CME CREDIT

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# Glucosamine in osteoarthritis: Questions remain

## ABSTRACT

Glucosamine is now widely used in the hope that it will relieve symptoms of osteoarthritis and stop its progression, yet studies have so far failed to prove convincingly that it works, how it might work, or whether it is safe to take long-term. This is an overview of the evidence to date for currently available glucosamine preparations, as well as for glucosamine used in combination with another popular nutraceutical, chondroitin sulfate.

## KEY POINTS

Claims that glucosamine modifies osteoarthritis rest primarily on animal studies showing decreased cartilage erosion and on two European trials in humans.

Studying the modifying effects of glucosamine on osteoarthritis will require years of observation, as the disease tends to progress very slowly, progression is not necessarily linear, and an agent that has disease-modifying or structure-modifying properties may have little or no immediate effect on symptoms.

To better assess for potential disease-modifying effects of glucosamine on osteoarthritis, most researchers now use radiography of the knee in a semi-flexed position with fluoroscopic positioning rather than imaging the knee fully extended with the patient standing.

Because most studies of glucosamine have been short (approximately 3 months) and have involved only small numbers of patients, the long-term safety of this nutraceutical is still not known.

*The author has indicated that he has received honoraria from Abbott and Wyeth corporations.

FROM ANCIENT TIMES, MAN has treated maladies using substances that occur in nature, and osteoarthritis (OA) has been particularly fertile ground for so-called natural remedies.

Glucosamine is a naturally occurring substance now sold in pill form and widely used by patients with OA, either on their own or on the recommendation of their physician. But what do we really know about the effects of this much-touted nutraceutical on OA?

Glucosamine is one of the most thoroughly studied nutraceuticals, and yet the studies have not answered key questions: eg, Does it work? How does it work? Is it safe for long-term use? Given the popularity of glucosamine, claims made in the mass media, and the number of clinical trials devoted to it, clinicians need to be familiar with the latest information—such as it is—so as to be ready to discuss it with their patients and help them make well-informed treatment decisions.

Let's examine the clinical evidence for the symptom-relieving efficacy of current glucosamine preparations, as well as the challenges of studying disease modification in OA.

## WHAT IS GLUCOSAMINE?

Glucosamine is an amino monosaccharide composed of glucose with a bound amino group. It is present in several tissues, including cartilage. Several molecules within the joint incorporate the glucosamine molecule into their structure, including the glycosaminoglycans (GAGs) heparan sulfate, keratan sulfate, and hyaluronan. Urinary excretion of glucosamine is elevated in both OA and rheumatoid arthritis.[1]

### Sulfate vs hydrochloride formulations

Most clinical trials of glucosamine supplementation in treating OA have used glucosamine sulfate because it is well absorbed from the gastrointestinal tract in its crystalline form, with linear pharmacokinetics reported at doses between 750 and 1,500 mg/day.[2] Its elimination half-life has been estimated at 15 hours. However, many of the products sold in the United States contain glucosamine hydrochloride, a compound about which there is considerably less information. As with other nutraceuticals, there is a problem with the lack of standardization in the actual amounts of active ingredient in commercially available products, which in the case of glucosamine may vary from 53% to over 100% of the amount stated on the package label.[3]

### Proposed mechanisms of action

The mechanism of action of glucosamine sulfate in OA is uncertain. Some in vitro experiments have shown stimulation of the synthesis of cartilage GAGs and proteoglycans.[4,5] Enhanced synovial production of hyaluronic acid has been proposed as a mechanism in one study.[6] Glucosamine has been reported to double steady-state levels of aggrecan mRNA[7] and also to inhibit aggrecanase activity induced by interleukin 1.[8] Other research has shown that, in normal human articular chondrocytes, glucosamine and *N*-acetylglucosamine inhibit nitric oxide production induced by interleukin 1β (IL-1β) and tumor necrosis factor-alpha.[9] *N*-Acetylglucosamine also suppressed production of IL-6 and cyclooxygenase-2 stimulated by IL-1β.[9]

**The mechanism of action of glucosamine sulfate is still unknown**

## DOES GLUCOSAMINE RELIEVE SYMPTOMS OF OA?

### Standard measures of symptom improvement

The two main measures of symptomatic relief in glucosamine trials have been the Lequesne Index and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and both have been validated in OA trials.

