

EDITORIALS



Nutritional Supplements for Knee Osteoarthritis — Still No Resolution

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Osteoarthritis is the most common form of arthritis, and when it affects the knee, as opposed to other joints, it is more apt to cause symptoms, including pain and stiffness, and functional limitation.¹ Treatment of symptomatic osteoarthritis of the knee is focused on controlling the pain, maintaining patients' functional independence, and improving their quality of life, in addition to preventing structural deterioration with the hope of delaying the need for total knee replacement. Published guidelines for the medical management of symptomatic osteoarthritis of the knee stress a multidisciplinary approach that includes nonpharmacologic measures (patient education, physical and occupational therapy, aerobic and muscle-strengthening exercises, weight control, and use of assistive devices) and pharmacologic agents (oral and topical analgesic agents, nonsteroidal antiinflammatory drugs [NSAIDs] including cyclooxygenase-2-selective inhibitors, and intraarticular therapies such as corticosteroids and hyaluronan preparations) as needed.²⁻⁶ Dietary and nutritional supplements, including glucosamine and chondroitin sulfate, are used frequently by patients and are increasingly recommended by practitioners.^{7,8}

Dietary supplements are regulated by the Food and Drug Administration (FDA) in a different manner from either over-the-counter or prescription drugs. As laid out in the Dietary Supplement Health and Education Act of 1994 (available at www.cfsan.fda.gov/~dms/supplmnt.html), the manufacturer is responsible for determining that the supplement is safe and that any representations or claims made about it are adequately substantiated. Dietary supplements do not need to be approved by the FDA before they are marketed.

In this issue of the *Journal*, Clegg and colleagues present the results of the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT), a randomized, placebo- and celecoxib-controlled trial of 1500 mg of glucosamine hydrochloride daily, 1200 mg of chondroitin sulfate daily, or the two in combination.⁹ The study was funded by the National Center for Complementary and Alternative Medicine and the National Institute of Arthritis and Musculoskeletal and Skin Diseases. The investigators obtained an investigational new drug application from the FDA and, working with the Veterans Affairs Cooperative Studies Program Pharmacy Coordinating Center, used glucosamine hydrochloride and chondroitin sulfate that were certified for purity, potency, and quality. The primary outcome, determined by expert consensus, was a 20 percent decrease in the summed score on the pain subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) from baseline to week 24.

The results failed to demonstrate a significant difference (as defined by a P value of 0.017 or less after the Bonferroni correction) in the percentage of patients who reached the primary outcome between any of the three supplement groups and the placebo group. The percentage of patients with a response in the celecoxib group did differ significantly from that in the placebo group, providing internal validity for the study. Numerous secondary outcomes were examined, including the response rate according to the criteria of the Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International, and these results were generally consistent with those for the primary outcome. Because there was an interaction between the severity of pain at baseline according to the

WOMAC pain score and the treatment effect in the combined-treatment group, the result in the overall group that received combination therapy must be interpreted with caution. Furthermore, the results for the patients in the combined-treatment group with moderate-to-severe pain at baseline (defined by a WOMAC pain score of 301 to 400) also need to be interpreted with caution, since celecoxib, the active control, had no significant effect in this subgroup. The study was limited by an attrition rate of at least 20 percent in the placebo group and each of the dietary-supplement groups, as well as a very high response rate in the placebo group. Furthermore, the analyses did not incorporate data from all time points (patients were evaluated at weeks 4, 8, 16, and 24) or use sophisticated methods for dealing with missing data (the last-observation-carried-forward method was used, rather than multiple imputation methods).¹⁰

How should physicians interpret and explain these results to their patients? The finding that glucosamine hydrochloride was not more efficacious than placebo is not surprising. Several systematic reviews and meta-analyses have examined the efficacy of glucosamine in the treatment of osteoarthritis of the knee.¹¹⁻¹³ In the most recent meta-analysis of eight randomized trials in which either glucosamine hydrochloride or glucosamine sulfate not manufactured by Rottapharm was compared with placebo, differences between the groups in the WOMAC scores did not reach significance.¹³ On the other hand, when the Rottapharm brand of glucosamine sulfate was compared with placebo in seven randomized trials and Lequesne's Disease Severity Index was used to assess outcomes, glucosamine sulfate was found to be significantly better at reducing pain and improving function. In the three studies that used WOMAC scores to assess outcomes, however, the differences between glucosamine sulfate and placebo were not significant. It is disappointing that the GAIT investigators did not use glucosamine sulfate, which is widely available as a dietary supplement in the United States, since the results would then have provided important information that might have explained in part the heterogeneity in the studies reviewed by Towheed and colleagues.¹³

