The main goal of the medical therapy of DJD is to restore and maintain normal joint function by alleviating joint pain, decreasing joint inflammation, and protecting the cartilage from further injury. The role of substances termed "chondroprotective agents" that counter the destructive inflammatory process and encourage normalization of the synovial fluid and cartilage matrix is explored in this paper.

*UPDATE AND CURRENT TRENDS*

# Oral Glycosaminoglycans in Treatment of Degenerative Joint Disease in Horses

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## Introduction

Articular cartilage is composed of chondrocytes which synthesize and deposit around themselves a predominately water matrix and giant molecules. This extracellular matrix, which gives cartilage its properties of resiliency and tensile strength, consists of collagen and proteoglycans. Aggregate proteoglycans consist mainly of hyaluronic acid and glycosaminoglycans (GAGs).[1,2] Cartilage is unique among body tissues by being avascular, aneural, and alymphatic. As a result, the supply of vital nutrients to cartilage is barely adequate to maintain normal turnover. Thus, any insult can easily affect the nutritional state of cartilage. These unavoidable insults are commonly encountered during the life of the horse and include:

- acute traumatic injury to joint structure;
- chronic joint overuse;
- focal points of loading on cartilage surfaces;
- atherosclerosis of blood vessels that contribute to cartilage nutrition;
- joint immobilization and even anti-inflammatory drugs (especially corticosteroids and many non-steroidal anti-inflammatory drugs [NSAIDs]).[3]

Such conditions result in a need for augmented synthesis of cartilage that often generates extremely large demands of raw materials for collagen and proteoglycans. If the raw materials (nutrients) are not available in the amounts required, the synthesis process is impaired and the cartilage loses its ability to replenish itself.

Degenerative joint changes have been discovered in prehistoric animal fossils and in the joints of Egyptian mummies.[4] Despite the long existence of this disease, little is known concerning its etiology and factors that trigger its development.[5] In degenerative joint disease (DJD), changes occur both in the articular cartilage matrix and synovial fluid. Destructive enzymes released in response to inflammation damage chondrocytes, degrade collagen and proteoglycans, and alter hyaluronic acid.[5] A decrease in GAG content in osteoarthritic cartilage is directly proportionate with the severity of the disease.[6-9] With a loss of GAG content the articular cartilage loses its elasticity and ability to bear and transmit forces efficiently, resulting in a cascading cycle of more cartilage insults.[1] This complex process results in the net loss of cartilage matrix and eventual death of the chondrocytes.[1]

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The usual symptoms are pain and dysfunction of the affected joint.

DJD and its associated joint pathology contributes significantly to musculoskeletal lameness and loss of function in performance and pleasure horses.[10,11] The pathologic changes characteristic of DJD are:

- wear lines, discoloration, fibrillation and ulceration of the articular cartilage;
- subchondral bone sclerosis and trabecular thickening; thickening of the joint capsule;
- lipping of joint margins due to remodeling of cartilage and subchondral bone;
- formation of periarticular osteophytes at capsular attachments;
- chip fractures of joint margins due to fragmentation of the margin or of the new bone.

Although the pathology of the problem is simplified to a certain extent by this overview, the fact remains that the clinician does not see all manifestations in all cases. As a result, a management plan should be proposed based upon the visible lesions and on an understanding of DJD generally, because when the clinician makes the diagnosis of DJD, the articular cartilage is already damaged.

## Treatment of DJD

The main goal of the medical therapy of DJD is to restore and maintain normal joint function by alleviating joint pain, decreasing joint inflammation, and protecting the cartilage from further injury (i.e., to control the progression of the disease). The current medical management of osteoarthritis is largely palliative, focusing on the amelioration of pain and the suppression of inflammation mostly through analgesics and/or steroidal and nonsteroidal drug therapy (NSAIDs).[12]

Uncertainties have been raised about the effects of NSAIDs on the progression of DJD, since conflicting results have been reported from in vitro,[13,14] and in vivo experiments[15,16] in animals and in humans.[17] Clinical data suggest that the apparent deleterious impact of some NSAIDs on DJD progression may be due to their inhibitory activity on the synthesis of prostaglandins.[17,18] These perplexities regarding the long-term use of NSAIDs, including their known pattern of common side effects, along with the expanding knowledge of the cartilage biochemistry and DJD pathophysiology,[5,11] has prompted research on a series of new agents that relieve pain and inflammation and limit or reverse cartilage degeneration without side effects.[19,20]

