A Review of Articular Cartilage Pathology and the Use of Glucosamine Sulfate

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Objectives: To refresh the athletic trainer’s knowledge of articular cartilage biomechanics, physiology, and structure and explore the role of glucosamine sulfate in treating articular cartilage pathologic conditions, including supplementation methods and clinical outcomes.

Data Sources: We searched MEDLINE from 1989 through 2000 and SPORT Discus from 1975 through 2000 using the following key words: glucosamine sulfate, articular cartilage, osteoarthritis, and proteoglycans.

Data Synthesis: Articular cartilage functions as a wear-resistant, smooth, nearly frictionless, load-bearing surface. Glucosamine sulfate can be thought of as a building block that helps restore the proteoglycan-rich extracellular matrix and thus balance articular cartilage catabolism and anabolism. Beneficial clinical effects of glucosamine sulfate in the osteoarthritic population have been documented. However, the use of glucosamine sulfate for athletic articular cartilage injuries is unproved.

Conclusions/Recommendations: Clinical studies indicate that glucosamine sulfate has been shown to be safe and relatively effective treatment for osteoarthritis. However, no evidence to date supports or refutes a carryover effect to the athletic population and the injuries that occur in sport.

Key Words: osteoarthritis, proteoglycans, outcomes, treatment, supplements

Glucosamine sulfate is being extensively marketed as a treatment for osteoarthritis. Glucosamine is an endogenous aminomonosaccharide synthesized from glucose.1–3 It is used in the biosynthesis of proteoglycans and glycosaminoglycans (GAGs) as a proposed substrate for the synthesis of these important cartilage components and perhaps a direct stimulator of their synthesis.1–3 Glucosamine can be thought of as a building block that helps restore the proteoglycan-rich matrix and thus balance cartilage catabolism and anabolism.1–3 Glucosamine is also proposed to protect damaged cartilage from metabolic impairment.4,5

Osteoarthritis is a gradual disease characterized by a continual wearing of the articular cartilage, resulting in changes in the underlying subchondral bone.5 Management of osteoarthritis currently includes weight reduction, physical therapy, occupational therapy, and the use of NSAIDs.4 NSAIDs have been shown to have both positive and negative effects on cartilage metabolism, but neither NSAIDs nor acetaminophen has been shown to reverse the degenerative process of osteoarthritis.4

The anatomic, physiologic, and biomechanical properties of articular cartilage should be considered in treating articular cartilage pathologic conditions. Understanding these articular cartilage properties allows the athletic trainer to better appreciate how glucosamine sulfate may affect articular cartilage. The purpose of our review was to explore the relationship between articular cartilage pathology and glucosamine sulfate.

THE ROLE OF HUMAN ARTICULAR CARTILAGE

Articular cartilage functions to distribute the load, minimize peak stresses on subchondral bone, and provide a friction-reducing, weight-bearing surface. Articular cartilage can be deformed and regain its original shape, because it is remarkably elastic. In comparison with other soft tissues, articular cartilage has a low level of metabolic activity and lacks blood vessels, lymphatic vessels, and nerves. Essentially, articular cartilage functions and stands alone. The simple homogeneous appearance of cartilage hides its highly ordered complex structure. This structure apparently remains unchanged unless affected by disease or injury.6

COMPOSITION AND STRUCTURE OF ARTICULAR CARTILAGE

Articular cartilage is typically depicted in 4 zones (Figure). Each zone has its own distinct matrix region. The superficial zone includes the gliding surface of the joint. This layer of cell-free matrix contains fine fibrils with few polysaccharides and adjoins a layer of elongated chondrocytes organized parallel to the articular surface. The cells in this zone are almost inactive but contain endoplasmic reticulum, Golgi membranes, and mitochondria. The next layer is the transitional zone, which includes active chondrocytes containing endoplasmic reticulum, Golgi membranes, mitochondria, glycogen, and intracytoplasmic filaments. The collagen fibrils of this zone are larger than those of the superficial zone. In this layer, collagen fiber orientation transitions from parallel to columnar. The
deep zone contains chondrocytes that are similar to those of the transitional zone but are organized in a columnar pattern perpendicular to the joint surface. These cells hold large amounts of intermediate filaments and glycogen granules. Furthermore, the largest collagen fibrils of articular cartilage and the highest content of proteoglycans are also contained here. As the number of proteoglycans increases, the amount of water decreases and the superficial matrix becomes more dense. The deepest zone of calcified cartilage divides the softer cartilage from subchondral bone. The cells from the deep zone bore directly into the calcified cartilage. These chondrocytes contain little cytoplasm and almost no endoplasmic reticulum but connect the articular cartilage to the underlying bone.6

