Intra-articular injections of corticosteroids rapidly resolve joint inflammation, synovitis, and signs of pain and are the gold standard of treatment for horses with osteoarthritis. Corticosteroids inhibit inflammation via 2 mechanisms. Corticosteroids suppress arachidonic acid metabolism through lipocortin-induced phospholipase inhibition. This inhibition helps to stabilize the phospholipids in the cell membrane, making them unavailable for entrance into the arachidonic cascade. Corticosteroids also block production of proinflammatory cytokines, such as IL-1, by binding to cytoplasmic receptors and modulating inflammatory gene transcription. Two corticosteroids that are frequently used are methylprednisolone acetate and triamcinolone acetonide. High doses of methylprednisolone acetate can have detrimental effects on normal and abnormal articular cartilage by impairing chondrocyte activity, inhibiting GAG and proteoglycan synthesis in the articular cartilage matrix, and decreasing expression of mRNA for collagen type II. In contrast, studies on triamcinolone acetonide reveal many beneficial effects on abnormal articular cartilage, including decreased IL-1-induced GAG degradation, increased proteoglycan synthesis, and enhanced chondrocyte viability. Six to 18 mg of intra-articularly administered triamcinolone acetonide is recommended for treatment of most equine joints.

Clinically, hyaluronic acid has been used as a treatment for osteoarthritis. In a clinically normal joint, hyaluronic acid is secreted into the synovial fluid by

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**Effects of sodium hyaluronate and triamcinolone acetonide on glucosaminoglycan metabolism in equine articular chondrocytes treated with interleukin-1**

Elycia C. Schaefer, DVM; Allison A. Stewart, MS, DVM; Sushmitha S. Durgam, BVSc; Christopher R. Byron, MS, DVM; Matthew C. Stewart, PhD, BVSc

**Objective**—To determine whether the effects of a high–molecular-weight sodium hyaluronate alone or in combination with triamcinolone acetonide can mitigate chondrocyte glycosaminoglycan (GAG) catabolism caused by interleukin (IL)-1 administration.

**Sample Population**—Chondrocytes collected from metacarpophalangeal joints of 10 horses euthanized for reasons unrelated to joint disease.

**Procedures**—Chondrocyte pellets were treated with medium (negative control), medium containing IL-1 only (positive control), or medium containing IL-1 with hyaluronic acid only (0.5 or 2.0 mg/mL), triamcinolone acetonide only (0.06 or 0.6 mg/mL), or hyaluronic acid (0.5 or 2.0 mg/mL) and triamcinolone acetonide (0.06 or 0.6 mg/mL) in combination. Chondrocyte pellets were assayed for newly synthesized GAG, total GAG content, total DNA content, and mRNA for collagen type II, aggrecan, and cyclooxygenase (COX)-2.

**Results**—High-concentration hyaluronic acid increased GAG synthesis, whereas high-concentration triamcinolone acetonide decreased loss of GAG into the medium. High concentrations of hyaluronic acid and triamcinolone acetonide increased total GAG content. There was no change in DNA content with either treatment. Triamcinolone acetonide reduced COX-2 mRNA as well as aggrecan and collagen type II expression. Treatment with hyaluronic acid had no effect on mRNA for COX-2, aggrecan, or collagen type II.

**Conclusions and Clinical Relevance**—Results indicated that high concentrations of hyaluronic acid or triamcinolone acetonide alone or in combination mitigated effects of IL-1 administration on GAG catabolism of equine chondrocytes. (Am J Vet Res 2009;70:1494–1501)

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**Abbreviations**

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<tr>
<th>Abbreviation</th>
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<tr>
<td>COX-2</td>
<td>Cyclooxygenase-2</td>
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<tr>
<td>CPM</td>
<td>Counts per minute</td>
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<td>GAG</td>
<td>Glycosaminoglycan</td>
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<td>IL</td>
<td>Interleukin</td>
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From the Department of Veterinary Clinical Medicine, College of Veterinary Medicine, University of Illinois, Urbana, IL 61802
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Address correspondence to Dr. Allison Stewart (aaw@illinois.edu).
joint capsule synoviocytes and serves to lubricate the joint. It is also an important component of the articular cartilage, where it binds to chondrocyte CD44 receptors and serves as a backbone of attachment sites for proteoglycan structures. Proteoglycans maintain the hydrostatic pressure of cartilage, allowing resistance to compressive forces during weight bearing, and are depleted first in the early stages of osteoarthritis. Documented beneficial effects of hyaluronic acid are increased chondrocyte metabolism, increased GAG content in the cartilage matrix, and decreased activity of pro-inflammatory mediators, which results in decreased matrix degradation. However, it remains uncertain whether the molecular weight of various hyaluronic acid products is an important factor in its efficacy. Several studies reveal that a high–molecular-weight hyaluronic acid may have longer efficacy and increased metabolic and anti-inflammatory properties, compared with a low–molecular-weight hyaluronic acid. However, results of other studies indicate little to no difference between high- and low–molecular-weight hyaluronic acid products.

