Glucosamine and Chondroitin Fail to Improve Knee Pain Caused by Osteoarthritis

Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006;354:795–808.

Study Overview

Objective. To evaluate the efficacy and safety of glucosamine hydrochloride and chondroitin sulfate, alone and in combination, as a treatment for knee pain from osteoarthritis (OA).

Design. Randomized, double-blind, placebo- and celecoxib-controlled trial.

Setting and participants. 1583 patients aged ≥ 40 years with radiographic and clinical evidence of knee OA. Patients were included if they had knee pain (defined as a pain score of 125 to 400 on the symptomatic knee according to the Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]) for at least 6 months and were in American Rheumatism Association functional class I, II, or III. Patients were randomized to 500 mg glucosamine hydrochloride 3 times daily, 400 mg chondroitin sulfate 3 times daily, 500 mg glucosamine and 400 mg chondroitin 3 times daily, 200 mg celecoxib daily, or placebo. Patients were allowed 4000 mg acetaminophen daily for pain relief.

Main outcome measures. Primary outcome measure was a 20% decrease in the summed score for the WOMAC pain subscale from baseline to week 24. Secondary outcome measures included scores for joint stiffness, joint function, and health-related quality of life; patient's and investigator's global assessments of disease status and response to therapy; the presence or absence of soft-tissue swelling, effusion, or both in the index knee; and acetaminophen use.

Main results. Glucosamine and chondroitin, either alone or in combination, were not significantly better than placebo in reducing knee pain by 20%. Compared with the placebo response rate (60.1%), the glucosamine response rate was 64% ($P = 0.30$), the chondroitin response rate was 65.4% ($P = 0.17$), combination therapy response rate was 66.6% ($P = 0.09$), and the celecoxib control group response rate was 70.1% ($P = 0.008$). In a secondary analysis of the primary outcome in patients with moderate-to-severe pain at baseline, the response rate was significantly higher with combination therapy compared with placebo (79.2% versus 54.3%; $P = 0.002$). Mild and infrequent adverse events were evenly distributed among groups.

Conclusion. Glucosamine hydrochloride and chondroitin sulfate, either alone or in combination, did not effectively reduce knee pain from OA. Combination therapy may be effective, however, in patients with moderate-to-severe knee pain.

Commentary

As the U.S. population ages, the prevalence of OA is expected to increase; by 2030, it is estimated that 25% of adults will have doctor-diagnosed OA, with two thirds of those diagnosed being women [1]. In 2004, Americans spent nearly $730 million on the dietary supplements glucosamine and chondroitin for improvement of OA symptoms. A recent meta-analysis evaluating the effectiveness of these dietary supplements suggested a possible benefit but raised concerns about the scientific rigor of previous studies [2]. Thus, Clegg and colleagues conducted this trial to evaluate the efficacy and safety of glucosamine hydrochloride and chondroitin sulfate under a U.S. Food and Drug Administration investigational new drug application, which certifies the purity, potency, and quality of these supplements, subject to pharmaceutical regulations. Of note, glucosamine is more widely available in the United States as glucosamine sulfate, which was not tested in this study.

When compared with placebo, glucosamine, chondroitin, and combination therapy all failed to demonstrate a significant difference in the primary outcome (ie, decreased knee pain). The only secondary outcome that reached significance was a decrease in joint swelling, effusion, or both with chondroitin monotherapy ($P = 0.01$). When stratified by severity of disease, the differences between combination therapy and placebo for those with more severe baseline pain became significant not only for the primary outcome but also for many secondary outcomes. Limitations of the study, which may explain why results on subgroup analysis were significant but not overall response rates, include the fairly high response rate to placebo (60.1%) and the inclusion of patients with mild pain and disease at baseline. In addition, the inclusion of patients with mild to moderate pain at baseline may also explain the smaller than usual effect size of the cele-

coxib control group in this study. Lastly, the study does not address the ongoing question of whether glucosamine and chondroitin may slow progression of OA via structural effects on joint space narrowing [3].

Applications for Clinical Practice

Physicians should inform patients with symptomatic knee OA that taking chondroitin sulfate and/or glucosamine hydrochloride is not better than placebo. Whether combination therapy might be efficacious in patient with more advanced disease remains to be proven by further studies.

–Review by Mark S. Horng, MD

References

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3. Richy F, Bruyere O, Ethgen O, et al. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. Arch Intern Med 2003;163:1514–22.