A chondrocyte cell membrane adheres directly to the pericellular matrix, which contains proteoglycans, noncollagenous proteins, and glycoproteins. A layer of territorial matrix encompasses the pericellular matrix. The matrix surrounds individual cells or pairs or clusters of chondrocytes. The interterritorial matrix forms the majority of articular cartilage and accounts for its mechanical characteristics.6

Chondrocytes provide 10% or less of the total volume of cartilage; consequently, the functional properties of cartilage, including stiffness, durability, and distribution of load, rely on the extracellular matrix. Overall, tissue fluid contributes 60% to 80% of the wet weight of cartilage and contains water with dissolved gases, small proteins, and metabolites. The structural macromolecules contribute 20% to 40% of the wet weight and include collagens, proteoglycans, and glycoproteins. The chondrocytes and matrix depend on each other. The material properties of articular cartilage depend on its extracellular matrix, but the existence and maintenance of the matrix depend on the chondrocytes.6

BIOMECHANICAL PROPERTIES OF ARTICULAR CARTILAGE

Articular cartilage functions as a wear-resistant, smooth, nearly frictionless, load-bearing surface. The composition and physicochemical properties of articular cartilage, the fundamental organization of the collagen network, and the molecular organization of collagen and proteoglycans all have profound effects on the intrinsic mechanical properties of the extracellular matrix and the fluid transport and diffusional properties of the cartilage. These characteristics provide articular cartilage with its normal function, lubrication, wear, and load-bearing features.6

When an external load is placed on the cartilage surface, immediate deformation is produced primarily by a change in the proteoglycan molecular domain. This external load can also make the interstitial fluid pressure in the porous solid matrix exceed the osmotic swelling pressure; therefore, the interstitial fluid begins to flow and exudation occurs. After exudation occurs and the load is removed, GAGs function hydrophilically, pulling the fluid back into the cartilage, similar to the action of a sponge soaking up water, in preparation for the next load. With a decrease in the interstitial fluid, the proteoglycan concentration within the solid matrix increases, which in turn increases the osmotic swelling pressure, charge-repellive force, and bulk compressive stress until they are balanced with the applied external load. In this manner, the physicochemical characteristics of the proteoglycan gel trapped within the collagen meshwork enable cartilage to resist compression. This mechanism supplements the role played by collagen fibers, which are strong in tension but can easily fold under compression.8

Articular cartilage demonstrates a viscoelastic response when placed under loads and deformation.7–10 It creeps under a constant applied load and stress relaxes under a constant applied deformation.7–10 This viscoelastic response of articular cartilage relies on 2 essentially different physical mechanisms: (1) the intrinsic viscoelastic properties of the macromolecules that form the organic solid matrix and (2) the frictional drag from the flow of the interstitial fluid through the permeable solid matrix.7–9 Each mechanism promotes the overall viscoelastic response of cartilage under tension, compression, and shear.8 Additionally, the rate at which a load is applied to articular cartilage affects its viscoelastic response. Under a slow, sustained force, articular cartilage is able to respond accordingly and accommodate this load. However, under a concentrated force, articular cartilage is unable to react to the load, and therefore, the tissue is vulnerable to injury.

Alterations associated with injuries, osteoarthritis, and other degenerative processes vary normal structure-function relationships that exist within the articular cartilage. Particular compositional, molecular, and structural changes detected in degenerated tissues include decreased proteoglycan and increased water content,11 collagen fibril network disorganization, and proteoglycan separation. These changes may alter the intrinsic mechanical properties of articular cartilage and produce swelling.8 The organizational structure of collagen and proteoglycans in conjunction with water normally determines the mechanical properties of articular cartilage. This structural relationship among collagen, proteoglycans, and water does not exist for healing articular cartilage or osteoarthritic cartilage.12

ARTICULAR CARTILAGE DAMAGE AND REPAIR

Acute injuries to articular cartilage can be categorized into 2 broad groups: (1) the loss of matrix macromolecules without mechanical damage to the chondrocytes or the collagen fibril meshwork (ie, prolonged joint immobilization) and (2) me-
NATURAL PRODUCTION AND ABSORPTION OF GLUCOSAMINE SULFATE

