Degenerative joint disease, also known as osteoarthritis, is one of the most common diseases affecting dogs and is an important cause of pain in dogs of all ages. Because there is no known cure for DJD, treatment has focused on decreasing pain and inflammation and slowing progression of the disease. This may include lifestyle changes (eg, weight management and physical therapy) and administration of NSAIDs and chondroprotectants such as Glu-CS.1,2

Glucosamine is an amino sugar that is synthesized from glucose and glutamine and is a precursor of glycosaminoglycans, which are a component of articular cartilage.3 It is most commonly administered as an oral supplement in combination with chondroitin sulfate, and has been used for the treatment of DJD in both humans4 and animals.3,6 Significant clinical improvement has been reported in dogs with DJD after 70 days of treatment with Glu-CS,7 and Glu-CS treatment has also resulted in clinical improvement in humans4 and horses5 with DJD. The decreased pain and improved mobility in patients receiving Glu-CS may result from decreased cartilage degradation or changes in expression or activity of inflammatory mediators.7,8

Previous studies have demonstrated that glucosamine is a safe, nontoxic product and that adverse effects are rare.9,11 The most common adverse effects that have been reported in dogs are gastrointestinal tract disturbances.10 There are no known contraindications or drug interactions,3 and glucosamine is highly bioavailable when administered PO to dogs.12

However, despite the apparent safety of glucosamine,13-15 veterinarians have expressed concern that glucosamine supplementation may cause diabetes mellitus or make the regulation of diabetic patients more difficult. For example, the effects of Glu-CS on the regulation of diabetes mellitus in dogs and cats is a common question posted to an online veterinarian-only discussion board.6 One reason for this concern is that previous studies14,17 have demonstrated that parental administration of glucosamine can be used to induce insulin resistance in skeletal muscle of normoglycemic rats. Because of the potential effect on glycemic control, veterinary practitioners have expressed concerns regarding the clinical use of glucosamine, even in healthy dogs.

Several methods can be used to assess glycemic control in diabetic patients, including single measurements of blood glucose concentration,16 use of glucose concentration-versus-time curves,18 assessment of urine glucose concentration,18 measurement of serum fructosamine18-23 and glycosylated hemoglobin concentration,21,23 and evaluation of the severity of clinical signs (eg, polyuria, polydipsia, polyphagia, and weight loss).18 Measurement of blood and urine glucose concentrations can provide

### Abbreviations

| DJD | Degenerative joint disease |
| Glu-CS | Glucosamine–chondroitin sulfate |

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information on short-term glycemic control, whereas measurement of serum fructosamine and glycosylated hemoglobin concentrations better assess long-term glycemic control. Serum fructosamine concentration reflects glycemic control over the 2 to 3 weeks prior to measurement, whereas glycosylated hemoglobin concentration reflects glycemic control over the past 3 to 4 months. Although measurement of serum fructosamine concentration and glycosylated hemoglobin concentration can both be useful tools for monitoring glycemic control, serum fructosamine concentration is affected much more rapidly than glycosylated hemoglobin concentration when persistent hyperglycemia occurs. Thus, the purpose of the study reported here was to determine whether short-term administration of an oral Glu-CS supplement affects serum fructosamine concentration in healthy dogs.

Materials and Methods

Study participants—Twelve dogs owned by veterinary students or employees of Colorado State University Veterinary Medical Center were used in the study. Dogs were selected for enrollment in the study after a clinical evaluation that included a medical history, complete physical examination, CBC, serum biochemical testing, and urinalysis. Dogs with abnormal physical examination findings or with initial laboratory test results outside the laboratory reference ranges were excluded from the study, as were dogs receiving medications other than parasite control. Dogs receiving a therapeutic joint diet were also excluded, as these diets may include glucosamine. Dogs were housed with their owners for the duration of the study and were fed their regular diets. The study protocol was approved by the Colorado State University Institutional Animal Care and Use Committee.

Study design—The data of Loste and Marca were used to perform an initial power calculation to determine the number of dogs that should be enrolled in the study. Using an SD of 52 µmol/L for serum fructosamine concentration in euglycemic dogs, we calculated that 12 dogs would be needed to provide a power of 85% to detect a difference in serum fructosamine concentration of 50 µmol/L between treatment groups, with an α of 0.05. The difference of 50 µmol/L was chosen because this would be regarded as clinically relevant.

