

Use of Nutraceuticals in the Management of Osteoarthritis

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INTRODUCTION

There are three types of joints in the body: fibrous, cartilaginous, and synovial. A synovial joint consists of bone, articular cartilage, joint capsule, ligaments, and a synovial membrane¹ (Figure 1). Articular cartilage, a thin layer covering the opposing ends of the articulations, is comprised of 95% extracellular matrix, which is secreted and maintained by a few chondrocytes localized in lacunae.² Composed of collagen fibers and proteoglycans, the matrix gives cartilage its tensile and compressive strength. Most proteoglycans in the cartilage are large aggregating complexes called aggrecans. They consist of hyaluronic acid and glycosaminoglycans, primarily chondroitin sulfate.^{3,4}

Articular cartilage provides a smooth surface for bones to move against each other with minimal friction. Its aneural and avascular tissue allows the joint to withstand tremendous pressure without pain. Because of the lack of blood supply, lesions to articular cartilage do not heal as they do in other tissues. Loss of articular cartilage exposes richly innervated underlying bone, converting a painless joint to a painful one.

OSTEOARTHRITIS

Osteoarthritis (OA), also known as osteoarthrosis, degenerative joint disease, and degenerative arthritis,⁵ is a heterogeneous group of disorders that result in articular cartilage degeneration. Considered the most common chronic

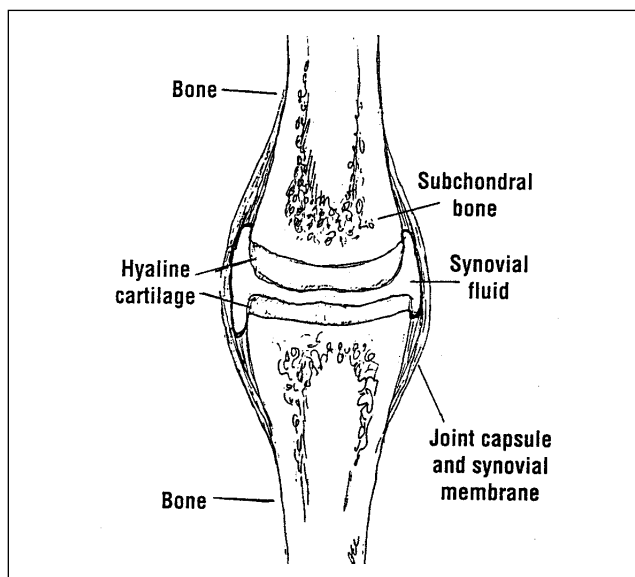


Figure 1: cross section of a normal synovial joint

joint disease, it is estimated that more than 21 million individuals in the United States have OA.⁶

The incidence of OA increases with age. Other risk factors are trauma to the joint earlier in life, fractures involving the joint surfaces, instability from ligament tears, and meniscal injuries that cause abnormal wear and tear of the joint. Postmenopausal women who are not taking estrogen replacement⁷ are also associated with increased risk of OA, as are those who have hyperglycemia, hypercholesterolemia, hypertension,⁸ or a relevant hereditary factor.⁹

OA is an imbalance between synthesis and degradation occurring in the joints.¹⁰ It is characterized by disturbance in the smooth property of the cartilage resulting in the formation of subchondral cysts and marginal osteophytes.¹¹ Bone spurs may also form around the joint as the body's

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response. These processes continue until the full thickness of cartilage is lost, leaving the bone exposed.

Diagnosis of OA is based on clinical and radiological findings.¹⁰ The first clinical manifestations are pain, stiffness, swelling, crepitus, and restriction of joint movement. X-ray is an essential tool for diagnosing the severity of OA.¹²

Currently, the aim of OA treatment is to reduce pain and stiffness. Its management consists of pharmacologic and nonpharmacologic therapies. Pharmacologic treatment begins with acetaminophen, adding a low-dose nonsteroidal anti-inflammatory drug (NSAID), salicylate, selective COX-2 inhibitor, or topical capsaicin cream if needed. Analgesics or NSAIDs are the most common prescribed non-invasive treatment for reducing pain associated with early cases of OA. Pain reduction can also be achieved by non-pharmacological treatment. Physical therapy and decreasing the load on the joint through lifestyle changes such as weight loss and stress reduction can be challenging, but of great benefit.¹³ In more severe cases, joint injections, irrigation, or arthroscopy may be beneficial. In patients who continue to have pain and limited function despite these measures, surgical intervention should be considered.¹⁰