The Lequesne Index is a questionnaire dealing with measurement of pain (five questions), walking distance (one question), and activities of daily living (four questions). The scores for each question are added into a combined pain-severity score.[10] The WOMAC is a self-administered questionnaire with 24 questions in the areas of pain, disability, and joint stiffness. The questions can be answered using either a five-point scale or a 100-mm visual analog scale of severity.

### Attempts to test improvement in symptoms

Several human studies and a meta-analysis have tested for improvement in symptoms of OA using oral and intramuscular forms of glucosamine sulfate:

**Reichelt et al**[11] found that intramuscular glucosamine sulfate 400 mg twice weekly for 6 weeks reduced the severity of pain as measured by the Lequesne Index when contrasted with placebo.

**Muller-Fassbender et al**[12] compared oral glucosamine sulfate 1,500 mg/day with moderate doses of ibuprofen (1,200 mg/day) for OA of the knee in a 4-week randomized, double-blind, parallel-group study. Pain reduction was more rapid with ibuprofen. However, at 4 weeks there was no significant difference in pain relief between the study groups. No group received high-dose ibuprofen (> 1,200 mg/day).[12] This study did not include a placebo group.

**Qiu et al**[13] performed a double-blind study of 178 patients with OA of the knee, comparing oral glucosamine sulfate 1,500 mg/day with ibuprofen 1,200 mg/day for 4 weeks. At the end of the study, a trend favored glucosamine in the reduction of knee pain. Adverse events were reported in 6% of patients in the glucosamine group and in 16% of patients in the ibuprofen group. No patients in the glucosamine group dropped out because of drug-related effects, as compared with 10% of the ibuprofen group. This study did not include a placebo group.

**A meta-analysis**[14] of trials published before the year 2000 found evidence of a moderate to large therapeutic effect, but quality issues and possible publication bias suggest that these effects may have been exaggerated.

**An industry-sponsored European trial**, Glucosamine Unum in Die Efficacy (GUIDE),[15] compared glucosamine sulfate with acetaminophen and placebo in 318 patients with knee OA. Study patients were

randomized to receive glucosamine sulfate soluble powder 1,500 mg once a day, acetaminophen 1,000 mg three times a day, or placebo for 6 months. The main efficacy measure was the 6-month change in the Lequesne Index. At 6 months, the glucosamine group achieved significantly better scores compared with the placebo group. Those taking acetaminophen failed to achieve a statistically significant benefit compared with placebo by either the Lequesne Index or WOMAC. There was no difference between the glucosamine, acetaminophen, and placebo groups in terms of safety.[15] It should be noted that the form of glucosamine used in this trial—glucosamine sulfate—is not comparable to the form of glucosamine most often used in the United States.

### Recent trials cast doubts

Over the past 3 years, trials and meta-analyses have cast doubt on early findings regarding the efficacy of glucosamine in OA.

**Hughes and Carr**[16] randomized 80 patients with knee OA to receive either glucosamine sulfate 1,500 mg/day or placebo for 6 months. No difference between glucosamine and placebo was noted in the primary variable of patients' global assessment of pain in the affected knee.

**McAlindon et al**[17] used a unique Internet-based recruiting system and followed 205 patients with knee OA randomized to receive glucosamine sulfate 1,500 mg/day or placebo for 12 weeks. The primary end point was the pain subscale of the WOMAC. At study conclusion, no difference was noted in the groups with regard to pain, physical function, or overall WOMAC scores. Stratification by severity of OA, glucosamine product used, or the use of nonsteroidal anti-inflammatory drugs (NSAIDs) did not alter the results.

**A Cochrane review** of glucosamine therapy in OA[18] analyzed a pool of 20 studies and 2,570 patients. Pain and function were seen to improve by 28% and 21%, respectively, by the Lequesne Index compared with placebo. No improvement was seen in the overall WOMAC pain and function scales. Some have speculated that these inconsistent study results are due to a lack of standardization in glucosamine preparations.