Two recently published studies have evaluated combination therapy with methylprednisolone acetone and hyaluronic acid on normal equine cartilage explants and an IL-1–induced inflammatory model of chondrocyte metabolism. The cartilage explant study revealed detrimental effects of methylprednisolone acetone on normal cartilage and that the addition of a medium–molecular-weight hyaluronic acid had little effect on the corticosteroid-induced proteoglycan catabolism of the cartilage matrix. The other study found beneficial effects on proteoglycan metabolism by use of lower doses of methylprednisolone acetone and a medium–molecular-weight hyaluronic acid on chondrocyte pellets in an inflammatory environment (ie, IL-1–treated). The purpose of the study reported here was to evaluate the effects of 2 of the most commonly used intra-articular treatments—a corticosteroid (triamcinolone acetone) and a high–molecular-weight hyaluronic acid. Our hypothesis was that administration of hyaluronic acid alone or in combination with triamcinolone acetone would mitigate the chondrocyte GAG catabolism caused by IL-1 administration.

Materials and Methods

Horses and pellet culture—All horses used in this study were euthanized for reasons unrelated to joint disease by use of a lethal dose of sodium pentobarbital administered IV. The Institutional Animal Care and Use Committee at the University of Illinois approved this study. Articular cartilage was aseptically collected from the metacarpophalangeal joints of 10 horses that ranged in age from 2 to 4 years. All joints were evaluated to ensure there was no gross evidence of joint disease prior to cartilage collection. On day 1, the cartilage was placed in chondrogenic medium consisting of Dulbecco modified Eagle medium, 10% fetal bovine serum, 1% l-glutamine, 1% penicillin-streptomycin, and ascorbic acid (50 µg/mL), and was digested overnight with 0.2% collagenase. After digestion, an estimation of total chondrocyte number and viability was made by use of a Reichart hemocytometer and trypan blue stain. The chondrocytes were suspended at a concentration of 500,000 cells/mL in chondrogenic medium. The medium containing the chondrocytes was transferred to an Eppendorf tube (0.5 mL/tube). The medium was centrifuged to form chondrocyte pellets containing 250,000 cells. The pellets were incubated at 37°C for 7 days to allow formation of an extracellular matrix, and the medium was changed every 2 to 3 days.

Treatments were administered on day 7, and the pellets were incubated for an additional 24 hours. There were 10 treatment groups with a minimum of 10 pellets in each group (Appendix). Treatment groups consisted of fresh medium only (negative control), fresh medium with IL-1β only (10 ng/mL [positive control]), IL-1 (10 ng/mL) and hyaluronic acid (0.5 mg/mL or 2 mg/mL [2 treatment groups]), IL-1 (10 ng/mL) and triamcinolone acetone (0.06 mg/mL or 0.6 mg/mL [2 treatment groups]), and IL-1 (10 ng/mL) with hyaluronic acid (0.5 mg/mL or 2 mg/mL) and triamcinolone acetone (0.06 mg/mL or 0.6 mg/mL [4 treatment groups]). The concentrations of hyaluronic acid and triamcinolone acetone were determined from a range of published concentrations likely to be present in the metacarpophalangeal joint 24 to 48 hours after an intra-articular injection. At the time of treatment, 4 pellets from each treatment group were radiolabeled with medium containing sulfur 35 (35S)–labeled sodium sulfate (10 µCi/mL). All pellets were removed from the treatment medium after 24 hours of incubation and were washed 3 times with PBS solution. For 7 horses, 4 radiolabeled pellets and exhausted medium were stored at –80°C until further analysis. For 3 horses, 2 pellets in each treatment group were snap-frozen in liquid nitrogen and saved at –80°C for RNA isolation. For 6 horses, 2 pellets/treatment group were saved for histologic examination.