Although NSAIDs have a definite effect in pain reduction, up to 20% of patients per year have severe gastrointestinal problems after prolonged intake.¹⁴ A prophylactic drug such as a proton pump inhibitor or sucralfate, or a cyclooxygenase 2-selective NSAID can be prescribed to decrease the risk of gastrointestinal complications.^{15,16} Long-term usage of some NSAIDs may inhibit synthesis of cartilage matrix.¹⁷

Drawbacks to the patient of long term use of NSAIDs have inspired researchers to investigate agents that have minimal or no side effects. Studies have been conducted on nutraceuticals such as chondroitin sulfate and glucosamine to demonstrate their efficacy in the symptomatic treatment of OA. Recent meta-analyses reviewed clinical trials of glucosamine and chondroitin in the treatment of osteoarthritis. Both showed substantial benefit in the treatment of osteoarthritis, although the clinical trials examined provided insufficient information about study design and conduct.¹⁸⁻²⁰

GLUCOSAMINE

The amino-monosaccharide glucosamine is a precursor of the disaccharide unit of glucosaminoglycan (GAG) and is reported to stimulate the production of proteoglycans, the ground substance of articular cartilage.^{21,22} Glucosamine also stimulates synovial production of hyaluronic acid (HA), which is responsible for the lubricating and shock-absorbing properties of synovial fluid.²³

Improvement in the symptoms of osteoarthritis associated with the use of glucosamine has been observed in several clinical trials.²⁴⁻²⁶ Houpt et al.²⁷ conducted a recent

double-blind study in Toronto, Canada, investigating the efficacy of the hydrochloride salt of glucosamine on pain and disability in knee OA. Although the primary endpoint, improvement in the pain score measured by the WOMAC questionnaire, was not met, a positive trend was noted for the glucosamine group. In addition, the secondary endpoint of cumulative pain reduction as measured by daily diary and knee examination was favorable, suggesting that glucosamine hydrochloride benefits some patients with knee OA.

CHONDROITIN SULFATE

Chondroitin sulfate is an important component of cartilage. The two types of chondroitin sulfate, chondroitin-4-sulfate and chondroitin-6-sulfate, vary in molecular weight and thus differ in their bioavailability and purity.²⁸ Chondroitin-4-sulfate is the most abundant GAG in growing mammalian hyaline cartilage. With age, chondrocytes secrete less chondroitin-4-sulfate and greater amounts of the other GAGs. This change has been observed in the initiation and progression of the degenerative process within the cartilage in OA.²⁹

Omata et al.³⁰ injected bradykinin into the left knee articular cavities of rats 3 times a day for 2 days. Chondroitin sulfate was administered orally to rats for 14 days and was shown to inhibit the bradykinin-induced proteoglycan depletion of the articular cartilage in a dose-dependent manner. These results suggest that a reduction of the proteoglycan content of cartilage, the same process associated with osteoarthritis, can be inhibited by chondroitin sulfate.

In another study chondroitin sulfate inhibited the aggrecanase enzyme in a dose-dependent manner, suggesting its protective effect. Aggrecanase has been believed to mediate aggrecans' degradation in OA.³¹ Several other studies reported similar inhibitory effects of chondroitin sulfate on many degradative enzymes.³²

Because of the large molecular size of chondroitin sulfate, earlier reports voiced their concerns about its bioavailability. However, radiolabelled chondroitin sulfate given orally to humans was 70% absorbed. Its affinity for synovial fluid and articular cartilage has also been demonstrated.³³ In addition, many clinical trials have documented the clinical efficacy of chondroitin sulfate in treating OA, showing significant symptomatic improvement and suggesting a structure-modifying effect.^{34, 35}

