# The Utility of Nutraceuticals in the Treatment of Osteoarthritis

*Tracy M. Frech, MD, and Daniel O. Clegg, MD*

**Corresponding author**
Daniel O. Clegg, MD
Division of Rheumatology, University of Utah School of Medicine, George E. Wahlen Veterans Affairs Medical Center, 4B200 School of Medicine, 50 North Medical Drive, Salt Lake, UT 84132, USA.
E-mail: daniel.clegg@hsc.utah.edu

**Current Rheumatology Reports** 2007, **9:**25–30
Current Medicine Group LLC ISSN 1523-3774


Osteoarthritis (OA) treatment is limited by the inability of prescribed medications to alter disease outcome. As a result, patients with OA often take food substances called nutraceuticals in an attempt to affect the structural changes that occur within a degenerating joint. The role of nutraceuticals in OA management can be defined only by an evidence-based approach to support their use. This paper reviews the clinical trials studying glucosamine, chondroitin sulfate, vitamin C, vitamin E, and avocado-soybean unsaponifiables. It highlights the need for additional randomized, placebo-controlled trials to further define the utility of nutraceuticals in OA treatment.

## Introduction

Osteoarthritis (OA) is the most common arthropathy in the United States, affecting approximately 15% of the population overall, 50% of those aged 65 years and older, and 85% of those 75 years and older [1]. It is a multifactorial disorder associated with considerable disability. As such, it is already the leading cause of functional disability, and its prevalence is projected to double by the year 2020, due in part to increases in obesity and longevity [1,2••].

The public health significance of OA is additionally underscored when considering the economic costs associated with time lost from work and early retirement [3]. The total annual cost of OA has been estimated to be $5700 per patient, and the cost of OA and associated conditions nationwide is estimated to be $86.2 billion per year [2••]. Nutraceuticals, which are included in this cost estimation, are food substances ingested with the aim to provide or stimulate production of needed components of articular cartilage. These supplements are promoted to maintain cartilage health by slowing cartilage damage in people with OA. In 2004, the estimated sales of these substances approached $730 million [2••]. Several different substances have very limited experimental data to support their use. Thus, many micronutrients and essential fatty acids studied in OA are beyond the scope of this paper. Instead, this article reviews the popular substances for which there exists considerable clinical data, including glucosamine, chondroitin sulfate, vitamin C, vitamin E, and avocado-soybean unsaponifiables (ASU).

## Pathogenesis of Osteoarthritis and Rationale for Nutraceutical Use

The American College of Rheumatology recognizes OA as a heterogeneous group of conditions characterized by progressive deterioration of articular cartilage, which results in debilitating pain and loss of normal joint motion [4]. OA most commonly affects the spine, hands, hips, and knees. Risk factors for the development of knee OA include mechanical stress, joint injury, age, gender, obesity, and genetic predisposition. The specifics of pathophysiology remain obscure; however, both biomechanical forces and biochemical processes are important in its pathogenesis, which ultimately affects hyaline cartilage, synovium, subchondral bone, and periarticular structures. The disruption of the delicate balance of anabolic and catabolic processes within these structures results in the progressive degradation of articular cartilage, bony sclerosis, osteophyte formation, subchondral bone collapse, and variable amounts of synovitis [5,6].

Articular cartilage is composed of type II collagen, hydrated glycoaminoglycans bound to large proteins (proteoglycans), and additional extracellular matrix components (ECM) such as laminin and fibronectin, which interact with chondrocytes. Alteration of chondrocyte–ECM interaction by proteolytic enzymatic activation and cytokine production by the synovium and chondrocytes lead to the pathologic lesion of OA. Focuses of future therapeutics include maintenance of the proper extracellular matrix and chondrocyte environment, as well as prevention of excessive proteolytic enzyme activation and expression of cytokine profiles [6]. Some believe that nutraceuticals have a role in rectifying the nutritional imbalance to which chondrocytes are susceptible, thus helping maintain its proper interaction with the ECM [7•].

The ability to modulate proteolytic enzyme activation and cytokine profiles by sustenance of the chondrocyte–ECM interaction is proposed but as yet unproven in vivo.