GAG synthesis—New GAG synthesis was determined via 35SO4 incorporation into the pellet and sub-
sequent release into the medium during a 24-hour period. Radiolabeled pellets were digested in papain (150 µg/mL) at 65°C for 24 hours. Radiolabeled medium was digested in papain (150 µg/mL) at 65°C for 4 hours. Aliquots of 25 µL of radiolabeled papain-digested pellets and 25 µL of radiolabeled papain-digested medium were placed in 96-well filtration plates.26 Precipitated with 0.2% Alcian blue dye solution, and counted for scintillation.26 Radioisotope decay was accounted for in all values, and scintillation counts were normalized for pellet digestion volume.

Total pellet GAG content—Total GAG content in the pellets and in the medium was determined by use of a dimethylmethylene blue binding assay.27 Pellets were digested in papain as described. Aliquots of 25 µL of papain-digested pellets were placed into 96-well microplates, 200 µL of 1,9-dimethylmethylene blue dye was added, and samples were analyzed for absorbance. All sample values were compared against a standard curve of chondroitin sulfate values to estimate the total GAG content and normalized for pellet digestion volume.

Pellet mRNA content—Real-time PCR data were obtained from chondrocyte pellet cultures of 3 horses. The RNA was extracted from 20 pellets/horse in each treatment group by use of the Trizol reagent according to the manufacturer’s suggested protocol. Complementary DNA was obtained by priming the sample with oligo-d(T) and then adding reverse transcriptase. Real-time quantitative PCR analysis was performed for collagen type II, aggrecan, and COX-2 and normalized to elongation factor-1α mRNA expression. A PCR detection system was used to perform the assay.1,2,20

Histologic examination—After 24 hours in 4% paraformaldehyde, pellets were transferred to a 4% agarose gel and stored at 4°C overnight. The pellets were dehydrated in alcohol, embedded in paraffin, sectioned, and stained with toluidine blue.

Statistical analysis—All nonnormally distributed data were logarithmically transformed and presented as mean ± SE log values. A 1-way repeated-measures ANOVA performed with a software program was used to compare the positive control (IL-1) with the negative control (no IL-1). The hyaluronic acid and triamcinolone acetonide values were evaluated by use of a 2-way repeated-measures ANOVA performed with the same software program. All post hoc tests were conducted when indicated by use of the Holm-Sidak method. Values of P ≤ 0.05 were considered significant.

Results

Pellet GAG synthesis—Pellet GAG synthesis was designated as the amount of newly synthesized (radio-labeled) GAG (CPM) retained in the pellet. Treatment with IL-1 significantly (P = 0.018) decreased GAG synthesis of the positive control (IL-1 only), compared with the negative control (no IL-1; Figure 1). Treatment with hyaluronic acid (2 mg/mL) significantly (P < 0.001) increased GAG synthesis, compared with the IL-1 control group. Treatment with 0.06 and 0.6 mg of triamcinolone acetonide/mL did not have a significant (P = 0.218) effect on GAG synthesis, compared with 0 mg of triamcinolone acetonide/mL. However, there was a significant (P = 0.004) effect of the combined treatment of hyaluronic acid and triamcinolone acetonide (2 mg of hyaluronic acid/mL combined with 0.06 or 0.6 mg of triamcinolone acetonide/mL), which increased newly synthesized GAG; the 0.06 and 0.6 mg/mL groups
were not significantly different. Similarly, results in pellets treated with 1 mg of hyaluronic acid/mL combined with 0.6 mg of triamcinolone acetonide/mL were not significantly different from pellets treated with 0.6 mg of triamcinolone acetonide/mL alone.

Total GAG synthesis—Total GAG synthesis was designated as the amount of newly synthesized GAG retained in the pellet, plus that released into the medium. Treatment with IL-1 resulted in no significant (P = 0.097) difference in total GAG synthesis, compared with the negative control (no IL-1; Figure 2). Treatment with hyaluronic acid (2 mg/mL) resulted in a significant (P = 0.026) increase in total GAG synthesis compared with the IL-1 control group. Treatment with triamcinolone acetonide did not have a significant (P = 0.607) effect on total GAG synthesis. There was no significant (P = 0.48) synergistic effect of hyaluronic acid and triamcinolone acetonide combined.