COMBINED THERAPY

From the previous sections it is evident that both chondroitin sulfate and glucosamine are effective in the treatment of osteoarthritis. Over the years the combined use of these nutraceuticals has become extremely popular.¹³ Their use has fewer side effects than NSAIDs, and is the only

treatment suggested to prevent progression of the disease in preliminary reports.³⁴⁻³⁶

It is important to note that experimental studies have documented a synergistic effect when glucosamine and chondroitin sulfate are administered together. Lippiello et al.³⁷ reported that the co-administration of TRH122™ low molecular weight sodium chondroitin-4-sulfate and FCHG49™ glucosamine hydrochloride resulted in a greater increase of GAG production (96.6%) than for either agent alone (glucosamine, 32%; chondroitin, 32%). The same study showed that while chondroitin inhibited Interleukin-1, glucosamine did not. Therefore, neither is superior; each has a different mechanism of action. The body responds best when glucosamine and chondroitin sulfate are consumed simultaneously.

In the same study, Lippiello et al.³⁷ investigated the efficacy of the same combination of nutraceuticals in modifying the cartilage in an OA model. Fifty percent of the rabbits were fed a regular diet while the rest were fed glucosamine and chondroitin sulfate in an amount equivalent to two percent of their body weight. At week 16, samples from the animals' medial condyles were evaluated histologically. They concluded that the nutraceutical combination used in the study (Cosamin®DS, Nutramax Laboratories) had a significant structure-modifying effect. (Figure 2). In addition, cartilage lesions were less severe in the combination therapy group in comparison to the individual components groups (Figure 3).

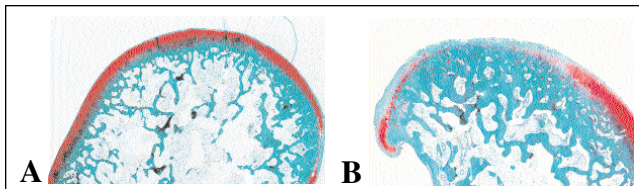


Figure 2: Cartilage matrix in the intervention group (Cosamin®DS) remained essentially intact (A), while in the placebo group (B) it was degraded.

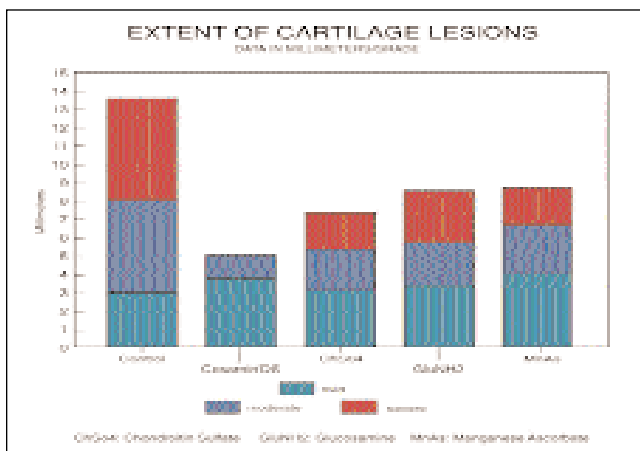


Figure 3: Extent of cartilage lesions as graded by Mankin's score in various study groups.

Two randomized, double-blind, placebo-controlled clinical trials investigated the efficacy of the same combination therapy in the management of OA. The first study was by Das and Hammad³⁸ who recruited 93 patients with knee OA. They found significant improvement in the treatment group of patients with mild or moderate knee OA at 4 and 6 months, compared to controls (Figure 4). The second 16-week crossover trial, conducted on 34 males from the U.S. Navy, showed that the same therapy combination relieves symptoms of knee OA.³⁹

