

Managing Osteoarthritis With Nutritional Supplements Containing Glucosamine, Chondroitin Sulfate, and Avocado/Soybean Unsaponifiables

Osteoarthritis (OA) is a painful, progressive degeneration of the joint characterized by progressive cartilage loss, subchondral bone remodeling, formation of periarticular osteophytes, and mild to moderate synovitis accompanied by an increase in pro-inflammatory cytokines, chemokines, and a variety of inflammatory mediators.¹ There is no cure for OA; therefore, once an individual is diagnosed, managing OA becomes a lifelong process. Although a physician initially diagnoses OA, pharmacists are the most accessible health care professional and play an integral role in managing each patient's joint discomfort by dispensing prescription medications (e.g., opioids, selective nonsteroidal anti-inflammatory drugs [NSAIDs], proton pump inhibitors); recommending nonprescription pain relievers (acetaminophen, ibuprofen, naproxen); and discussing adverse events (AEs) associated with these drugs. Another important role of the pharmacist is counseling patients regarding the use of oral joint health supplements (OJHSs). This review will provide relevant and timely information on

successfully recommending OJHSs containing a combination of glucosamine, chondroitin sulfate (CS), and avocado/soybean unsaponifiables (ASU) for the management of OA. It will briefly review the available pharmacokinetics/pharmacodynamics and safety profile of OJHSs containing a mixture of glucosamine, CS, and ASU, outline strategies to identify appropriate patients for OJHSs containing these ingredients, and provide web-based resources (TABLE 1) that will assist pharmacists in educating and counseling patients.

CURRENT RECOMMENDATIONS FOR THE MEDICAL MANAGEMENT OF JOINT DISCOMFORT AND CARTILAGE BREAKDOWN

A multitude of treatment modalities exist for OA, including surgical, pharmacologic, and nonpharmacologic therapies.²⁻⁵ According to these guidelines, oral and topical NSAIDs, cyclooxygenase (COX)-2 inhibitors, opioids, and intra-articular injections of corticosteroids or hyaluronic acid may be prescribed as adjuncts to nonpharmacologic therapies. Nutritional supplements may also be chosen, as they are prescription products in some countries, even though they are nonprescription products in the United States.

Although no universally accepted

treatment algorithm exists for managing patients with OA, acetaminophen is a first-line drug recommended to help control pain and increase mobility. Acetaminophen is associated with both hepatic and renal damage, particularly in patients who exceed the recommended daily dose or use it in combination with moderate amounts of alcohol.⁶ Worsening pain, disease progression, and inefficacy of acetaminophen often necessitate initiating prescription NSAIDs (such as COX-2 inhibitors), which carry the risk of gastrointestinal effects (e.g., gastropathy), renal toxicities, and serious cardiovascular events.^{1,6,7} Patients unable to tolerate these options or who do not receive adequate pain relief can be prescribed opioids; however, pruritus, nausea, vomiting, constipation, and physical dependence are problematic.⁷

Table 1. Web-based Patient Resources

Food and Drug Administration:

www.fda.gov/food/dietarysupplements/consumerinformation/ucm110567.htm

Center for Disease Control and Prevention:

www.cdc.gov/arthritis/data_statistics/arthritis_related_stats.htm

Arthritis Foundation:

www.arthritis.org/osteoarthritis.php

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As a result of the AEs inherent with the use of most OA therapies, OJHSs have become extremely popular for managing joint pain and dysfunction. Trade sources report that yearly sales of OJHSs containing glucosamine and/or chondroitin sulfate were over \$425.8 million, making OJHSs the most popular form of nutritional supplement.⁸

The following section describes the available chemistry, pharmacokinetics, and clinical data for glucosamine and CS, two of the most popular OJHS ingredients, as well as ASU.

The Role of CS, Glucosamine, and ASU in Joint Health

Description, Pharmacokinetics, and Pharmacodynamics

1. Glucosamine is a water-soluble amino monosaccharide that is available as glucosamine hydrochloride, glucosamine sulfate, and N-acetyl-D-glucosamine. Both the sulfate and hydrochloride forms generate glucosamine free base at gastric pH. Ninety-nine percent pure glucosamine hydrochloride generates approximately 80% glucosamine free base whereas glucosamine sulfate only generates 50%–60% glucosamine free base. Thus, if apparently comparable supplements contain equal amounts of glucosamine, but one contains glucosamine sulfate and the other contains glucosamine hydrochloride, more free glucosamine will be generated by the product containing the hydrochloride form.^{9–11} Following oral administration, glucosamine is rapidly absorbed and yields plasma concentrations in excess of 30 times the baseline levels with once-daily dosing (using a standard dose of 1500 mg).¹²