This imbalance between anabolism and catabolism can be amplified in the presence of inflammation. This is evident by the hastened appearance of OA in a joint that is inflamed due to trauma, though it is recognized that variable amounts of synovitis may characterize any osteoarthritic joint. Prostaglandins and leukotrienes have been shown to regulate proinflammatory cytokine and interstitial collagenase synthesis in human OA synovial membrane explants [8]. The inconsistent response of prostaglandin production to nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase enzyme 2 inhibitors may be secondary to the variable level of inflammation present within an osteoarthritic joint.

Part of the inflammatory reaction within a joint is mediated by reactive oxygen products [9]. Hyaluronic acid has been projected as having an antioxidant function [10]. However, there is a paucity of antioxidant enzymes within a joint. Thus, the importance of additional micronutrient antioxidants such as ascorbate (vitamin C) and ÿ-tocopherol (vitamin E) are proposed as additional possible modulators of possible oxidative damage to chondrocytes.

The influence of nutrition on the anabolic and catabolic processes involved in OA development has not been established. Part of the challenge of determining the effect of nutraceuticals is that the U.S. Food and Drug Administration does not require efficacy data for food substances applied for health benefit, complicating the proper incorporation of these substances into the current therapeutic approach and attesting to the importance of performing clinical trials of these substances.

## Current Therapeutic Approach

The current therapeutic approach to OA is to alleviate symptoms and preserve function, as disease modification has yet to be demonstrated. It is beneficial to attain and maintain an ideal body weight, but there is no data to support that this is the trend in adult Americans. Nonpharmacologic management of OA consists of patient education, self-management programs, aerobic exercise, muscle conditioning, physical and occupational therapy, bracing, patellar taping, assist devices, and joint protection programs. Surgical therapies, including osteotomy, arthrodesis, arthroplasty, and arthroscopy are considered for refractory symptoms and/or progressive disability [11].

Pharmacologic treatment of osteoarthritis is empiric and not entirely successful at controlling joint pain and preserving function. Acetaminophen in doses to 4000 mg/day is recommended as first-line therapy followed by NSAIDs first as a low dose, 1.2 g/day, and then titrated up to high dose, 2.4 g/day, if the patient remains symptomatic [12]. These agents have limited efficacy and are associated with a number of potentially serious toxicities including renal insufficiency and gastrointestinal bleeding. The attendant gastrointestinal risks of NSAIDs led to the development of more cyclooxygenase-2 selective agents. However, despite some improvement in gastrointestinal safety, no increased efficacy has been observed, and additional safety concerns have surfaced (ie, an increase in the incidence of ischemic cardiovascular events). Opioids, topical analgesics, and intra-articular steroids are other pharmacologic treatment options for OA patients [12]. Nutraceuticals have been proposed to supplement the required substrate for the repair of cartilage and connective tissues needed for maintenance of optimal cellular [7•]. Investigators are currently defining the role of nutraceuticals as well as the regular provision of vitamins, essential fatty acids, and mineral cofactors for treatment and prevention OA.

## Glucosamine and Chondroitin Sulfate

Glucosamine and chondroitin sulfate (CS) alone and in combination with each other are proposed as effective agents for the treatment of pain and possibly disease modification. In Europe, these agents are accepted treatment for OA [13]. As will be reviewed in detail later, clinical studies of these agents have yielded varied results. In general, studies conducted with smaller numbers of patients and under the sponsor's direction have been positive, whereas independently funded trials have been negative. The most rigorous evaluation of these agents is the recently completed Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) [2••].

### Glucosamine

Glucosamine, a normal constituent of glycosaminoglycan (GAG), is an amino sugar crucial for the normal growth and repair of articular cartilage. Glucosamine compounds are available in a crystalline form and are available as nutraceuticals, which are suggested to prevent the breakdown of cartilage and help with its maintenance. Many of the controlled clinical trials with glucosamine in OA patients have been of marginal quality [14] due to insufficient sample size, lack of statistical rigor, potential for sponsor bias, inadequate concealment, and lack of intention-to-treat principles. The most recent Cochrane review of glucosamine analyzed 20 research studies including over 2500 patients and concluded that there is "platinum" level evidence that pain does not improve when glucosamine is taken for 2 to 3 months, and improvement of function depended on the scale used [15••]. This finding was in contrast to the previous Cochrane review that found a benefit on function and a decrease in pain over a 6-week period.