Glucosamine is a building block for articular cartilage’s extracellular matrix. Specifically, it is used to produce GAGs and proteoglycans.\(^4\) Glucosamine is synthesized by chondrocytes from glucose to produce GAGs,\(^5\) and the production of GAGs stimulates proteoglycan production.\(^4\) The lack of proteoglycans can lead to degeneration of articular cartilage.\(^5\) Glucosamine is present in meat, fish, poultry,\(^5\) and almost all human tissue and has a special positive attraction for cartilaginous tissue.

Glucosamine sulfate was rapidly absorbed into the bloodstream regardless of the route of administration.\(^4\) Approximately 90% of orally administered glucosamine sulfate was absorbed through the digestive tract.\(^1\) However, only 26% of this oral dose of glucosamine was available for processing by the body’s tissues.\(^5\) Glucosamine concentrates in the liver, where it is combined with plasma proteins, reduced into smaller molecules, or used for other biologic processes.\(^1\) The highest concentrations are found in liver, kidney, and articular cartilage.\(^4\) Glucosamine is used in GAG synthesis.\(^4\)

ACTION OF GLUCOSAMINE SULFATE

Glucosamine sulfate is the salt of D-glucosamine with sulfuric acid. In solution, glucosamine sulfate separates into the D-glucosamine ion and the sulfate ion.\(^4\) Glucosamine ions are used to synthesize GAGs, which are combined with proteins to form proteoglycans, critical components of articular cartilage ground substance. Researchers\(^4\) believe that the glucosamine ion is the active element, but some evidence indicates that a benefit of the glucosamine sulfate is related to sulfur residues, because sulfur is an essential nutrient for the stabilization of the connective tissue matrix. Glucosamine sulfate stimulates the uptake of sulfate ions, which can be used as an indicator of GAG synthesis by the chondrocytes.\(^4\) Sulfate is also an important component of proteoglycans.\(^4\) Glucosamine sulfate, which provides both glucosamine and sulfate ions, facilitates GAG production and synthesis of proteoglycans as a whole.\(^4\) Glucosamine also hinders hyaluronidase, the tissue-damaging enzyme, and helps to rebuild the damaged articular cartilage. In addition, glucosamine sulfate improves the lubricant properties of synovial fluid.\(^4\)

THE ROLE OF GLUCOSAMINE SULFATE

Glucosamine sulfate is proposed to be a safe and effective treatment of osteoarthritis.\(^6\) Glucosamine supposedly plays a part in the repair and maintenance of joint cartilage, stimulating cartilage cells to produce GAGs and proteoglycans.\(^5\) Investigators have compared glucosamine sulfate with placebos\(^1\) and with common NSAIDs (ie, ibuprofen).\(^4\) Glucosamine sulfate has been described as a slow-acting drug in osteoarthritis by the International League Against Rheumatism.\(^4\) However, the Arthritis Foundation does not recognize glucosamine sulfate as a treatment for osteoarthritis or any other form of arthritis.\(^5\) The National Collegiate Athletic Association has classified glucosamine sulfate as a nonpermissible supplement for institutions to provide to their athletes.\(^6\)

SUPPLEMENTATION METHODS

Various methods have been used to provide glucosamine supplementation to subjects (Table). These methods included oral supplements,\(^4\,42,46,50,58\) intravenous injections,\(^7\) intramuscular injections,\(^3\) and intra-articular injections.\(^4\,46\) However, oral supplementation has been deemed the most effective because of the mode of delivery and is the most commonly used method.\(^1\) The current recommended dosage is 1500 mg of glucosamine sulfate daily. This typical 1500-mg dosage is generally divided into 3 doses (500 mg each) per day.

