

# **Extracts from: A CME Accredited Special Report; August 1999.**

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## **Osteoarthritis Treatment and Potential Structure Modification with Nutraceuticals**

### **NEEDS STATEMENT**

*Treatment and structure modification of diseased hyaline cartilage have generated great interest for those managing patients with osteoarthritis (OA). Most of the attention to date has focused on a group of dietary supplements known as "nutraceuticals." While interest in some of these compounds dates back 30 years or more, it is only recently that clinical studies proving their efficacy have been completed in the United States. Many of these nutraceuticals are well known among the general population. Clinicians need to understand the medical foundations for their use in order to be able to counsel their patients effectively.*

### **ACCREDITATION AND CREDIT DESIGNATION STATEMENTS**

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Dannemiller Memorial Educational Foundation and McMahon Publishing Group. The Dannemiller Memorial Educational Foundation is accredited by the ACCME to provide continuing medical education for physicians.

### **INTENDED AUDIENCE**

This activity is intended for orthopedists and primary care physicians.

### **FACULTY DISCLOSURE**

Dr. Robert C. Schenck, Jr., Associate Professor, Department of Orthopedics, University of Texas at San Antonio, has indicated that he has no relationship or affiliation that impacts on this activity.

### **OBJECTIVES**

1. State the reasons physicians should become familiar with nutraceuticals for the treatment of OA.
2. Explain the medical foundation for the use of nutraceuticals in the treatment of osteoarthritis.

3. Discuss the concept of structure modification in OA.
4. Identify and discuss the conclusions of recent experimental and clinical studies using glucosamine and chondroitin sulfate.

### **Introduction**

Studies have shown that osteoarthritis (OA) is a common clinical occurrence. An estimated 15% (40 million) of Americans had some form of arthritis in 1995.<sup>1</sup> The burden of OA disability and dependence among older Americans is second only to chronic heart disease as the primary diagnosis leading to Social Security disability payments to adults.<sup>1</sup> Each year, there are 65 million work-loss days attributable to OA.<sup>2</sup>

Current pharmacologic therapy for OA relies upon acetaminophen; nonsteroidal anti-inflammatory drugs (NSAIDs); opioid and nonopioid analgesics; topical analgesics; and intra-articular corticosteroids and hyaluronic acid. Each of these pharmaceutical interventions offers palliation of symptoms only. None has the potential to positively impact the underlying pathophysiology and consequently change the sequela of OA. Several have potential adverse effects as well.

In particular, NSAIDs, the most widely prescribed group, are well known for their propensity for gastric complications, ranging from mild GI discomfort to rare but life-threatening hemorrhage.<sup>3</sup> In addition, a number of these drugs can be nephrotoxic.<sup>4</sup> There is also some evidence that certain of the NSAIDs actually expedite articular cartilage degradation.<sup>5</sup> The recent approval of COX-2-specific NSAIDs, celecoxib and rofecoxib, promises a reduced side effects profile, although GI side effects are still cited in product information statements.<sup>33</sup>

The risk of abuse and tachyphylaxis prevents opioids from being a desirable treatment over the long haul, and although intra-articular injections of steroids can provide symptom relief, articular injury and risk of infection with multiple injections mitigates against their long-term application.

Physicians treating patients suffering from OA report increasing consumer interest in the use of certain dietary supplements, or "nutraceuticals," to help relieve symptoms. Word of mouth among patients and coverage by the media have thrust these compounds into

the limelight, resulting in many OA sufferers asking their health care providers about such OTC products; furthermore, many patients begin a course of therapy on their own.

There are dozens of self-proclaimed remedies for OA available as dietary supplements. SAME (S-adenosylmethionine); MSM (methylsulfonylmethane); green-lipped mussel (*Perna canaliculus*); CMO (cerasomal-cis9-cetylmyristoleate); and various homeopathic and herbal preparations all describe themselves as being effective treatments for OA symptoms. Some even state that they have the ability to reverse the disease. Of this list the only preparation that seems to have some documented benefit by clinical studies is SAME.<sup>6</sup> Interestingly, these studies finding SAME efficacious used divided dosages of 1200 mg per day (greater than the dose of 200 mg/day commonly recommended).