**A recent discontinuation trial**[19] has added to the uncertainty about glucosamine's efficacy, finding that 137 patients clinically classified as moderate responders to glucosamine sulfate were no less likely to experience an OA flare if they continued or discontinued the glucosamine. No statistically significant differences between the groups were noted in pain and WOMAC function scores after 6 months.[19]

## PRINCIPLES OF DISEASE MODIFICATION IN OA

According to one estimate,[20] OA significantly disables 10% to 30% of those affected by it, making it the leading cause of chronic disability in the United States. The occurrence and progression of OA were long regarded as inevitable, but these perceptions are changing as the study of disease-modifying and structure-modifying therapies evolves. Successful intervention and disease modification would have significant personal and societal impact.

As pain is the most common symptom in OA, the traditional medical treatment for OA has focused on pain management,[21] and medical societies such as the American College of Rheumatology have published recommendations for symptomatic management.[22] To date, disease-modifying interventions have been limited to using exercise and weight loss to reduce risk factors such as obesity, repetitive stress, or joint trauma. Research into pharmacologic disease modification in OA has included relatively straightforward approaches such as antibiotics, hyaluronate, and polysaccharides, and more complex therapies such as manipulation of growth factors and cytokines, stem-cell grafting, and genetic manipulation.[23] These so-called chondroprotective therapies were originally intended to preserve cartilage from the arthritic process, but their potential role may now extend to preventing, retarding, stabilizing, or reversing the development of the disease itself, not just protecting cartilage.

**Is OA really inevitable? This perception is changing**

## CHALLENGES TO TESTING DRUG EFFECTIVENESS IN OA

Proving an agent has disease-modifying or structure-modifying properties may involve

years of observation, because OA progresses slowly: for example, OA of the knee may progress at a rate of 0.1 mm/year[24] in joint-space width, which is difficult to measure radiographically. In addition, progression doesn't necessarily occur in linear fashion throughout the natural history of the disease. Adding to the difficulties in finding and investigating these compounds, an agent that has disease-modifying or structure-modifying properties may have little or no immediate effect on symptoms, and we have no direct way to examine the progression of disease.

### Markers of modification

Hence, clinical trials for these drugs are challenging. Surrogate markers are often used to measure disease modification or structural modification. At present, the most commonly used is the joint-space width assessed via fluoroscopically positioned anteroposterior radiography of the semi-flexed knee.[25] Also under study are surface imaging or cartilage volume determination by magnetic resonance imaging (MRI), arthroscopic scores, and serum biomarkers.[26,27]

US and European guidelines for the design of trials to establish the efficacy of disease-modifying drugs for OA stipulate that trials must demonstrate both modulation of joint-space narrowing and clinical efficacy.[28] Therefore, assessments of structural progression (ie, joint-space width) must also include measurement of pain, stiffness, and function.

**Glucosamine studies now use semi-flexed, not standing-extended knee imaging**

Radiography of the semi-flexed knee with fluoroscopic positioning is now preferred to radiography of the standing, fully extended knee,[29] for reasons to be discussed later.

## ARE CLAIMS OF DISEASE MODIFICATION JUSTIFIED?

Claims that glucosamine modifies OA rest primarily on animal studies showing decreased cartilage erosion[30] and on two European trials in humans. In one European trial,[31] 212 patients with OA of the knee were randomized to receive placebo or glucosamine sulfate 1,500 mg/day and were followed prospectively for 3 years. Anteroposterior radiography of each knee fully extended and bearing weight was performed at enrollment, at 1 year, and at 3 years. At 3 years, the treatment group had a joint-space reduction of .06 mm while the placebo group had a reduction of .31 mm. Whether this is a clinically meaningful difference in joint space is unclear. Patients taking glucosamine also showed symptomatic improvement by WOMAC of 20% to 25%, while those on placebo had a slight worsening of symptoms, as judged by WOMAC. No significant adverse events were attributed to the use of glucosamine sulfate.

A second trial randomized 202 patients to receive placebo or glucosamine sulfate 1,500 mg/day for 3 years.[32] The width of the narrowest medial joint space of the tibiofemoral joint was measured serially, using visual assessments with a 0.1-mm graduated magnifying glass on anteroposterior radiographs of each knee fully extended and bearing weight. At 3 years, a significant difference in joint-space width was noted in the glucosamine group, with a 0.19-mm decrease in joint space in the placebo group and a 0.04-mm increase in joint space in the glucosamine sulfate group. Patients receiving glucosamine also had significantly greater improvements in the WOMAC score and the Lequesne Index in the glucosamine group.