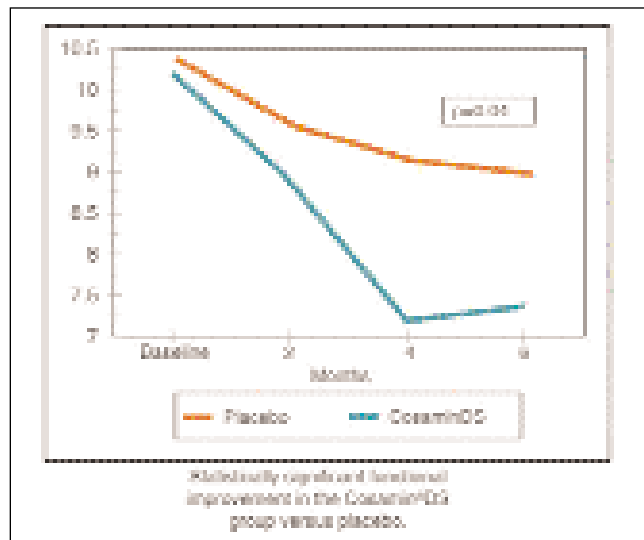


Figure 4: Significant functional improvement in the Cosamin®DS group versus placebo.

The scientific community, nevertheless, has expressed a high degree of skepticism towards nutraceuticals based in part on concerns about quality control and scientific testing of claims. Nutraceuticals are not FDA regulated; there is no requirement for rigorous scientific testing prior to marketing, there is no requirement of Good Manufacturing Practices (GMPs) to guarantee high quality and batch-to-batch consistency, and no validated method to analyze raw materials for purity. Consequently, studies have revealed that a number of preparations claiming to contain certain doses of glucosamine or chondroitin sulfate have significantly lower amounts (or none) of the dosages described.²⁰ Therefore, it is not surprising to know that the Arthritis Foundation has recently recommended that “when a supplement has been studied with good results, find out which brand was used in the study, and buy that.”⁴⁰

FUTURE APPLICATIONS

It has been recently hypothesized that nutraceutical preparations may have benefit in patient populations different from the osteoarthritic group. In the field of sports medicine, athletes are always looking for an edge to avoid injury and, when injured, to recuperate quickly. Natural treatment preparations appeal to athletes, and many now

use nutraceuticals as an adjunct in their treatment regimens for aching joints.

Theoretically, the use of nutraceuticals in sports medicine applications is appealing. In the areas of prophylaxis to avoid injury, initial treatment after injury to possibly avoid surgical intervention, and as an adjunct after surgical intervention, nutraceuticals are being added to the armamentarium of those who treat athletes predisposed to chondral and osteochondral injuries. In a recent placebo-controlled experimental study, pretreatment with a combination of glucosamine and chondroitin sulfate (Cosamin®DS) resulted in significantly less inflammation in the intervention group.⁴¹ In another pretreatment study using the same combination, there was a significantly lower incidence and severity of arthritis.⁴²

Chondral wear and injury can occur during long runs and workouts, and many distance runners suffer occasional bouts of effusions in the knees and ankles. Use of nutraceuticals before long runs and routinely during a season of training may reduce the incidence of effusions, leading to less training days lost to swollen joints. Many runners train by building up mileage, and days lost to injury mean lessened readiness for an event.

Contact and cutting sports can lead to chondral and osteochondral injuries, primarily seen in conjunction with ligamentous injury. Whether the injuries are clinically diagnosed or first seen on magnetic resonance imaging, treatment has been difficult due to the avascular nature of articular cartilage. Recent use of nutraceutical preparations in this application is supported by animal studies where treatment of acute (chemically induced and surgical instability) chondral injuries with nutraceuticals had beneficial, structure-modifying effects.^{37,41-44} When patients are treated surgically with osteochondral pinning or grafting, it follows that post-surgical application of nutraceuticals may also be of benefit.

Meniscal tears are common in weekend and professional athletes alike. Nutraceutical preparations that enhance meniscal healing, especially after surgical repair, are sure to be developed as the meniscus is the main protector of the knee joint.

Future use of nutraceuticals in these areas is exciting and opens an opportunity for extensive study of efficacy.

REFERENCES:

1. Anderson MA. Oral Chondroprotective Agents. *Part I, Compendium on Continuing Education*, 21:7, July 1999.
2. Mankind HJ, Johnson ME, Lippiello L. Biochemical and metabolic abnormalities in articular cartilage from osteoarthritic human hips II, correlation of morphology and biochemical and metabolic data. *J Bone Joint Surg* 1971;53:523.