Current research in the medical management of osteoarthritis has focused on slowing the process of cartilage degradation and promotion of cartilage matrix synthesis.[20] This research identified substances, termed "chondroprotective agents", that counter the destructive inflammatory process and encourage normalization of the synovial fluid and cartilage matrix.[21] A chondroprotective agent provides the following attributes:

- supported chondrocyte synthesis of collagen and proteoglycans;
- supported production of hyaluronans;
- inhibition of cartilage degradative enzymes; and
- prevention of fibrin formation in synovial fluid and plaque formation in subchondral vessels.[22]

Macromolecules endogenous to cartilage and their semisynthetic or synthetic analogues have been shown to accomplish some, but not all of these objectives.[23-26] Because the roles and functions of endogenous macromolecules are integral to cartilage metabolism, they alone appear able from a pharmacological perspective to meet multiple objectives.[23,27,28] However, at present, no single macromolecule appear able to accomplish all of the stated objectives. Combining the use of anti-inflammatory or analgesic drugs with macromolecules has met some but not all of the objectives.[28,29] However, adverse side effects of the drugs reduced therapeutic benefits of the combination.

Thus, a new approach to combine compounds of complimentary functions without causing adverse side effects is needed. Such a combination may exist by combining glucosamine salts and chondroitin sulfate. This combination has been used in veterinary medicine for 3 years in the US to treat DJD with favorable results and no side effects.[30-35] Such compounds may be useful as prophylactic and/or therapeutic agents in the management of DJD. The orally bioavailable products of these agents would be particularly useful in routine clinical management of DJD, especially in light of the chronicity of DJD and the need of long-term management.

Glucosamine (GlAm) is an amino-monosaccharide nutrient. It is a precursor of the disaccharide unit of GAGs, which is the building block of the ground substance of the articular cartilage, the proteoglycans.[21,36-38] Biochemical and pharmacological studies indicate that administration of GlAm tends to normalize cartilage metabolism and stimulates the synthesis of proteoglycans so that articular function is partially restored.[21,36-38] GlAm has not been shown to inhibit the synthesis of prostaglandins and has no known toxicity at high dose

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levels. Compared to indomethacin, the therapeutic margin with regard to prolonged treatment was 10 to 30 times more favorable for GlAm.[29,36,37] Exogenous glucosamine salts significantly enhance chondrocyte synthesis of glycosaminoglycans and collagen, and ameliorate the clinical signs of DJD in humans without side effects.[21,27,28,36-38] Furthermore, they have been hypothesized to enhance synthesis of synovial fluid hyaluronan.[3] The physicochemical properties of glucosamine account for a favorable pharmacokinetic profile including oral bioavailability and specific cartilage tropism, as was shown in animals and humans using radiolabeled compounds. Excretion is primarily via urine and feces, with 87% of orally administered glucosamine being absorbed.[39,40]

Chondroitin sulfate (CS) is a long chain polymer of a repeating disaccharide unit: galactosamine sulfate and glucuronic acid. It is the predominant GAG found in articular cartilage and is a natural component of several other tissues (i.e., tendons, bone, vertebral discs, heart and cornea) found in the body.[41] Different from glucosamine, CS stimulate glycosaminoglycan and proteoglycan synthesis by extracellular as well as intracellular mechanisms. CS, by virtue of its long chain length, competitively inhibits degradative enzymes of proteoglycans in cartilage and synovial fluid.[3,26,30,42-43] Bioavailability has been well documented with 70% absorption following oral administration in experimental animals and in humans.[41,44,45] Its affinity for synovial fluid and articular cartilage has also been demonstrated.[45] CS has been shown to be effective in reducing the symptoms of DJD and is well tolerated systemically in many clinical studies[46-48] and in many randomized, double-blinded, controlled clinical trials.[49,50] There is a reduction of pain and improved mobilization in sufferers of arthritis treated with CS. A reduction in use of concomitant NSAIDs and a favorable carry-over effect after termination of the treatment has also been reported.[49,50]