Percentages of GAG retained in pellet and released into the medium—Percentages of GAG retained in the pellet and released into the medium were calculated by dividing the amount of newly synthesized GAG (CPM) in the pellet and medium by the total GAG (CPM) in the pelleted cells. Treatment with IL-1 only significantly (P = 0.04) decreased the percentage of GAG retained in the pellet and significantly (P = 0.04) increased the percentage of GAG released into the medium, compared with the negative control (no IL-1; Figures 3 and 4). Treatment with hyaluronic acid did not have a significant (P = 0.26) effect on percentage of GAG retained within the pellets or on the percentage of GAG released into the medium. Treatment with triamcinolone acetonide (0.06 and 0.6 mg of triamcinolone acetonide/mL) resulted in a significant (P = 0.004) increase in percentage of GAG retained in the pellet and decrease in percentage of GAG released into the medium, compared with the 0 mg/mL treatment group. There was no significant (P = 0.67) synergistic effect of hyaluronic acid and triamcinolone acetonide combined.

Total GAG pellet content—Total GAG pellet content was designated as the total GAG content retained in the pellet after treatment, and this included the newly synthesized GAG. Treatment with IL-1 alone did not have a significant (P = 0.101) effect on the total GAG content, compared with the negative control (no IL-1; Figure 5). Treatment with hyaluronic acid (2 mg/mL) significantly (P = 0.002) increased the total GAG content within the pellet, compared with the IL-1 control group. Treatment with 0.6 mg of triamcinolone acetonide/mL significantly (P = 0.036) increased total GAG pellet content, compared with the 0 mg/mL treatment group. There was no significant (P = 0.73) synergistic effect of hyaluronic acid and triamcinolone acetonide combined.
Total DNA pellet content—Treatment with IL-1 ($P = 0.217$), hyaluronic acid ($P = 0.781$), or triamcinolone acetonide ($P = 0.982$) had no significant effect on the DNA content of pellets.

Pellet mRNA content—Treatment with IL-1 only significantly ($P = 0.026$) increased collagen type II mRNA, compared with the negative control (no IL-1; Figure 6). Treatment with hyaluronic acid had no significant ($P = 0.102$) effect on collagen type II mRNA, compared with the IL-1 control group. Treatment with 0.06 and 0.6 mg of triamcinolone acetonide/mL significantly ($P = 0.001$) decreased collagen type II mRNA, compared with the IL-1 control. There was no significant ($P = 0.121$) synergistic effect of hyaluronic acid and triamcinolone acetonide combined.

Treatment with IL-1 only significantly ($P = 0.045$) increased aggrecan mRNA, compared with the negative control (no IL-1; Figure 7). Treatment with hyaluronic acid did not have a significant ($P = 0.725$) effect on aggrecan mRNA, compared with the IL-1 control. Treatment with triamcinolone acetonide had a significant ($P = 0.007$) effect on aggrecan mRNA. Specifically, the 0.06 and 0.6 mg of triamcinolone acetonide/mL treatment groups had significantly decreased aggrecan mRNA, compared with the IL-1 control. There was no significant ($P = 0.11$) synergistic effect of hyaluronic acid and triamcinolone acetonide combined.

Treatment with IL-1 only significantly ($P = 0.021$) increased COX-2 mRNA, compared with the negative control (no IL-1; Figure 8). Treatment with hyaluronic acid did not have a significant ($P = 0.126$) effect on COX-2 mRNA, compared with the IL-1 control. Treatment with triamcinolone acetonide had a significant ($P = 0.007$) effect on COX-2 mRNA. Specifically, the 0.06 and 0.6 mg of triamcinolone acetonide/mL treatment groups had significantly decreased COX-2 mRNA, compared with the IL-1 control group. There was no significant ($P = 0.464$) synergistic effect of hyaluronic acid and triamcinolone acetonide combined.

Histologic examination—The chondrocyte pellets varied in size among horses. The size of the pellets was not measured; instead the pellets were only evaluated for proteoglycan production through the use of the toluidine blue stain. Subjectively, pellets treated with hyaluronic acid, triamcinolone acetonide, or the combination had increased proteoglycan staining, compared with the IL-1 treated control, throughout the pellet matrix (Figure 9).