The DSHEA (Dietary Supplement Health and Education Act) of 1994 provides for the sale of dietary supplements to the public without the intervention of licensed health care providers. The FDA (Food and Drug Administration) is responsible for regulating the dietary supplement industry and monitoring compliance with those regulations. Unlike the pharmaceutical industry, however, there is no requirement that manufacturers of nutraceuticals use pharmaceutical cGMPs (Good Manufacturing Practices). Validated assay methods don't exist for many of the products available and raw materials for producing nutraceuticals such as glucosamine and chondroitin sulfate, and consequently the end products, vary greatly in purity and content. Frequently, the material in the package may differ from the ingredients and/or amounts listed on the label.<sup>7,8,9</sup> There is no requirement that a particular product be efficacious, and many products make outrageous claims. It is not unusual to find declarations such as cures arthritis; "regenerates, renews, and rebuilds;" or "pain free" in advertising. Indeed, the statement that a nutraceutical has been "clinically proven" seldom means that it has withstood the rigors of a randomized, double-blind research protocol.

Despite the loose regulations and lack of monitoring, there are some companies who self-impose the use of pharmaceutical cGMPs and quality control measures that mimic those found in the pharmaceutical industry. However, it is up to the patient to discern which companies produce products that meet these standards. Amal Das, MD, orthopedic surgeon, has cautioned that, "physicians should request documentation of quality control programs, such as pharmaceutical GMPs, validation of raw materials/finished product, and brand name use in clinical trails."<sup>10</sup>

Whether or not physicians have formed an opinion about the utility of nutraceutical therapy, it is important that they become knowledgeable about the use of these products for a number of reasons. Certainly the widespread popularity of these compounds is one reason. Also, recently completed double-blind placebo-controlled studies using a highly purified and patented combination of FCHG49<sup>TM</sup>\* glucosamine hydrochloride and TRH122<sup>TM</sup>†, a low molecular weight (LMW) chondroitin sulfate, showed that this nutraceutical is efficacious in controlling the symptoms of OA.<sup>32,11</sup>

Additionally, these particular compounds have a low risk of side effects and display no known drug-to-nutraceutical interactions. For this reason they represent an attractive choice for OA treatment, particularly for the elderly who are likely to have problems with polypharmacy and are susceptible to GI ulceration and nephrotoxicity. Lastly, there is increasing evidence, in experimental models, that glucosamine hydrochloride in combination with LMW chondroitin sulfate may alter the typical course of OA.<sup>12</sup>

Intact articular cartilage is vital for efficient joint functioning. The initial insult in OA is the insidious failure of the articular cartilage due to some force or action that destabilizes the natural homeostasis of articular cartilage metabolism and a consequent reduction in glycosamino-glycan (GAG) production. The severity of OA in part is related to the level of GAG content in the osteoarthritic cartilage matrix. As the disease progresses, the cartilage loses its elasticity and ability to efficiently transmit forces, resulting in the net loss of cartilage matrix, and increased permeability. Over time, this phenomenon leads to changes in the entire joint and the underlying bone.

Changing the course of the disease is the subject of the latest initiatives in OA research. The Osteoarthritis Research Society determined that the term "chondroprotection" misrepresents the pathology associated with OA by suggesting that the disease is limited to the articular cartilage. Because OA involves not only softening, fraying, and loss of articular cartilage, but also the presence of marginal osteophytes, subchondral cysts, sclerosis and varying degrees of synovial inflammation, the term "structure modification" better describes the therapeutic goals.<sup>13</sup> Regardless, the concept of disease-altering treatments for OA is new and of great interest to the clinician.