### Radiography of semi-flexed knee may be preferable

The favorable results of these studies in terms of disease modification have been questioned because of the radiographic technique they used to assess joint space, ie, with the knee fully extended and bearing weight. At issue is whether the joint-space width seen on radiographs of the knee fully extended while standing could be significantly affected by knee pain and whether radiography of the semi-flexed knee would be preferable in these studies.

In a study by Mazzuca et al,[33] 19 patients with painful knee OA underwent baseline radiography after a "washout" period during which analgesics and NSAIDs were withheld. Each patient underwent both standing-extended and semi-flexed fluoroscopically positioned radiography. Analgesic or NSAID treatment was then reinstated, and radiography was repeated 2 to 8 weeks later. Knee pain was rated using the five-point Likert scale, an assessment of the impact of disease on quality of life. The authors found that changes in

joint pain in these patients produced significant changes in joint-space width on the standing-extended view, whereas changes in joint pain produced no significant changes in joint-space width on radiographs of the semi-flexed knee.

This suggests an effect of therapy on pain rather than a disease-modifying effect, and past studies that used the standing-extended technique may need to be redone with the semi-flexed position. Most trials have now adopted the semi-flexed fluoroscopically positioned technique for assessing potential disease modification.

### Glucosamine plus chondroitin, other combinations

One double-blind, placebo-controlled, crossover trial evaluated the combination of glucosamine HCl, the form of glucosamine used most often in the United States, 1,500 mg/day, chondroitin sulfate 1,200 mg/day, and manganese ascorbate 228 mg/day in a 16-week trial in men with pain and radiographic knee OA or low-back pain believed to be related to OA.[34] Patients with knee OA had improvement based on a visual analog scale for pain, patient self-assessment of treatment effect, and a summary disease score (pain questionnaire, functional questionnaire, physical examination score, and running time). No benefit was reported in patients with spinal OA.

Another small, placebo-controlled trial randomized patients with knee OA to a regimen of glucosamine HCl 1,000 mg, chondroitin sulfate 800 mg, and manganese ascorbate 152 mg twice a day, or placebo.[35] Patients were evaluated at baseline and then every 2 months for 6 months using the Lequesne Index of pain severity. At 4 and 6 months, those with radiographically mild to moderate knee OA showed significant improvement by the Lequesne Index when compared with those on placebo. Those with severe radiographic OA of the knee had no significant symptomatic benefit. The study did not evaluate for disease modification or structure modification.

The Glucosamine/chondroitin Arthritis Intervention trial (GAIT),[36] sponsored by the National Institutes of Health, randomized 1,583 patients with OA of the knee to receive one of five treatments: glucosamine HCl 1,500 mg/day; chondroitin sulfate 1,200 mg/day; glucosamine HCl plus chondroitin sulfate; celecoxib 200 mg/day; or placebo. The primary end point was the percentage of patients achieving at least 20% improvement on the WOMAC pain subscale at 6 months. The only statistically significant response compared with placebo occurred in those on celecoxib (70.1% vs 60.1%, $P = 0.008$). Patients were then stratified by baseline severity according to their WOMAC pain score, most of them falling into the category of mild OA pain. In a subgroup analysis, in those with moderate to severe OA pain (WOMAC Pain 301–400 mm), the combination of glucosamine HCl and chondroitin sulfate was more efficacious than placebo as measured by a dichotomous response rate (positive = 50% improvement in pain) of 79.2% vs 54.3% for placebo ($P = .002$).

From these results, it appears that patient selection may be important in maximizing any potential benefit from therapy with combined glucosamine-chondroitin therapy. The study also had a particularly high placebo response rate, which may have been due to the enrollment of patients with less symptomatic OA.

### Glucosamine HCl vs glucosamine sulfate

In addition, the GAIT study used glucosamine HCl instead of glucosamine sulfate,[36] the form used in most other studies, particularly those that have shown efficacy. This raises the question of whether the choice of glucosamine HCl negatively affected efficacy in the trial. However, a small Chinese trial (142 patients) randomized patients with knee OA to glucosamine sulfate 1,500 mg/day or to glucosamine HCl 1,440 mg/day for 1 month[37] and found no differences in efficacy, while a clear majority of patients achieved symptomatic improvement by Lequesne scores in each group. The study had no placebo group. Safety assessments continued for 2 additional weeks with no significant adverse events reported.