Discussion

Results of the study reported here indicated the beneficial effects of hyaluronic acid alone and in combination with triamcinolone acetonide on IL-1–treated equine articular chondrocyte pellets. Hyaluronic acid increased both the new GAG synthesis by chondrocytes and the total GAG content retained in the pellets, compared with the IL-1 control. Treatment with triamcinolone acetonide increased the total GAG content retained in the chondrocyte pellet. These results were similar to those of another study in which triamcinolone acetonide mitigated IL-1–induced GAG degradation. Treatment with triamcinolone acetonide also reduced COX-2 mRNA expression, compared with the IL-1 control. Most of these benefits were detected at the high concentration of hyaluronic acid (2 mg/mL) and the high concentration of triamcinolone acetonide (0.6
mg/mL). The combination of 2 mg of hyaluronic acid/mL and 0.6 mg of triamcinolone acetonide/mL resulted in the highest concentrations of total pellet GAG following treatment with IL-1, although a significant synergistic effect was not found.

Treatment with IL-1 had several detrimental effects on chondrocyte metabolism. Administration of IL-1 caused a decrease in retention of newly synthesized GAG by the pellet, compared with the negative control (no IL-1). Treatment with IL-1 also increased COX-2 mRNA expression, compared with the negative control. In addition, IL-1 administration caused an increase in aggrecan and collagen type II mRNA production, compared with the negative control. This may have been caused by an increase in chondrocyte metabolism of aggrecan and collagen type II in response to an IL-1-mediated cytokine cascade.3

Treatment with hyaluronic acid increased GAG synthesis and total GAG pellet content, compared with the positive control (IL-1 treatment), but did not have an effect on mRNA of COX-2, aggrecan, or collagen type II. Specifically, addition of hyaluronic acid (2 mg/mL) was beneficial in negating the effects of IL-1 administration and increasing new GAG synthesis, compared with the positive control. Lower concentrations of hyaluronic acid did not have a significant effect on GAG synthesis. Although hyaluronic acid was beneficial for GAG synthesis, treatment with hyaluronic acid had no effect on COX-2 mRNA, suggesting that matrix degradation continued to occur in these treatment groups. Hyaluronic acid also had no effect on collagen type II or aggrecan mRNA, but resulted in maintained expression rates similar to the IL-1–treated control. The disparity between the aggrecan mRNA expression data and new GAG synthesis suggested that hyaluronic acid may have increased synthesis of products other than aggrecan, such as biglycan and decorin. Alternatively, the retention of aggrecan in the pellet after synthesis may have been more effective in the presence of hyaluronic acid. Ultimately, the GAG synthesis, GAG release, and total GAG retained in the pellet matrix are probably the most important data.

Treatment with triamcinolone acetonide increased total pellet GAG content and decreased mRNA of COX-2, aggrecan, and collagen type II, compared with the IL-1–treated control. Specifically, treatment with triamcinolone acetonide increased total GAG pellet content by increasing GAG retention within the pellet while decreasing GAG lost into the medium. In addition, triamcinolone acetonide was beneficial in suppressing COX-2 mRNA that increased with IL-1 treatment. As seen in other studies using a corticosteroid, treatment with triamcinolone acetonide was effective at a cellular level in blocking mediators of inflammation. In the present study, treatment with triamcinolone acetonide suppressed mRNA of aggrecan and collagen type II. However, the mRNA expression associated with triamcinolone acetonide treatment was similar to the baseline expression of treatment groups with no IL-1. Corticosteroid-induced suppression of aggrecan and collagen type II mRNA has been detected before.31 Corticosteroid suppression of aggrecan and collagen type II mRNA may have detrimental effects in a longer-term study. These results suggest triamcinolone acetonide predominantly works by suppressing inflammation to retain GAG in the pellet, not by increasing the synthesis of GAG in the pellet.

Combination treatment with hyaluronic acid and triamcinolone acetonide mitigated the effects of IL-1 administration by increasing new GAG synthesis and retention within the pellet. The high concentrations of both drugs—hyaluronic acid at 2 mg/mL and triamcinolone acetonide at 0.6 mg/mL—in combination had the most profound effect on GAG synthesis. These results suggest that hyaluronic acid and triamcinolone acetonide mitigate the detrimental effects of IL-1 administration through different mechanisms to increase the total GAG content within the pellet. In an inflammatory environment such as that created by IL-1 administration, high concentrations of hyaluronic acid may be beneficial in supporting chondrocyte GAG production, whereas high concentrations of triamcinolone acetonide may act in an additive or synergistic fashion by retaining GAG within the chondrocyte matrix.