3. Clark DM. The biochemistry of degenerative joint disease and its treatment. *Comp Cont Ed Pract* 1991;13:275-281.
4. Palmer JL, Bertone AL. Joint structure, biochemistry and biochemical disequilibrium in synovitis and equine joint disease. *Equine Vet J* 1994;26:263-277.
5. Felson DT. Epidemiology of hip and knee osteoarthritis. *Epidemiologic Reviews* 1988;10:1-27.
6. Lawrence RC, Helmick CG, Arnett FC. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998; 41(5): 778-799.
7. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum* 1998;41(8):1343-1355.
8. Hart DJ, Doyle DV, Spector TD. Association between metabolic factors and knee osteoarthritis in women. The Chingford study. *J Rheumat* 1995;22(6):1118-1123.
9. Cooper C, McAlindon T, Snow S, Vines K, Young P, Kirwan J, Dieppe P. Mechanical and constitutional risk factors for symptomatic knee osteoarthritis: differences between medial tibiofemoral and patellofemoral disease. *J Rheumat* 1994;21(2):307-313.
10. Rehman Q, Lane NE. Getting control of osteoarthritis pain: an update on treatment options. *Postgrad Med* Oct 1, 1999;106(4):127-134.
11. Buckwalter JA, Lane NE. Athletics and osteoarthritis. *Am J Sports Med* Nov-Dec 1997;25(6):873-81.
12. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. *Ann Rheum Dis* 1957;16:494-501.
13. Hungerford DS. Treating osteoarthritis with chondroprotective agents. *Orthopedic Special Edition* 1998;1:39-42.
14. Schoenfeld P, Kimmey MB, Scheiman J, Bjorkman D, Laine L. Nonsteroidal anti-inflammatory drug-associated gastrointestinal complications--guidelines for prevention and treatment. *Aliment Pharmacol Ther* Oct 1999;13(10):1273-1285.
15. Hirschowitz BI. Minimizing the risk of NSAID-induced GI bleeding. *Cleve Clin J Med* Oct 1999; 66(9):524-527.
16. Plosker GL, Lamb HM. Diclofenac/misoprostol: pharmacoeconomic implications of therapy. *Pharmacoeconomics* Jul 1999;16(1):85-98.
17. Brandt K. Nonsteroidal anti-inflammatory drugs and articular cartilage. *J Rheumat* 1987;14(suppl):132-133.
18. McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin treatment for osteoarthritis. A systematic quality assessment and meta-analysis. *JAMA* 2000;283,1469-1475.