2. CS is a sulfated, heterogeneous macromolecule comprised of galac-

tosamine sulfate and glucuronic acid that varies in molecular weight from 6000–50,000 daltons.^{13,14} Commercially available CS products vary markedly in source (bovine trachea, shark cartilage, other animal cartilage sources), purity, content variability, contamination (other dietary supplements, trace elements), and manufacturing procedures.¹³ CS varies in its efficacy depending on its origin, molecular weight/chain length, and degree of sulfation.¹⁵ This variation in commercially available CS products explains why the CS selected for inclusion in the NIH-funded Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) was a specific pharmaceutical grade of CS rather than a non-specific commercial source.¹³ Some commercially available OJHSs sold in the United States contain lower quality CS.

CS is well-absorbed following oral administration.¹⁶ A pharmacokinetic study in 20 healthy male volunteers reported a significant increase in plasma CS levels 2–6 hours after administration with the peak (>200% increase in levels) at 2 hours. First-order kinetics was observed for doses up to 3000 mg, and bioavailability of oral CS ranged from 15% to 24%.¹⁷

3. ASU is a mixture of avocado and soybean unsaponifiable fractions, which are the oily substances that remain after hydrolysis (saponification) of avocado and soybean oils. The major components of ASU are phytosterols such as beta-sitosterol, campesterol, and stigmasterol, which are considered anti-inflammatory compounds with both antioxidant and analgesic activities.^{18–21}

Clinical Evidence

A number of studies have demonstrated the efficacy of glucos-

amine and CS, and the superiority of the two ingredients in combination has been reported.²² One randomized, double-blind, placebo-controlled study included 21 men with chronic knee pain (20 due to OA) who consumed daily supplements of a commercial nonprescription preparation of glucosamine (1500 mg), and CS (1200 mg); they experienced symptomatic relief after eight weeks.²³ In a larger study, the same commercial product was taken by 93 patients with knee OA; a significant improvement in severity of OA pain was noted in patients with mild to moderate OA.²⁴ Subjects received 1000 mg of glucosamine and 800 mg of CS twice daily for 6 months. That study also reported a strong trend in the reduction of NSAID use by patients receiving CS and glucosamine in months 2 through 6 compared to those in the placebo group. The GAIT study found that the 72 subjects with moderate to severe OA experienced a statistically significant improvement in pain scores ($\geq 20\%$) after 24 weeks of daily supplementation with 1500 mg glucosamine and 1200 mg of CS.²⁵

Four high-quality, randomized clinical studies of ASU,^{26–29} one meta-analysis,³⁰ two systemic reviews,^{31,32} and one *Cochrane Review*³³ have been published supporting 300 mg ASU once daily for the management of hip and knee OA. In the first study, Blotman et al. (1997) found that patients with OA experienced a reduced need for NSAIDs after 6 weeks of supplementation. Patients exhibited increased function and decreased pain compared to those in the placebo group.

In the second study, Maheu et al. (1998) reported improved func-

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tion and decreased pain in both the ASU and placebo groups; however, the improvement was significantly greater in the ASU group. Further, fewer NSAIDs were consumed in the ASU group.

In a third study, Appelboom et al. (2001) also found a significant decrease in NSAID usage and a significant increase in function in the ASU group compared to the placebo group.

In the final study, Lequesne et al. (2002) found that patients severely affected by hip OA who took ASU experienced significantly less joint space width loss, but no difference in joint space loss was noted between the ASU and placebo group patients with less severe joint space loss measured at baseline. In that study, no other clinical differences were noted between the ASU and placebo groups, including function, NSAID usage, and subjective patient assessments.

To date, no clinical trials assessing the efficacy of the combination of glucosamine, CS, and ASU have been conducted; however, *in vitro* studies summarized in a recent review article suggest that anti-inflammatory effects of the three ingredients combined may exceed those from individual administration.³⁴

Contraindications and AEs

Glucosamine, CS, and ASU are safe and well tolerated. In the GAIT trial, AEs were mild and infrequent, and included headache and nausea. Das and Hammad (2000) reported an incidence of AEs of 19% in the placebo group and only 17% in the treatment group ($P>0.05$).²⁴ Typical AEs were transient and included gastrointestinal symptoms (gas, indigestion, constipation), fatigue, and muscle cramping. ASU appears equally safe. In the four

randomized clinical trials cited previously, AEs included slight to mild gastric disorders, pyrosis, nausea, vomiting, febrile colitis, headache, drowsiness, allergy, urticaria, and pruritus. AEs were reported in 26.1%, 32.6%, and 27.9% of the placebo group, 300 mg ASU group, and 600 mg ASU group, respectively ($P>0.05$), by Appelboom et al. (2001). Lequesne et al. (2002) noted that 99% and 97% of the patients rated tolerability of the treatment as either “excellent” or “good” in the ASU and control groups, respectively.