Similar to a previous study, IL-1 was administered to create an inflammatory environment.3 Although IL-1 caused expected detrimental effects in this study, other inflammatory mediators are also known to be present in osteoarthritic joints. These proinflammatory mediators include tumor necrosis factor-α, IL-6, IL-8, IL-11, IL-17, and leukemia inhibitory factor.32 Studies33,34 have documented the detrimental effects of these inflammatory cytokines, suggesting that they may act along different pathways or in a synergistic fashion with IL-1. Results of the present study may have been amplified if other proinflammatory mediators had been used with IL-1 administration to create a model of inflammation.

This study used an in vitro model to study the effects of inflammation on cartilage metabolism. Although an in vitro study provided a controlled environment to evaluate the effect of multiple concentrations of hyaluronic acid and triamcinolone acetonide on a standardized cartilage matrix, many important in vivo influences were lost. Specifically, an in vitro study does not allow for clearance of metabolites from the local environment or for systemic metabolism of administered medications. Therefore, results may not accurately represent what would occur in an in vivo situation. Further in vitro studies evaluating the effects of hyaluronic acid and triamcinolone acetonide in osteoarthritic equine joints may provide further insight into the benefits and deficiencies of intra-articular hyaluronic acid and triamcinolone acetonide administration.

The range of hyaluronic acid and triamcinolone acetonide concentrations used in this study was based on estimated joint concentrations following commonly used intra-articular dosages. In a previous study,35 triamcinolone acetonide at 1.2 mg/mL decreased IL-1–induced GAG degradation, but was unable to maintain GAG synthesis; an overall decrease in GAG synthesis was detected. In the present study, the highest dose of triamcinolone acetonide (0.6 mg/mL) had a protective effect against IL-1–induced GAG degradation without any decrease in GAG synthesis. On the basis of these findings, it is possible that triamcinolone acetonide concentrations...
The effects of triamcinolone acetonide in the present study were similar to results from a previous study that used a similar model and used methylprednisolone acetonide. The response to corticosteroid administration was similar for pellet GAG synthesis, total pellet GAG content, total pellet DNA content, and mRNA expression. Both methylprednisolone acetonide and triamcinolone acetonide increased pellet GAG synthesis in combination with hyaluronic acid, suggesting a substantial benefit when corticosteroids and hyaluronic acid are used together. Both corticosteroids, methylprednisolone acetonide and triamcinolone acetonide, significantly increased the total pellet GAG content. Both methylprednisolone acetonide and triamcinolone acetonide had no effect on the total pellet DNA content. Methylprednisolone acetonide and triamcinolone acetonide both had a significant effect on reducing mRNA of COX-2 in the presence of IL-1 administration. The findings of these 2 studies illustrate the beneficial effects corticosteroids have on reducing inflammation and retaining GAG content in the matrix. These studies also revealed that the combination of corticosteroids and hyaluronic acid had the most beneficial effect on increasing GAG synthesis of the pellet and retaining the total GAG content within the pellet.

In the present study, a high–molecular-weight (3,000,000 kDa) hyaluronic acid was used. In previous studies, use of a medium–molecular-weight (500,000 to 730,000 kDa) hyaluronic acid resulted in no significant effects on new GAG synthesis when used alone. In the present study, a high increase in new GAG synthesis and an increase in total pellet GAG with only hyaluronic acid administration at 2.0 mg/mL. These results suggest that a high–molecular-weight hyaluronic acid may be more beneficial in mitigating IL-1–induced proteoglycan catabolism. However, the efficacy of different molecular weights of hyaluronic acid still remains a controversial subject that needs further conclusive in vivo evaluation.

The high concentration of hyaluronic acid in combination with triamcinolone acetonide had the most beneficial effects on proteoglycan matrix metabolism in the presence of IL-1 administration. This was a result of both an increase in GAG synthesis and an increase in retention of pellet GAG through decrease in inflammatory mediators. Future studies may be useful to evaluate the in vivo effects of triamcinolone acetonide and a high–molecular-weight hyaluronic acid in osteoarthritic equine joints.

References