## Glucosamine

Chondrocytes are responsible for producing glucosamine from glucose and glutamine. Glucosamine, an amino sugar, functions as the raw material for glycosaminoglycans (GAGs) such as hyaluronic acid. Absorption of glucosamine has been documented at 90% using labelled animal studies.<sup>14</sup> It is commonly found as a HCl or SO<sub>4</sub> salt. Another form, N-acetyl glucosamine, is also available but has been shown to be ineffective in cell culture.<sup>15</sup>

There appears to be more than a chemical difference between the sulfate and hydrochloride forms of glucosamine. These two compounds differ in their purity, sodium content, amounts of bioactive glucosamine, and equivalent dosages (see Table). The disparity in purity equates to the patient receiving different amounts of glucosamine base depending upon which form of the compound is ingested.<sup>8</sup> A typical capsule containing 500 mg of glucosamine sulfate will yield about 239 mg of bioactive glucosamine, while that same dosage of glucosamine hydrochloride will provide 407 mg of bioactive glucosamine - approximately 70% more. To date, all U.S. trials have used glucosamine hydrochloride in combination with LMW chondroitin sulfate.<sup>11, 12, 16, 32</sup>

## Sulfate and Hydrochloride Salts of Glucosamine: A Comparison \*

	Purity	Additives	Bioreactive Glucosamine (as free base)	Equivalent Doses
Glucosamine Sulfate	80%	20% sodium	47.8%	2608 mg
Glucosamine HCl	99.1%	None	81.3%	1500 mg

\*Based on Deal CL Moskowitz RW: *Nutraceuticals as therapeutic agents in osteoarthritis Rheum Dis Clin of N Amer* 1999; 25:379.

Early European studies found that glucosamine sulfate was safe and offered reduction in the symptoms of OA sufferers.<sup>17,18</sup> There has been some speculation that glucosamine may increase serum glucose levels. In vivo, the chemical reaction of glutamine and glucose to form glucosamine is irreversible. Animal studies measuring serum glucose after oral administration of high doses of glucosamine HCl in combination with chondroitin sulfate in dogs showed no elevation in serum glucose levels.<sup>19</sup> Diabetics should be instructed to continue on their regular glucose monitoring regimen.

It appears that the mechanism of action for glucosamine is to stimulate chondrocytes to secrete glycosaminoglycans.<sup>20</sup> Based on such mechanisms, theoretically, glucosamine may have structure-modifying capacity; but to date, no human trials have proven disease modification with the use of glucosamine alone.<sup>8</sup>

### Chondroitin

Chondroitin sulfate, the most abundant GAG in articular cartilage, is normally synthesized in the body from glucuronic acid and galactosamine. Unlike glucosamine, chondroitin sulfate is a large molecule whose molecular weight can vary from 5,000 to over 50,000 daltons.<sup>21</sup> Commercially available sources of chondroitin sulfate are the cartilaginous rings of bovine trachea, whale nasal septum, and pork by-products (ears and snout). Although shark cartilage and raw cartilage powders are promoted as treatments for OA because of their chondroitin sulfate content, in reality this content is low.

Absorption of chondroitin sulfate has been the subject of some controversy among researchers and clinicians. Early bioavailability studies on oral chondroitin sulfate have been criticized for using crude methods of detection when they indicated that this very large molecule could not be absorbed.<sup>22,23</sup> More recent studies on highly purified (95%) radiolabeled LMW oral chondroitin sulfate have documented a greater than 70% absorption from the gut with a documented presence in joint tissue.<sup>24</sup>

As seen with glucosamine, there are multiple sources of chondroitin sulfate and purity and molecular weight

can vary greatly.<sup>8</sup> All of the recent U.S. clinical trials and bioavailability studies have used a specific LMW product that is purified to 95%.<sup>11,24,32</sup> It is unknown if less pure and/or higher molecular weight compounds are absorbed, or at what level.