**Results with glucosamine sulfate may not apply to glucosamine HCl**

## KEY ISSUES UNRESOLVED

As we have seen, the clinical trials to date have left key issues about glucosamine in OA unresolved.

- The studies that have more clearly shown efficacy have used glucosamine sulfate as a single agent, and we still do not know if it is correct to expect the same results with the hydrochloride form, which is widely available in the United States.
- Recent trials cast doubt on whether glucosamine sulfate is effective at all in knee OA.
- Currently, we have no significant clinical evidence to recommend the use of the combination of glucosamine (sulfate or hydrochloride) and chondroitin sulfate over glucosamine alone.
- The results of GAIT[36] suggest that subgroups of patients with OA may derive benefit from glucosamine while others may not, highlighting the potential importance of patient selection in the use of glucosamine.
- In the numerous clinical trials of glucosamine published over the past decade, no major adverse effects have emerged, yet we must keep in mind that the number of patients followed for longer than 3 months is exceedingly small, so long-term safety remains to be proven.

The treatment of OA will be increasingly important given the aging of the population in the United States and other Western countries. It is hoped that research on the appropriate use of not only glucosamine, but also other nutraceuticals and natural remedies, will yield important insights that will lead to enhancing our management of OA.

## REFERENCES


1. **Krajickova J, Macek J.** Urinary proteoglycan degradation product excretion in patients with rheumatoid arthritis and osteoarthritis. Ann Rheum Dis 1988; 47:468–471.
2. **Persiani S, Roda E, Rovati LC, Locatelli M, Giacovelli G, Roda A.** Glucosamine oral bioavailability and plasma pharmacokinetics after increasing doses of crystalline glucosamine sulfate in man. Osteoarthritis Cartilage 2005; 13:1041–1049.
3. **Towheed TE.** Current status of glucosamine therapy in osteoarthritis. Arthritis Rheum 2003; 49:601–604.
4. **Karzel K, Domenjoz R.** Effects of hexosamine derivatives and uronic acid derivatives on glycosaminoglycane metabolism of fibroblast cultures. Pharmacology 1971; 5:337–345.
5. **Bassleer C, Reginster JY, Franchimont P.** Effects of glucosamine on differentiated human chondrocytes cultivated in clusters [abstract]. Rev Esp Reumatol 1993; 20(suppl 1):Mo 96.
6. **McCarty MF.** Enhanced synovial production of hyaluronic acid may explain rapid clinical response to high-dose glucosamine in osteoarthritis. Med Hypotheses 1998; 50:507–510.
7. **Jimenez SA, Dodge GR.** The effects of glucosamine sulfate on human chondrocyte gene expression. Abstract presented at XVIIIth meeting of the International League of Associations of Rheumatology, Singapore, June 1997.
8. **Sandy JD, Boyer H, Hymer SS, et al.** Control of chondrocyte aggrecanase by glutamine supply. Transactions of the 44th annual meeting of the Orthopedic Research Society, New Orleans, 1998; Abstract no. 853.
9. **Shikhman AR, Kuhn K, Alaaeddine N, Lotz M.** N-Acetylglucosamine prevents IL-1 beta-mediated activation of human chondrocytes. J Immunol 2001; 166:5155–5160.
10. **Lequesne M, Mery C, Samson M, Gerard P.** Indexes of severity for osteoarthritis of the hip and knee. Validation—value in comparison with other assessment tests. Scand J Rheumatol Suppl 1987; 65:85–89.
11. **Reichelt A, Forster KK, Fischer M, Rovati LC, Setnikar I.** Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee. A randomised, placebo-controlled, double-blind study. Arzneimittelforschung 1994; 44:75–80.
12. **Muller-Fassbender H, Bach GL, Haase W, Rovati LC, Setnikar I.** Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. Osteoarthritis Cartilage 1994; 2:61–69.
13. **Qiu GX, Gao SN, Giacovelli G, Rovati L, Setnikar I.** Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. Arzneimittelforschung 1998; 48:469–474.
14. **McAlindon TE, LaValley MP, Gulin JP, Felson DT.** Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. JAMA 2000; 283:1469–1475.
15. **Herrero-Beaumont G, Roman JA, Trabado MC, et al.** Effects of glucosamine sulfate on 6-month control of knee osteoarthritis symptoms vs placebo and acetaminophen: results from the Glucosamine Unum in Die Efficacy (GUIDE) trial. Arthritis Rheum 2005; 52 (suppl):S460 (Abstract 1203).
16. **Hughes R, Carr A.** A randomized, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. Rheumatology (Oxford) 2002; 41:279–284.
17. **McAlindon T, Formica M, LaValley M, Lehmer M, Kabbara K.** Effectiveness of glucosamine for symptoms of knee osteoarthritis: results from an internet-based randomized double-blind controlled trial. Am J Med 2004; 117:643–649.
18. **Towheed TE, Maxwell L, Anastassiades TP, et al.** Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev 2005; (2):CD002946.
19. **Cibere J, Kopec JA, Thorne A, et al.** Randomized, double-blind, placebo-controlled glucosamine discontinuation trial in knee osteoarthritis. Arthritis Rheum 2004; 51:738–745.
20. **Peyron JG, Altman RD.** The epidemiology of osteoarthritis. In: Moskowitx RW, Howell DS, Goldberg M, Mankin HI, editors. Osteoarthritis, Diagnosis, and Medical/surgical Management. 2nd ed. Philadelphia: WB Saunders, 1992:15–37.
21. **Lozada CJ, Altman RD.** Osteoarthritis: a comprehensive approach to management. J Musculoskeletal Med 1997; 14:26–38.
22. **American College of Rheumatology Subcommittee on Osteoarthritis Guidelines.** Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000; 43:1905–1915.
23. **Lozada CJ, Altman RD.** Management of osteoarthritis. In: Koopman WJ, editor. Arthritis and Allied Conditions: A Textbook of Rheumatology. 13th ed. Baltimore: Williams & Wilkins, 1997:2013–2025.
24. **Altman RD.** Measurement of structure (disease) modification in osteoarthritis. Osteoarthritis Cartilage 2004; 12(suppl A):S69–S76.
25. **Brandt KD, Mazzuca SA.** Lessons learned from nine clinical trials of disease-modifying osteoarthritis drugs. Arthritis Rheum 2005; 52:3349–3359.
26. **Lozada CJ, Altman RD.** Chondroprotection in osteoarthritis. Bull Rheum Dis 1997; 46:5–7.
27. **Kraus VB.** Biomarkers in osteoarthritis. Curr Opin Rheumatol 2005; 17:641–646.
28. **Abadie E, Ethgen D, Avouac B, et al; Group for the Respect of Excellence and Ethics in Science.** Recommendations for the use of new methods to assess the efficacy of disease-modifying agents in the treatment of osteoarthritis. Osteoarthritis Cartilage 2004;