A synergistic, rather than an additive effect would be expected by combining glucosamine and chondroitin sulfate, since both agents are endogenous to chondrocytes, and chondroitin sulfates possess extracellular properties not found with glucosamine.[31,33,35] Both of these connective tissue compounds have been purified to homogenicity, and are available for use as oral or injectable agents. These agents work synergistically in forming GAGs, inhibiting degradative enzymes, and upregulating cartilage and metabolism and matrix production.[3,51]

## Current Clinical Evidence

Hanson and associates[52] conducted a clinical efficacy study on 25 horses with naturally occurring DJD for 6 weeks. A significant improvement of the horses treated with the tested glucosamine-chondroitin sulfate compound (Cosequin®:Nutramax Laboratories, Inc., Baltimore, MD; consists of glucosamine, chondroitin sulfate, manganese and ascorbate) was observed irrespective of age, joint affected, or use of the horse. All of the clinical parameters measured (lameness, flexion test score and stride length) showed trends of improvement of clear clinical importance, which was statistically significant ($p = 0.001$). In most cases the exercise and activity of the horses was increased, while some horses returned to competition soon after therapy. The findings of that study are in agreement with previous reports about the efficacy of the studied agents in management of DJD in horses[10,53] and in small animals.[30-34] They are further in agreement with human randomized double-blind controlled clinical trials that used preparations of glucosamine salts[54-62] and chondroitin sulfate[46-50] and have substantiated its efficacy in the management of DJD without side effects.[63] These findings are also in agreement with previous reports about the synergistic effects of the studied agents in forming GAGs, inhibiting degradative enzymes, and upregulating cartilage metabolism and matrix production.[51] The study lacked a placebo group. However, the fact that the results for both the objective (stride length) and subjective outcomes (lameness and flexion test) were consistent allay the concern about the examiner's bias.

Researchers at the Marion duPont Scott Equine Medical Center and the Virginia-Maryland Regional College of Veterinary Medicine are investigating the efficacy of the same glucosamine-chondroitin sulfate compound (Cosequin) in horses with DJD. Using a force plate designed to analyze the gait and provide a lameness score, lame horses were given the oral glucosamine-chondroitin sulfate compound or a placebo. Investigators were blinded to horses' alignment. Lameness in the horses receiving the compound resolved, whereas the lameness in the placebo group remained.[64]

On the other hand, White and associates[65] conducted a study to assess the efficacy of the same glucosamine-chondroitin sulfate compound (Cosequin) where intra-articular Freund's adjuvant was used to induce synovitis in 12 horses. They reported no benefit from administering the compound within the parameters measured. However,

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the model used in the study was a chemically induced severe synovitis that has been criticized as being excessively inflammatory.[24] As a result, the study's clinical relevance is questionable.[66] The study assessment of the measured outcomes was carried out for 26 days, which is not enough time to show the efficacy of any nutraceutical intervention in such a severe model. Trotter and associates[67] reported in a study lasting for 12 weeks that even injectable polysulfated GAGs had no effect on healing of articular cartilage lesions, and minimal chondroprotection from chemically induced lesions. Furthermore, the horses were treated simultaneously by analgesics. Given that the horses were treated simultaneously by analgesics, and that the induced synovitis operated mainly through pain, it is likely the results are biased. This is because horses in the control group are more likely to "suffer from undue pain" which was the criterion established by the investigators as an indication to use analgesics. Once a horse in the control group receives the analgesic, its condition may improve temporarily, and dilute the effect of the tested product, especially in light of the very short follow-up period. There is no mention about the type, dose, or frequency of the analgesics used in the study group. Moreover, there is no information about the standard deviations of the measurements which precludes the ability to calculate the study power where the minimum scientifically acceptable study power is 80%.[68-70] If the study is underpowered, it might be considered as inconclusive, and not necessarily a negative one.

## Future Directions

The therapeutic potential of a nutritional approach, like the studied agents, is extremely promising in horses. However, future controlled clinical trials are needed to assess the magnitude of the improvement in horses with DJD in the appropriate model or preferably in naturally occurring cases. The author is currently involved in a controlled double-blinded study in horses. The logical future of chondroprotection will involve determining and correcting abnormal joint load forces; providing chondroprotective nutritional agents, improving health and exercise habits in general, and judicious use of selected analgesics as needed.

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