After careful consideration, five studies are selected here for review [16–20]. As a group, these studies showed a positive effect, and the pooled effect size was deemed moderate. Cibere et al. [21] published a discontinuation study, wherein 137 knee OA patients who judged themselves mod-

erately improved while taking glucosamine were randomly continued on glucosamine or discontinued and followed until prespecified flare criteria were met. This study found no difference in flare rate in patients who were withdrawn from glucosamine and those who were not.

Three additional studies merit specific comment. Two of these studies examined serially obtained standard anteroposterior, weight-bearing knee x-rays in patients who received long-term glucosamine therapy with the objective to evaluate symptomatic improvement and a change in the progressive loss of cartilage. The first study reports 212 patients followed for 3 years on glucosamine, 1500 mg/day, versus placebo [22]. The study assessed change in medial compartment joint space width as the primary outcome. The authors reported that patients taking glucosamine experienced no loss in joint space, whereas placebo patients continued to show progressive cartilage loss. Glucosamine-treated patients also experienced improved symptoms based on total Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index using intent-to-treat statistical principles.

In the second study, 202 patients received glucosamine, 1500 mg per day, or placebo [23]. Once again, radiographic medial joint space was the primary outcome measure. In this trial, patients taking glucosamine showed no progression of medial joint space narrowing, but the placebo-treated patients experienced progressive narrowing. The study also reported a completer's analysis that demonstrated significant improvement in symptoms based on both the Lequesne and WOMAC indices. Substantial concerns have been raised about the validity of the radiographic outcome measure, which may be influenced by joint pain at the time the film was taken [24]. Finally, the recently reported Glucosamine Unum In Die (once-a-day) Efficacy (GUIDE) trial, a 6-month double-blind, multicenter trial in Spain and Portugal, examined placebo versus glucosamine sulfate, 1500 mg once daily, versus acetaminophen, 3000 mg/day [25]. The primary efficacy variable was change in the Lequesne algofunctional index severity-knee (ISK) [26]. Although there was a numeric difference in improvement in the ISK between acetaminophen and placebo, only the improvement in the ISK for glucosamine sulfate versus placebo was significant ($P = 0.032$). Consistent among these three trials is the agent, co-crystallized glucosamine sulfate/sodium chloride administered 1500 mg once daily, the primary outcome measure, the ISK (improvement of WOMAC pain is not consistently observed), and manufacturer sponsorship.

**Chondroitin sulfate**

CS is a normal constituent of aggrecan, the major proteoglycan of articular cartilage. Its hydration plays a major role in creating osmotic pressure within the ECM, which is important for cartilage compressive resistance. As with glucosamine, clinical trials with CS often suffer from poor study design, potential sponsor bias, inadequate concealment, and/or lack of intention-to-treat principles. In 1992, Mazieres et al. [27] randomized 114 patients with OA of the knee or hip to receive CS, 2000 mg daily, or placebo for 3 months followed by a 2-month observation phase. Kellgren-Lawrence (K-L) radiographic scores of I to III and pain scores greater than 40 mm on a visual analogue scale (VAS) were required for inclusion. Statistically significant improvement in the pain, the ISK, and overall patient and physician assessments was demonstrated. That same year, L'Hirondel [28] reported on 125 patients with knee OA randomized to treatment with CS, 1200 mg, or placebo. After 6 months, significant improvement in the VAS pain score and ISK was demonstrated for the CS-treated group.

Five studies were reported in 1998, which further evaluated CS against placebo in knee OA. Bucsi and Poor [29] treated 85 patients with CS, 800 mg daily, or placebo for 6 months. All patients had K-L radiographic scores in the I to III range. CS produced a significant improvement in the ISK and pain VAS. A timed 20-m walk evaluated mobility and showed a significant improvement in the CS-treated patients. In a study of longer duration, Conrozier [30] reported on 104 patients with K-L I to III who were randomized to treatment with CS, 800 mg daily, or placebo for 12 months. Significant improvement in the ISK was observed with CS where a suggestion of radiographic improvement was also present. Bourgeois et al. [31] compared the effect of single and divided dosing by treating 127 patients with CS, 1200 mg daily, 400 mg three times daily, or placebo for 90 days. Significant improvement for both CS groups was seen in joint pain, the ISK, and physician and patient overall pain assessment compared to placebo. No difference in efficacy or tolerability was seen between the divided and single daily dose treatment groups.