All dogs in the study received a 3-week course of Glu-CS capsules and a placebo. Six dogs were randomly allocated to receive Glu-CS treatment first, followed by the placebo treatment. The remaining 6 dogs received the placebo treatment first, followed by the Glu-CS treatment. In all dogs, a washout period of at least 4 weeks was observed between the 2 treatments. The Glu-CS treatment was administered PO once daily in capsule form, according to the manufacturer’s recommended dose for initial treatment (body weight, 10 to 24 lb: 1 capsule daily; 25 to 49 lb: 2 capsules daily; 50 to 100 lb: 3 capsules daily; and > 100 lb: 4 capsules daily). The Glu-CS product used contained glucosamine hydrochloride (300 mg), sodium chondroitin sulfate (400 mg), and manganese (5 mg). The placebo contained only an inert ingredient, microcrystalline cellulose, and was also administered once daily PO, with the same number of capsules as for the Glu-CS treatment. Placebo and Glu-CS capsules were prepared by the manufacturer specifically for use in this study and were identical in appearance. As such, study investigators and dog owners did not know whether dogs were receiving Glu-CS or the placebo during each of the treatment periods. Venous blood samples were obtained from each dog for measurement of serum fructosamine concentration at the beginning and end of each treatment period (ie, a total of 4 blood samples from each dog).

Sample analysis—Serum fructosamine concentration was measured at Colorado State University Diagnostic Laboratories by means of a colorimetric assay based on nitrotetrazolium-blue reduction.

Statistical analysis—A paired t test was used to compare pre- and posttreatment serum fructosamine concentrations for the Glu-CS and placebo treatment periods. A t test was also used to compare the change in serum fructosamine concentration for dogs that received Glu-CS treatment with the change in serum fructosamine concentration for dogs that were treated with the placebo. For all analyses, a value of P ≤ 0.05 was considered significant.

Results

The 12 dogs enrolled in the study consisted of 2 Labrador Retrievers, 2 German Shorthaired Pointers, 2 Pomeranians, 2 mixed-breed dogs, 1 Australian Shepherd, 1 Chesapeake Bay Retriever, 1 Jack Russell Terrier, and 1 Rhodesian Ridgeback. The dogs ranged in age from 14 months to 15 years. Median weight was 25 kg (55 lb; range, 3.6 to 33 kg [7.9 to 72.6 lb]). There were 5 spayed females and 7 castrated males. All 12 dogs that were enrolled in the study completed the full 3 weeks of treatment with Glu-CS and the full 3 weeks of treatment with the placebo. Duration of the washout period between treatments ranged from 4 to 14 weeks. No dog required treatment with additional medications during the study, with the exception of 1 dog that required surgery for medial luxation of the patella during the washout interval after the first treatment period. The second treatment period for this dog was delayed until 6 weeks after completion of a 3-day course of postoperative NSAID treatment. No dogs developed any adverse effects related to treatment with Glu-CS or the placebo.

Mean ± SD serum fructosamine concentration prior to the Glu-CS treatment period was 302.2 ± 36.1 µmol/L (range, 233 to 354 µmol/L), and mean serum fructosamine concentration at the end of the Glu-CS treatment period was 311.1 ± 28.4 µmol/L (range, 269 to 362 µmol/L). There was no significant (P = 0.20) difference between the serum fructosamine concentrations before and after Glu-CS supplementation. Mean serum fructosamine concentration prior to the placebo treatment period was 311.3 ± 35.9 µmol/L (range, 242 to 363 µmol/L), and mean serum fructosamine concentration at the end of the placebo treatment period was 322.7 ± 34.2 µmol/L (range, 258 to 380 µmol/L). There was no significant (P = 0.08) difference between the serum fructosamine concentrations before and after placebo administration. Mean change in serum fructosamine concentration during the study was 20.2 ± 37.9 µmol/L (range, 0 to 100 µmol/L).
amine concentration after Glu-CS treatment was 8.9 ± 22.7 µmol/L, which was not significantly (P = 0.79) different from the mean change in serum fructosamine concentration after placebo treatment (11.4 ± 20.4 µmol/L). Serum fructosamine values measured at all time points in the study ranged from 233 to 380 µmol/L (reference range, 175 to 360 µmol/L). Fructosamine values were noted to exceed the reference range in 3 dogs. In 1 dog, serum fructosamine concentration was 361 and 380 µmol/L before and after placebo administration, respectively. In 1 dog, serum fructosamine concentration was 363 µmol/L before placebo administration. In 1 dog, serum fructosamine was 362 µmol/L after Glu-CS supplementation. All other serum fructosamine concentration values in all dogs at all time points fell within the reference range.