12:263–268.
20. **Mazzuca SA, Brandt KD, Lane KA, Katz BP.** Knee pain reduces joint space width in conventional standing anteroposterior radiographs of osteoarthritic knees. Arthritis Rheum 2002; 46:1223–1227.
30. **Mathieu M, Piperno S, Annefeld M, Vignon RE.** Glucosamine sulfate significantly reduced cartilage destruction in a rabbit model of osteoarthritis. Arthritis Rheum 1998; 41(suppl):S147 (Abstract no. 689).
31. **Reginster JY, Deroisy R, Rovati LC, et al.** Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001; 357:251–256.
32. **Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC.** Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 2002; 162:2113–2123.
33. **Mazzuca SA, Brandt KD, Surber J.** Reduction of severe joint pain increases joint space width (JSW) in standing extended-view X-rays of patients with knee osteoarthritis (OA). Arthritis Rheum 2001; 44:S155 (Abstract no. 614).
34. **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: a randomized, double-blind, placebo-controlled pilot study. Mil Med 1999; 164:85–91.
35. **Das A Jr, Hammad TA.** Efficacy of a combination of FCHG49 glucosamine hydrochloride, TRH122 low molecular weight sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis. Osteoarthritis Cartilage 2000; 8:343–350.
36. **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.
37. **Qiu GX, Weng XS, Zhang K, et al.** [A multi-center, randomized, controlled clinical trial of glucosamine hydrochloride/sulfate in the treatment of knee osteoarthritis.] Zhongua Yi Xue Za Zhi 2005; 85:3067–3070.

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