Pavelka et al. [32] conducted a 3-month dose-finding study in which patients were randomized to receive CS 1200 mg, 800 mg, and 200 mg daily, or placebo. Statistical significance was achieved in the ISK and joint pain only for the 800 mg and 1200 mg treatment groups, but no difference in efficacy was demonstrated between these two doses. Uebelhart et al. [33] studied the efficacy and tolerability of CS, 800 mg daily, compared to placebo over 12 months. There were 23 patients in both the treatment and placebo groups. A significant reduction in pain and comparable improvement in mobility was demonstrated in the CS group. Authors reported an apparent stabilization in joint space narrowing and serum osteocalcin levels, suggesting the possibility of chondroprotection associated with CS therapy. In 2001, Mazieres et al. [34] reported on 63 patients treated with CS compared to 67 treated with placebo. A 3-month treatment period was followed by 3 months of observation. At the end of the treatment period, a trend toward significant improvement was seen for the CS group in ISK, pain, physician assessment and efficacy criteria, which persisted through the observation period.

Two meta-analyses have reviewed the literature for randomized, double-blind, placebo-controlled trials of at

least 4 weeks' duration and included the same eight clinical trials for inclusion in their respective analyses [35,36]. Both concluded that CS was likely beneficial in alleviating the symptoms of knee OA to some degree, but they felt the magnitude of the clinical effect was likely smaller than reported [37]. These meta-analyses further emphasized problems with design methodology (eg, inadequate allocation, concealment, and absence of an intention-to-treat approach), industry sponsorship, and publication bias and advised caution regarding the validity of the data.

Only one study has compared the efficacy of CS in OA to an NSAID. In this randomized, multicenter double-blind trial reported in 1996, 74 patients were randomized to CS, and 72 patients were randomized to diclofenac sodium [38]. The diclofenac group was treated with 50 mg/day for the first month of the study and then with placebo for months 2 and 3. The CS group received 400 mg CS for months 1, 2, and 3. Both groups received only placebo for months 4 to 6. Patients in the diclofenac group showed a prompt improvement with the initiation of therapy. However, their symptoms returned with the discontinuation of treatment at month 2 and increased through month 6. In comparison, the CS group showed a more modest improvement in symptoms with initiation of therapy but continued to improve through month 3. Symptoms reappeared thereafter but not to the same extent as in the diclofenac cohort. These data suggested that CS may have a gradually progressive benefit, which may persist following discontinuation of therapy.

**Combination glucosamine and chondroitin sulfate**

Prior to the Glucosamine/chondroitin sulfate Arthritis Intervention Trial (GAIT) [3], scant information was available regarding the use of CS combined with glucosamine, although ingestion of the two with other nutraceuticals was not uncommon. Typical of available reports is a pilot study in 1999 that reported benefit in knee OA following oral ingestion of glucosamine, CS, and manganese ascorbate in 34 patients [39] and a 2001 trial suggesting similar benefit following topical administration of glucosamine, CS, and camphor after 8 weeks in 63 patients [40]. In addition to the available clinical reports, a possible biologic effect has been suggested from animal studies in which combination glucosamine and CS was observed to increase GAG synthesis compared with the use of either agent singly. An anti-inflammatory action was also reported following combination therapy in horses and dogs.

GAIT was developed to rigorously evaluate the efficacy of glucosamine, 1500 mg/day, CS, 1200 mg/day, and the combination of the two in the same doses for the treatment of painful knee OA. The study design was a 24-week randomized, double-blind, parallel, placebo and celecoxib-controlled trial of 1583 patients at 16 centers. Patients had clinical and radiographic evidence of OA. Qualifying patients were required to have summed WOMAC Pain scores of 125 mm to 400 mm on a 0 to 500 scale. Patients were stratified by clinical site and WOMAC Pain (ie, 125–300 classified as "mild pain" and 301–400 classified as "moderate-to-severe pain"). Patients with 20% improvement in summed WOMAC Pain from baseline to 24 weeks were classified as responders.