Discussion

Results of the present study suggest that short-term (ie, 21 days) administration of an oral Glu-CS supplement does not adversely affect glycemic control in healthy dogs, in that serum fructosamine concentration was not significantly increased after 3 weeks of supplement administration, and the change in serum fructosamine concentration associated with supplement administration was not significantly different from the change in concentration associated with administration of a placebo.

One proposed mechanism for glucosamine-induced insulin resistance relates to the hexosamine pathway.14,15 The hexosamine pathway is an alternative pathway for glucose metabolism that may produce endogenous glucosamine from fructose-6-phosphate and glutamine via the enzyme glutamine:fructose-6-phosphate amidotransferase.16 It is believed that this pathway is usually activated when glucose uptake is adequate, signaling that cellular glucose stores are sufficient and thus resulting in shunting of excess glucose and the creation of endogenous glucosamine.15 An inappropriate increase in activity of the hexosamine pathway may result in insulin resistance, even when hyperglycemia is present and insulin stimulation is normal.24,25 It has been suggested that excess glucosamine, including exogenous glucosamine, could signal that cells do not need to activate glucose transport; the presence of glucosamine could thus mimic the result of activation of the hexosamine pathway, resulting in insulin resistance.15

After studies16,17 demonstrated that parenteral administration of glucosamine can be used as an experimental tool for the induction of insulin resistance in rats, subsequent studies found that oral glucosamine administration at standard recommended doses (ie, 1,500 mg of glucosamine, q 24 h) does not cause insulin resistance in healthy humans,18 nor does it worsen insulin resistance in humans with type II diabetes mellitus.19 In addition, a study17 in which clinically normal dogs were evaluated, revealed no change in serum biochemical profiles, including glucose concentration, after treatment with Glu-CS for 30 days.

Despite evidence that glucosamine treatment does not affect blood glucose concentration when given orally, the relationship between glucosamine treatment and diabetes mellitus remains of concern to many veterinarians. This may result from some awareness of the continued use of glucosamine for studies inducing insulin resistance in insulin-sensitive tissues such as skeletal muscle, or because glucosamine is a derivative of glucose. Because glucosamine is an amino sugar synthesized from glucose and glutamine, veterinarians may be concerned that it may be broken down after administration, resulting in hyperglycemia. However, in humans, the reaction that produces glucosamine from glucose and glutamine is irreversible.19 Although there are no data demonstrating this irreversibility in dogs, results of a previous study19 and those of the present study suggest that administration of Glu-CS for 21 to 30 days does not result in hyperglycemia or altered glycemic control in dogs.

Assessment of serum fructosamine concentration is a useful tool for monitoring glycemic control, and it is a sensitive and specific test for the diagnosis of diabetes mellitus.1,22 Thus, if glucosamine supplementation had altered glycemic control during the treatment period or had caused diabetes mellitus in the study dogs, serum fructosamine concentration would likely have changed significantly. Three dogs had serum fructosamine concentrations that ranged from 1 to 20 µmol/L higher than the upper reference limit. However, these mild increases in concentration, compared with the reference range, would not be considered clinically important. When serum fructosamine concentration is used to assess diabetic control, changes of approximately 50 µmol/L are considered to be clinically relevant. For example, glycemic control in a dog with diabetes mellitus would be regarded as excellent if serum fructosamine concentration was 350 µmol/L and good if the value was 400 µmol/L.16 The present study was designed to have a power of 85% to detect a difference in serum fructosamine concentration of 50 µmol/L. The SDs obtained were in fact less than those used in the initial power calculation, and the actual power of the study for the detection of a difference in serum fructosamine concentration of 50 µmol/L was 99%.

An important limitation of the present study is that we did not determine whether Glu-CS supplementation is safe for dogs with diabetes mellitus. A considerably larger number of dogs would be needed to perform such a study because of the substantial variability in serum fructosamine concentration typically found in dogs with diabetes mellitus. Applying a power calculation with the data of Loste and Marca19 for serum fructosamine concentrations typically found in dogs with hyperglycemia, we calculated that approximately 40 dogs would be required to detect a change in serum fructosamine concentration of 50 µmol/L.

This study did not address the effects of oral Glu-CS on insulin resistance in healthy dogs. The present study also did not assess the effect of long-term Glu-CS administration on serum fructosamine concentration. If hyperglycemia had occurred during the treatment period, measurement of serum fructosamine concentration would probably have indicated this. However, it is possible that glycemic control may be significantly affected by long-term administration of Glu-CS. Further studies are necessary to investigate this.

References