A concern with oral supplementation of glucosamine sulfate is that it does not require Food and Drug Administration approval. “The Dietary Supplement Health and Education Act
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| Crolle and D’Este, 1980 | 30 Inpatients (8 men, 22 women)  
- Evaluated pain at rest and during active and passive range of motion  
- Evaluated restricted function  
- Walking time for 20 m | Group 1 (15 subjects): 1 intramuscular (IM) injection of 400 mg of glucosamine sulfate (GS) daily for 7 days, then 14 days of 1.5 g of oral GS  
Group 2 (15 subjects): IM injection of 100 mg of piperazine/100 mg of chlorbutanol for 7 days, the 14 days of oral placebo | No significant improvement was seen in either group from IM injections  
During oral treatment, the GS group continued to improve over the placebo group |
| Tapadinhas et al, 1982 | 65 Patients  
- Semiquantitative scoring of pain at rest, pain during active and passive range of motion, and limitation of joint function | Group 1 (15 subjects): 1 intravenous (IV) or IM injection of 400 mg of GS daily for 7 days, followed by 14 days of 1.5 g of oral GS  
Group 2 (15 subjects): IM or IV injection of 100 mg of piperazine/100 mg of chlorbutanol for 7 days, followed by 14 days of oral placebo | Significant overall symptom score decreased during injectable GS (P < .05)  
Further significant decrease with GS oral therapy (P < .01)  
Initial gains of group 2 lost during oral placebo treatment |
| D’Ambrosio et al, 1994 | 80 Inpatients  
- Evaluated joint pain, tenderness, swelling, active and passive range of motion  
- 2 patients had cartilage removed with subsequent electron microscopy | Group 1: oral GS, 1.5 g, for 30 days  
Group 2: oral lactose placebo | Symptom intensity decreased significantly in both groups (P < .05)  
GS group’s symptoms decreased sooner  
On scanning electron microscopy, the articular cartilage appeared normal after treatment  
Significant improvement in the patient assessment of treatment and in the visual analog scale while on GS (P = .02)  
No signs of significant improvement in other assessment areas |
| Leffler et al, 1999 | 34 Male subjects  
- Subjective questionnaire (Lequesne Index or Roland)  
- Physician assessment of severity  
- Time to run 100 yd (91.44 m) and down 80 stairs  
- Pavelka physical examination | Group 1: 1 capsule daily containing 1500 mg of GS, 1200 mg of chondroitin sulfate, and 228 mg of manganese ascorbate, followed by 8 weeks of placebo  
Group 2: 1 capsule daily, followed by 8 weeks of 1 daily capsule containing 1500 mg of GS, 1200 mg of chondroitin sulfate, and 228 mg of manganese ascorbate | Lequesne index demonstrated a significant (P < .05) improvement in the GS group |
| Noack et al, 1994 | 252 Outpatients  
(100 men, 152 women)  
- Evaluated function by the Lequesne Index | Group 1: 1.5 g of sugarcoated oral GS for 4 weeks  
Group 2: 1.5 g of an oral placebo for 4 weeks | GS group significantly improved in composite scores (P < .01)  
GS group experienced earlier alleviation of symptoms (P < .01) |
| Pujalte et al, 1980 | 24 Outpatients  
- Physician assessment of articular pain, joint tenderness, swelling, and movement restriction  
- Subjective assessment | Group 1: 1.5 g of oral GS daily for 6–8 weeks  
Group 2: 1.5 g of oral lactose placebo capsules for 6–8 weeks | Significant improvement of pain and movement limitation in GS group throughout the 6 weeks (P = .012)  
Improvement maintained through the 2-week follow-up  
Objective assessment of therapeutic efficacy: 58.7% good, 36.0% sufficient, 5.3% insufficient  
Concomitant illness affected GS effectiveness  
Significant reduction in overall intensity of articular symptoms during treatment (P < .001) |
| Reichelt et al, 1994 | 155 Outpatients  
- Assessed using the Lequesne Index | Group 1: 400 mg of GS IM 2 times per week for 6 weeks  
Group 2: placebo IM 2 times per week for 6 weeks | |
| Tapadinhhas et al, 1982 | 1208 Patients  
(516 men, 692 women)  
- Physician objective and subjective assessment | All subjects received 1.5 g of oral GS for 6–8 weeks | |
of 1994 provides for the use of various types of statements on the label of dietary supplements, although claims may not be made about the use of a dietary supplement to diagnose, prevent, mitigate, treat, or cure a specific disease (unless approved under the new drug provisions of the Federal Food, Drug, and Cosmetic Act). For any "dietary supplement," the consumer should investigate the quality of the product before supplementation.