Glucosamine, CS, and ASU each appear to be almost completely void of any demonstrated or hypothetical detrimental herb-nutrient-drug interactions. Further, a number of studies have shown that glucosamine does not alter glucose metabolism and is theoretically safe for diabetics.³⁵ One study reported no AEs in 3063 patients administered oral glucosamine for approximately 66 weeks, and AEs were reported less frequently following glucosamine administration than either the placebo or NSAID.³⁶ This conclusion was echoed by Stargrove et al. (2008), who wrote, “significant interactions with either insulin or oral hypoglycemic agents are improbable.” Additionally, a 2010 published meta-analysis by Simon et al. (2010) found no effects on blood glucose levels. The authors of that review concluded from all available evidence that “Glucosamine has no effect on fasting blood glucose levels, glucose metabolism, or insulin sensitivity at any oral dose level in healthy subjects, individuals with diabetes, or those with impaired glucose tolerance.”³⁷ Only routine monitoring of glucose levels in diabetic patients taking glucosamine is necessary.

Clinical Recommendations for the Use of Glucosamine, CS, and ASU for Joint Health

“Patient safety and a significant degree of efficacy are excellent reasons to recommend a glucosamine and chondroitin sulfate product to patients with OA pain,” wrote Nicholas DiNubile, MD, a clinical assistant professor in the department of orthopedic surgery at the University of Pennsylvania Hospital.³⁸ More recently, DiNubile described the combination of glucosamine, CS, and ASU as a first-line treatment for OA for any patient who has undergone a surgical procedure for cartilage regeneration.^{34,39}

Published *in vitro* studies demonstrate that the combination of glucosamine, CS, and ASU exerts greater anti-inflammatory effect than glucosamine and/or CS alone. In addition, administration of OJHSs containing these ingredients may reduce the need for acetaminophen or NSAIDs. Data generated from the randomized clinical trials described herein support the administration of 1500 mg glucosamine, 800 mg CS, and 300 mg ASU per day for individuals with OA. Using quality OJHSs that contain glucosamine, CS, and ASU at recommended doses as part of a multimodal treatment protocol that includes patient education, weight management, and other nonpharmacologic therapies appears to play an integral role in successfully managing patients with OA by reducing pain and inflammation and improving function.

Recommending a Quality Product

The FDA does not have a role in the approval process for OJHSs. The clinical data regarding safety and efficacy of OJHSs discussed above should be viewed in that light.

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Manufacturing of OJHSs is regulated by the FDA; however, poor quality products continue to slip through the cracks and are unknowingly purchased by consumers. Poor quality supplements include those that do not contain the type or amount of ingredient listed on the manufacturer's label, recommend subtherapeutic dosages, and/or are potentially contaminated by harmful chemicals such as pesticides, lead, or other supplement ingredients during the manufacturing process. These types of supplements are unlikely to be effective, delay the use of effective supplements, are economically draining for consumers, and are an important safety

concern. Independent testing by ConsumerLab.com found that only 16 of 21 OJHSs met quality standards and FDA labeling requirements. An even more sobering analysis by Adebowale et al. (2000) reported 26 of 32 products containing CS failed to have even 90% of the CS amount claimed on the label, and 17 had <40% of the label claim.¹⁵ To lessen concerns regarding product quality (ergo safety), the pharmacist might recommend products that appear to be manufactured in a quality manner. The ACCLAIM system (TABLE 2) can help pharmacists rapidly and confidently select quality supplements to recommend. ■

Table 2. The Seven-Step ACCLAIM System for Selecting High Quality Nutritional Supplements

- Does the product have the following characteristics?
- A** name you recognize?
- C**linical Experience. Is this product supported by published, peer-reviewed research?
- C**ontents clearly indicated?
- L**abel Claims substantiated by scientific studies, not testimonials?
- A**dministration recommendations. Are they clear and easy to follow?
- I**dentification of lot provided?
- M**anufacturer Information listed on the label?

Source: Reference 34

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