Some critics have questioned chondroitin sulfate's effect on coagulation parameters as the molecule has a structure similar to heparin sulfate. However, no impact on prothrombin time (PT) or partial thromboplastin time (PTT) has been documented in animal or human studies.<sup>11,19,25</sup>

Pure chondroitin sulfate has been shown in numerous clinical trials to be an effective symptomatic treatment for OA.<sup>26,27</sup> Unlike glucosamine, chondroitin sulfate acts by competitively inhibiting the degradative enzymes that besiege articular cartilage in OA.<sup>28</sup>

In a recent study, investigators explored nitric oxide (NO) synthesis in the presence of chondroitin sulfate and glucosamine. Arthritic cartilage releases NO to a greater degree than non-diseased cartilage, suggesting that NO may have a damaging impact on normal cartilage. The presence of chondroitin sulfate reduced the synthesis of NO, thereby protecting the non-diseased cartilage. The presence of glucosamine did not inhibit NO synthesis.<sup>29</sup>

Unlike glucosamine, chondroitin sulfate has been shown to exhibit structure-modifying properties in animal as well as human trials.<sup>26,27,30</sup> In one study, the medial tibiofemoral joint space was measured in OA patients taking either purified LMW chondroitin sulfate or placebo. The tibiofemoral joint space decreased significantly in placebo patients after 1 year, but was unchanged in the treatment group ( $p < 0.05$ ).<sup>30</sup> In a three year study, hand radiographs of 34 patients receiving LMW chondroitin sulfate 400 mg tid were compared with 85 patients taking placebo capsules. Radiographs covered a 3-year period. Patients in the chondroitin group experienced significantly fewer instances of erosive OA.<sup>27</sup> In the latter study, the methodology in obtaining and reading the hand radiographs was not clearly outlined and could be questioned. In both studies, the authors noted the need to reconfirm these findings due to the small number of patients.

## Combination Product Studies

Because of the success of both glucosamine and chondroitin sulfate in numerous European studies, interest in a therapy using both components together developed. U.S. researchers performing a meta-analysis on the European data concluded that, while the two compounds showed benefit in the treatment of OA, insufficient information and issues of study design precluded them from drawing any definitive conclusions on the individual compounds.<sup>34,35</sup> However, a recent review of the data concluded that it is probably reasonable to use combination therapy pending further studies.<sup>8</sup> There are several companies that are currently marketing glucosamine/ chondroitin sulfate combination products. Some of these include; Sundown, Schiff, Twinlab, Inholtra, and Solgar, as well as many others. To date, only Nutramax Laboratories' patented product, containing FCHG49™ glucosamine hydrochloride and TRH122™ LMW sodium chondroitin sulfate (Cosamin®DS), has been used as the intervention material in any published placebo-controlled safety and efficacy studies performed in the United States.

<sup>11,12,16,19,25,31,32</sup>

In a recent experimental study by Lippiello, et al, these two agents, FCHG49™ glucosamine hydrochloride and TRH122™ sodium chondroitin sulfate, were tested individually and in combination. Results indicated a significant synergistic effect of the combination on production of cartilage matrix by chondrocytes.<sup>31</sup>

Robert C. Schenck, Jr., MD, speaking at the most recent annual meeting of the American Academy of Orthopaedic Surgeons (AAOS), reviewed clinical studies of glucosamine and chondroitin sulfate. He cited a human study previously presented at the annual meeting of the American Association of Hip and Knee Surgeons and presented as a paper at the AAOS. In it, Das et al. undertook a randomized, double-blind, placebo-controlled clinical trial of 93 knee OA patients, using the same patented combination of FCHG49™ glucosamine hydrochloride, TRH122™ LMW sodium chondroitin sulfate and manganese ascorbate as was used in the Lippiello study. The study found that patients with mild to moderate OA (n = 72) showed significant improvement in Lequesne index scores at four and six months. Interestingly, there were more adverse events in the placebo group than the study group, but this did not reach statistical significance. However, study participants did report a clinically significant drop in NSAID use.<sup>32</sup>

