GLUCOSAMINE SULFATE THERAPY TREATMENT FOR ARTICULAR DAMAGE IN A CANINE MODEL

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INTRODUCTION:
Osteoarthritis (OA) is becoming progressively more prevalent as the mean age of the population increases. Pharmacological interventions such as analgesics and/or nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently utilized to help reduce symptoms, minimize functional disability, and limit disease progression. For some patients, these treatment methods have only marginal efficacy. The ineffectiveness of traditional treatments is made evident by the increasing number of OA patients requiring total joint arthroplasty. The limited effectiveness of current medications in some patients combined with factors, such as the toxicity of NSAIDs, suggest the need to develop disease-modifying drugs.

The ability to provide these drugs is largely dependent on the level of understanding of the underlying biochemical and metabolic changes associated with the disease. Recent studies have helped advance this understanding by demonstrating the association of proteoglycan deterioration and loosening of the collagen network with OA. The loss of proteoglycan is mediated by increased matrix degradation and enhanced by metallo-proteinases, decreased matrix synthesis, and changes in gene expression and enzyme activity in chondrocytes.

Recent clinical observations have that shown glucosamine sulfate may be an alternative treatment option for OA as it has been identified as a symptom-modifying agent capable of preserving joint space. However, despite their broad acceptation and use by patients, the medical community remains sceptical regarding efficacy. The purpose of this study was to evaluate the potential use of glucosamine sulfate as a treatment modality for OA by comparing the effects on cartilage repair of intra-articular and oral glucosamine sulfate to a placebo in an animal model of OA.

METHODS:
The left stifle (corresponding to the human knee) of 32 canines was destabilized by transection of the anterior cruciate ligament (ACL) using a mini-arthrotomy. Under these conditions, OA develops with defined morphological and biochemical characteristics. The nonoperated (right) stifle served as (normal) control. The study was performed on 32 skeletally mature beagles (closed epiphyses on radiographic examination) who had a median age of 15 months (range, 13-18) and a body weight of 12 kg (range, 10-21).

Sixteen animals were treated for 8 weeks with intra-articular glucosamine sulfate (400 mg) or intra-articular placebo, the other sixteen canines with oral glucosamine sulfate (200 mg/kg body weight) or oral placebo. After 8 weeks, the cartilage from both the operated and nonoperated knee joints was dissected and five specimens taken from the lateral and medial condyles of the femur, the patellae, and the lateral and medial plateau of the tibiae. Macroscopic assessment of the five specimens included cartilage thickness, cartilage discoloration, fibrillation, eburnation, subchondral cysts, and affected area. For the histopathological classification of the severity of osteoarthritic lesions of cartilage, a modified Mankin score was employed. This modified score includes a histological and histochemical assessment of degenerative changes of the hyaline articular cartilage in paraffin sections and can range from 0 points (no lesions) to 32 points (severe lesions). Each specimen was scored twice by three different raters and an arithmetic mean was calculated by adding the single scores of the five joint localizations. For a comparison between the different treatment groups, an analysis of the mean scores utilizing the Mann-Whitney-U test was applied. Differences were considered statistically significant at \( p < 0.05 \).

RESULTS:
Eight weeks after the operation, changes in the cartilage could be found macroscopically in all 32 operated knee joints. The cartilage exhibited a livid bluish discoloration compared to the glossy white surface of all non-operated right joints. In comparison with the normal control (Fig 1), the thickness of the cartilage in the operated joints had visibly decreased (Fig 2). The decrease was mainly localized in weight-bearing areas (lateral and medial plateau of the tibia). No macroscopic difference between the placebo- and (intra-articular and oral) glucosamine sulfate-treated canines was visible.

Quantitative analysis of data from final follow-up showed the Mankin scores were significantly higher in the operated than in the nonoperated joint in both the placebo- and the glucosamine sulfate-treated animal joints. In all comparisons, the Mankin scores were significantly lower in the glucosamine sulfate-treated groups than in the placebo groups (\( p<0.05 \)); the overall histologic score for intra-articular glucosamine sulfate was 8.1 (range 7.9-8.8) (Fig 3) and intra-articular placebo 13.9 (range 11.6-15.9) (Fig 4), (\( p<0.002 \)) and the oral glucosamine sulfate score was 12.1 (range 9.9-12.7) (Fig 5) versus the oral placebo 15.1 (range 12.5-17.0) (Fig 6), (\( p<0.002 \)). The intra-articular glucosamine sulfate group also had less severe changes than the oral glucosamine sulfate group (\( p<0.002 \)). The scores of the intra-articular placebo-treated animals did not differ significantly (\( p>0.172 \)) from those of the oral placebo-treated animals.

DISCUSSION:
Glucosamine sulfate has recently begun to be used in the management of OA. This small molecule is a constituent of normal articular cartilage and is easily absorbed into the bloodstream and joints when taken as a supplement. In many clinical trials the oral formulation of glucosamine sulfate has been shown to relieve OA symptoms and, recently also to have structure (disease) modifying properties.

In order to better characterize the mode of action of glucosamine sulfate, its effects on articular cartilage degradation induced by ACL transection in the dog were examined. In addition to the oral formulation of GS used in the treatment of OA, a new intraarticular formulation was tested and compared to placebo. The GS-treated animals demonstrated fewer gross and histologic changes than the groups treated with placebo.

Both intra-articular and oral glucosamine sulfate appeared to reduce the cartilage damage that occurs after ACL transection in a canine model of osteoarthritis. Less severe changes were present in the intra-articular glucosamine sulfate- than in the oral glucosamine sulfate-treated animals. This suggests that there is both an administration mode and a dose-response effect of glucosamine sulfate on retarding the osteoarthritic process.

FIGURES:

Figure 1 Figure 2 Figure 3
Figure 4 Figure 5 Figure 6

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