TOLERANCE

All studies reported low incidence of adverse effects with glucosamine supplementation. The few adverse effects that were reported, all mild to moderate in intensity, included abdominal pain, epigastric pain or tenderness, heartburn, vomiting, diarrhea, nausea, drowsiness, headache, and itching. Increased insulin resistance has been reported after intravenous glucosamine doses in laboratory animals and after a 12-week course of oral glucosamine supplementation in humans. Insulin resistance decreases the ability of insulin receptors to transmit glucose into tissue's cells. Certainly, further investigation into this phenomenon is necessary; patients with diabetes may need to be followed closely during glucosamine treatment.

CLINICAL OUTCOMES

Bassleer et al showed a stimulatory effect of glucosamine sulfate on the biosynthetic activity of human chondrocytes. Their findings agree with other reports that glucosamine exerts a protective action in animal models of experimental osteoarthritis. Glucosamine counteracts the damage induced on chondrocytes by dexamethasone and some NSAIDs, and its effect in patients with osteoarthritis compares favorably with that of NSAIDs. Glucosamine sulfate also displays a definite, although mild, anti-inflammatory activity in vivo models of inflammation and arthritis. Glucosamine did not show any inhibiting activities of prostaglandin biosynthesis; therefore, the mild anti-inflammatory activities described are most likely achieved through this prostaglandin-independent mechanism. This may also explain its low toxicity and better therapeutic index when compared with NSAIDs.

In one study, NSAIDs reduced pain within 2 weeks; however, this action tended to fade away as treatment continued. Researchers concluded that treatment with glucosamine sulfate was slower to become effective, but it was consistent and progressive throughout the trial period and overall produced significantly better results than the NSAID. Additionally, the effects from treatment with glucosamine sulfate lasted longer, even after treatment was discontinued.

Authors of recent reviews noted that the studies conducted thus far have indicated improved pain and mobility. However, Barclay et al reported that most of the studies have shown significant flaws in design or data analysis. Although glucosamine sulfate does not appear to have negative short-term side effects, long-term effects are unknown. Rovati explained that long-term studies are difficult to perform, whereas the short-term studies often have several methodologic problems. The most common problems associated with clinical trials of disease-modifying drugs in osteoarthritis can be summarized into the following categories: (1) number of patients, (2) experimental design, (3) diagnosis, (4) disease status, and (5) evaluation criteria and end points.

One unique report has been published by Drovanti et al. Like many other studies, these researchers administered 1500 mg of glucosamine sulfate or an identical placebo daily. Articular pain, joint tenderness and swelling, and restriction of active or passive motion, as well as other diagnostic tests, were assessed, with promising results. However, these authors, unlike any others, also used electron microscopy scanning to evaluate the integrity of the articular cartilage surface of 5 subjects. They examined 1 healthy subject with no articular cartilage damage, 2 subjects from the placebo treatment group, and 2 subjects from the glucosamine sulfate treatment group. Glucosamine sulfate supplementation appeared to help rebuild the articular cartilage of the 2 subjects who underwent that treatment.

Studies comparing glucosamine sulfate to placebos have demonstrated significant reduction in knee pain, improved range of motion, decreased swelling, and improved function. Improved patient or physician (or both) qualitative assessment. Glucosamine sulfate and NSAIDs both significantly decreased knee pain, decreased swelling, and improved patients' subjective assessments, but glucosamine tended to elicit greater improvements in function. In investigations without a control group, glucosamine sulfate significantly decreased pain and range-of-motion limitation and increased function. No published studies have shown that supplementation of glucosamine sulfate is an effective prophylactic measure against osteoarthritis.
CONCLUSION

Glucosamine assists the body in providing the components necessary to synthesize proteoglycans, which are required for articular cartilage synthesis. It appears to slow the process of articular degeneration and facilitate the recovery of normal joint mobility. In osteoarthritis, changes occur in the articular cartilage (due to mechanical insult) and in its metabolism. Glucosamine sulfate appears to have a positive effect on the metabolism of articular cartilage. However, whether sports injuries result in the same articular cartilage changes found in osteoarthritis is unclear. Mechanical insults associated with sports are common, but no clinical trials on this population are currently available. Further research needs to be completed on the use of glucosamine sulfate in patients without osteoarthritis.

REFERENCES

70. Almada AL, Harvey PW, Platt KJ. Effect of chronic oral glucosamine sulfate upon fasting insulin resistance index (FIRI) in nondiabetic individuals. Paper presented at: Annual Meeting of Professional Research Scientists; April 15–18, 2000; San Diego, CA.