The finding that chondroitin sulfate was not more efficacious than placebo is unexpected, given the opposite finding in meta-analyses of randomized, placebo-controlled trials.^{11,12,14} Howev-

er, in their recent randomized, placebo-controlled trial, Michel and colleagues also failed to demonstrate that two years of treatment with chondroitin sulfate reduced symptoms or improved function in patients with osteoarthritis of the knee.¹⁵ Hence, on the basis of the results of the two most recent studies, it is difficult to recommend the use of this agent alone for symptomatic osteoarthritis of the knee.

Two randomized, placebo-controlled trials showed that three years of treatment with glucosamine sulfate slowed radiologic progression of osteoarthritis of the knee (a structure-modifying effect)^{16,17}; chondroitin sulfate was also found to slow radiologic progression of osteoarthritis of the knee in a two-year, placebo-controlled trial.¹⁵ In Europe, both these compounds are considered to be slow-acting drugs for symptomatic osteoarthritis that also have a structure-modifying effect, in contrast to acetaminophen and NSAIDs, which have a rapid onset of action and no evidence of an effect on structure.¹⁸ Should glucosamine sulfate and chondroitin sulfate be given in conjunction with other treatments for symptomatic osteoarthritis of the knee because of their potential ability to modify the rate of structural deterioration, even if they have no effect on symptoms? More data to help answer this question may become available later this year when the GAIT group releases its findings on the structure-modifying effect of these agents.

On the basis of the results from GAIT, it seems prudent to tell our patients with symptomatic osteoarthritis of the knee that neither glucosamine hydrochloride nor chondroitin sulfate alone has been shown to be more efficacious than placebo for the treatment of knee pain. If patients choose to take dietary supplements to control their symptoms, they should be advised to take glucosamine sulfate rather than glucosamine hydrochloride and, for those with severe pain, that taking chondroitin sulfate with glucosamine sulfate may have an additive effect. Three months of treatment is a sufficient period for the evaluation of efficacy; if there is no clinically significant decrease in symptoms by this time, the supplements should be discontinued. Furthermore, there is no evidence that these agents prevent osteoarthritis in healthy persons or in persons with knee pain but normal radiographs.

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The Long and the Short of Bone Therapy

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In 2004, the Surgeon General's report on bone health highlighted osteoporosis as an important and growing national medical problem.¹ The authors of this report recognized that identification and treatment of this condition in women and men alike has lagged behind the increasing availability of instruments with which to detect low bone mass and the advancing pharmacologic approaches for prevention and therapy.

Lack of compliance with approved drug regimens can hinder progress in the treatment of osteoporosis.² In this issue of the *Journal*, from a study that was sponsored, designed, and analyzed by Amgen, McClung et al.³ report on the safety and efficacy of various doses of denosumab (formerly known as AMG 162), a humanized monoclonal antibody to the receptor activator of nuclear factor- κ B (RANK) ligand (RANKL). The antibody was administered subcutaneously either every three months or every six months for one year

to a relatively small number of postmenopausal women selected because they had low bone mineral density on the basis of dual-energy x-ray absorptiometry results.

RANKL, a member of the tumor necrosis factor superfamily of ligands and receptors, is essential for the differentiation, activation, and survival of bone-resorbing osteoclasts.⁴ It is expressed on the surface of marrow stromal cells, activated T cells, and precursors of bone-forming osteoblasts (Fig. 1).⁴ RANKL accelerates osteoclastogenesis when it binds to its receptor, RANK, on osteoclast precursor cells to enhance nuclear factor- κ B and other signaling pathways.⁴ Osteoprotegerin that is produced by osteoblasts, the key modulator of RANKL, acts as a soluble decoy receptor for RANKL and blocks its effects.⁴ McClung et al. report that denosumab, mimicking the function of osteoprotegerin, caused especially rapid, potent, dose-dependent decreases in biochemical