having improved bioavailability, but there is no research to document this claim. A recent study[24] showed that some products contain none of the label ingredients. In response to these findings, the Arthritis Foundation recommends using caution when choosing products for the treatment of OA.[36]

Because this report evaluated only a single dog, it is impossible to assess whether the treatment slowed the progression of the OA disease process. There currently does not exist a validated method to radiographically assess OA progression in animals. It is also unknown whether 6 months is enough time to show significant change. Human trials have used validating techniques to show that the low-molecular-weight chondroitin sulfate found in Cosequin® has slowed the progression of OA in knees and hands.[26,37] Experimental placebo-controlled trials in animal models of arthritis have also shown a cartilage protective effect of the same studied combination.[1,13,14,33]

CONCLUSION

Osteoarthritis in young dogs is a variable disease process. The Great Dane treated in this case study responded quickly to treatment and maintained improvement. Other dysplastic dogs treated for a 40-day period with injectable low-molecular-weight chondroitin sulfate have also shown clinical improvement.[12] However, a large percentage of young dogs with secondary OA will improve over an 18-month period without clinical treatment.[38] Therefore, further controlled studies should be completed in young dogs to confirm or dismiss the results found in this study.

The knowledge base regarding the use of oral nutraceuticals continues to grow; however, much remains unknown about their relevance in veterinary medicine. Also, when evaluating slow-acting, disease-modifying agents, the outcome measurements used to study faster-acting antiinflammatory agents may be inappropriate. However, the combined qualitative and quantitative evaluations used in this study may be an acceptable protocol in which to monitor patients with joint insta-

bility, regardless of the treatment selected.

At the 28-month follow-up evaluation, the patient was reported to be showing little or no clinical signs of joint discomfort while continuing treatment with Cosequin®.

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