19. Barclay TS, Tsourounis C, McCart GM. Glucosamine. *Ann Pharmacother* May 1998; 32(5):574-579.
20. Deal CL, Moskowitz RW. Nutraceuticals as therapeutic agents in osteoarthritis. The role of glucosamine, chondroitin sulfate, and collagen hydrolysate. *Rheum Dis Clin North Am* May 1999; 25(2):379-395.
21. Burkhardt D, Gosh P. Laboratory evaluation of antiarthritic drugs as potential chondroprotective agents. *Seminars in Arthritis and Rheumatism* 1987; 17:3-34.
22. Hellio MP, Vigron E, Anfeld M. The effects of glucosamine on the human osteoarthritis chondrocytes, in vitro investigations. *Proc 9th Eular Symp* 1996;11-12.
23. McCarty MF. Enhanced synovial production of hyaluronic acid may explain rapid clinical response to high-dose glucosamine in osteoarthritis. *Med Hypotheses* Jun 1998; 50(6):507-510.
24. Reichelt A, Forster KK, Fischer M, Rovati LC, Setnikar I. Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee. *Arzneimittelforschung* 1994; 44(1):75-80.
25. Drovanti A, Bignamini AA, Rovati AL. Therapeutic activity of oral glucosamine sulfate in osteoarthritis: a placebo-controlled double-blind investigation. *Clin Ther* 1980; 3:260-272.
26. Vaz AL. Double-blind clinical evaluation of the relative efficacy of ibuprofen and glucosamine sulphate in the management of osteoarthrosis of the knee in outpatients. *Curr Med Res Opin* 1982; 8:145-149.
27. Houpt JB, McMillan R, Wein C, Paget-Dellio SD. Effect of glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee. *J Rheumat* Nov 1999;26(11):2423-30.
28. Das A. Treatment of osteoarthritis with chondroprotective agents. *Orthop Special Ed* 5 1999; 1-4.
29. Ronca G. Anti-inflammatory activity of chondroitin sulfate. *Proc 3rd Int Cong Osteoathr Res Soc* 1997; 2.
30. Omata T, Segawa Y, Itokazu Y, Inoue N, Tanaka Y. Effects of chondroitin sulfate-C on bradykinin-induced proteoglycan depletion in rats. *Arzneimittelforschung* Jul 1999; 49(7):577-581.
31. Sugimoto K, Takahashi M, Yamamoto Y, Shimada K, Tanzawa K. Identification of aggrecanase activity in medium of cartilage culture. *J Biochem (Tokyo)* Aug 1999; 126(2):449-455.
32. Paroli E, Antonilli L, Biffoni M. Pharmacological approach to glycosaminoglycans. *Drugs Exp Clin Res* 1991;8:9-20.
33. Conte A, Volpi N, Palmiera L, Bahous I, Ronca G. Biochemical and pharmacokinetic aspects of oral treatment with chondroitin sulfate. *Drug Res* 1995; 45: 918-925.
34. Uebelhart D, Thonar EJ, Delmas PD, Chantaine A, Vignon E. Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study. *Osteoarthritis Cartilage* 1998;6(suppl A):39-46.
35. Verbruggen G, Goemaere S, Veys EM. Chondroitin sulfate: S/DMOAD (structure/disease modifying anti-osteoarthritis drug) in the treatment of finger joint osteoarthritis. *Osteoarthritis Cartilage* 1998;6(suppl A):36-38.
36. Fillmore CM, Bartoli L, Bach R, Park Y. Nutrition and dietary supplements. *Phys Med Rehabil Clin N Am* Aug 1999;10(3):673-703.
37. Lippiello L, Woodward J, Karpman R, Hammad TA. Beneficial effect of cartilage structure modifying agents tested in chondrocyte cultures and a rabbit instability model of osteoarthrosis. *Arthritis and Rheumatism* 1999; 42(suppl):S256.
38. Das AK, Hammad T, Eitel J. Efficacy of a combination of glucosamine hydrochloride, sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis: a randomized double-blind placebo-controlled clinical trial. Paper #180, 66th Annual Meeting, American Academy of Orthopedic Surgeons, Anaheim, Calif, Feb 6, 1999. Accepted for publication in *Osteoarthritis Cartilage*.
39. Leffler CT, Philippi AF, Leffler SG, Mosure JC, Kim PD. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back. *Mil Med Feb* 1999;164(2):85-91.
40. Horstman J. Arthritis Foundation's Guide to Alternative Therapies. Atlanta, *Arthritis Foundation*, 1999.
41. Canapp SO, McLaughlin Jr. RM, Hoskinson JJ, Rough JK, Butine MD. Scintigraphic evaluation of dogs with acute synovitis after treatment with glucosamine hydrochloride and chondroitin sulfate. *AJVR* 1999; 60:1550-1556.
42. Beren J, Hill SL, Rose NR. "Therapeutic Effect of Cosamin® on Autoimmune Type II Collagen-Induced Arthritis in Rats." Presented at the 1997 North American Veterinary Conference (*Proceedings of Innovations and New Product Applications in Veterinary Practice*). Jan: 35. Accepted for publication in the Proceedings of the Society for Experimental Biology and Medicine 2000.
43. Personal Communication Terry Clyburn, MD. The University of Texas Houston Health Center.
44. Uebelhart D, Eugene J, Thonar A, Zhang J, et al. Protective effect of exogenous chondroitin 4,6 sulfate in the acute degradation of articular cartilage in the rabbit. *Osteoarthritis Cartilage* 1998; 6 (suppl A):6-13.