Another study looking at this same nutraceutical combination therapy was performed by the Medical Department of the Naval Special Warfare Group. This 16-week, randomized, double-blind, placebo-controlled crossover trial identified 34 males from the Navy's Special Warfare community with chronic pain and degenerative joint disease of either the knee or lower back. Participants were randomized to receive placebo or a combination of FCHG49™ glucosamine HCl (1500 mg/d), TRH122™ LMW chondroitin sulfate (1200 mg/d) and manganese ascorbate (228 mg/d). The study used patient assessment, visual analog scores, physical

examination, and clocked running times. The investigators concluded that the combination therapy effectively relieved the knee OA symptoms. However, they determined that the data set was insufficient to reach a conclusion concerning the therapy's effect on low back patients.<sup>11</sup>

One of the papers presented at the AAOS described an animal instability model using rabbits. Animals were pretreated with placebo or the patented combination of FCHG49™ glucosamine HCl and TRH122™ low molecular weight chondroitin sulfate prior to creating an ACL-deficient knee. In this study, the combination product protected cartilage from degradation (see Figure 1) in comparison to placebo (see Figure 2) under histologic evaluation with Safranin-O stain. The articular matrix from the rabbits in the treatment group remained essentially intact, while the control group's cartilage matrix was severely degraded.<sup>12</sup> Another study showed that dogs, when pretreated with this product, were protected against chemically induced (with chymopapain) inflammatory synovitis and associated bone remodelling. Additionally, the pretreated dogs demonstrated improved limb function.<sup>16</sup> These studies show that this patented combination meets most if not all of the criteria of a complete structure-modifying agent.

For Dr. Schenck, the recent studies of these nutraceutical agents for OA are of great interest, particularly because they have shown evidence of structure-modification. However, as he noted at the conclusion of his presentation at the AAOS, "It would take a leap of faith to say that these supplements reverse arthritis. It will take a larger study before we can discuss chondroprotection as a reversal of OA." Dr. Schenck believes that such studies might be completed over the next few years. In fact, this year the NIH will undertake a large multicenter study examining the efficacy and the structure-modifying capacity of these compounds.

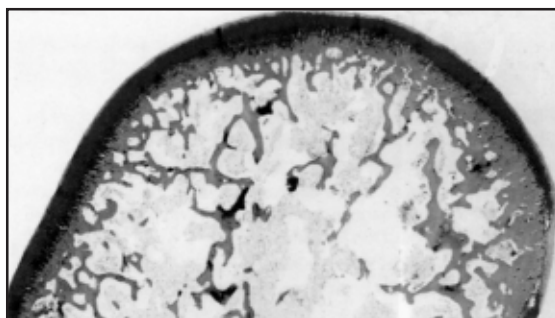


Figure 1. Cartilage from treated group remained essentially intact.

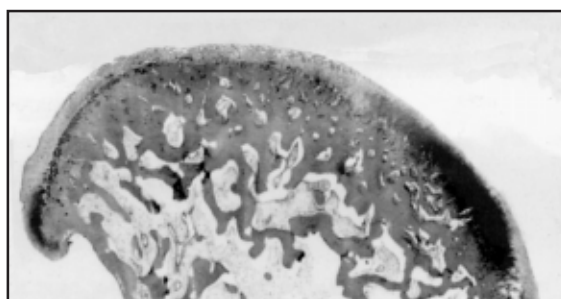


Figure 2. Placebo group's articular matrix was degraded.

\* FCHG49™ is a trademark of Nutramax Laboratories®, Inc. for the proprietary specifications for glucosamine hydrochloride contained in its products.  
† TRH122™ is a trademark of Nutramax Laboratories®, Inc. for the proprietary specifications for sodium chondroitin sulfate contained in its products.

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