In May 2004, Outcome Measures in Rheumatology Clinical Trials (OMERACT) and OA Research Society International (OARSI) published osteoarthritis treatment responder criteria [41•]. To be classified as an OMERACT-OARSI responder, patients must achieve improvement 50% or greater and 20 mm or greater in pain or function, or improvement of 20% or greater and 10 mm or greater in at least two of three criteria (pain, function, or patient global assessment).

For GAIT patients overall, there was no difference among the supplements alone and in combination compared to placebo. Celecoxib was significantly better than placebo ($P = 0.008$). However, in the moderate-to-severe WOMAC Pain patients, the combination of glucosamine and CS was significantly better than placebo (24.9% better, $P = 0.002$). Celecoxib (15.1%, $P = 0.06$), glucosamine (11.5%, $P = 0.17$), and CS (7.1%, $P = 0.39$) were not significantly better than placebo. Similarly, OMERACT-OARSI response ranged from 26.4% (glucosamine plus CS, $P = 0.001$) to 10% (CS, $P = 0.24$) better than placebo.

Among the secondary outcomes in the supplement groups, the only statistically significant improvement noted was that of joint swelling/effusion in the CS group ($P = 0.01$). Further evaluation of this finding suggests that CS may differentially improve knee pain in patients with earlier radiographic disease [42]. Overall, use of rescue acetaminophen was low (1.6–1.9 500-mg tablets/day) with the glucosamine/CS combination and celecoxib groups taking the fewest tablets daily.

Interpretation of GAIT results is hampered by a high placebo response rate (60.1%) as well as an apparent insensitivity of the primary outcome to detect change in the mild pain group, whereas the OMERACT-OARSI response in general lowered placebo response and was more sensitive to change. For example, in the overall group, the OMERACT-OARSI placebo response rate was 56.9%, the celecoxib group performed 10.4% better than the placebo group ($P = 0.008$), and combination glucosamine and CS was 8.7% better than placebo ($P = 0.02$). In the moderate-to-severe pain group, OMERACT-OARSI outcomes were more striking with a placebo response of 48.6%, celecoxib bested placebo by 18.1% ($P = 0.03$), and the combination glucosamine and CS response rate was 26.4% better than the placebo response ($P = 0.001$). These data suggest that the OMERACT-OARSI is more discriminating than the GAIT 20% improvement in summed WOMAC Pain.

## Vitamin C

In addition to antioxidant mechanism, vitamin C is needed for production and quality of cartilage, because it stimulates both collagen and GAG biosynthesis. The

Framingham OA cohort epidemiologic data support that higher vitamin C may reduce OA progression but not incidence [43]. In this study, 640 participants had knee films taken at baseline and 8 years later. Nutrient intake was calculated from a food frequency questionnaire administered to participants. The progression of radiographic knee OA based on K-L grading system was threefold reduced for those with the middle and highest tertiles of vitamin C intake (highest vs lowest intake adjusted odds ratio [OR] = 0.3; 95% CI 0.1–0.6). These same highest tertile patients also has reduced risk of developing knee pain (OR = 0.3; 95% CI 0.1–0.8). The ability of vitamin C to affect pain outcomes was also supported in another longitudinal study of knee OA in 324 participants evaluated by food questionnaire and followed for 30 months. People with low intake of vitamin C (200 mg for men, 150 mg for women) had more significant knee pain scores measured by the WOMAC pain subscale [44].

## Vitamin E

The ability of vitamin E to block the formation of arachidonic acid is one reason this substance is touted as a reducer of modest synovial inflammation seen in OA. The above mentioned Framingham OA cohort study found vitamin E efficacy in reducing progression of OA only in men (OR = 0.07; CI 0.01–0.6) [43]. Wluka et al. [45] used MRI to assess whether 500 IU of vitamin E affected cartilage volume loss in 117 patients with knee OA. They saw no significant difference in cartilage loss or improvement in symptoms. Thus, there is no clear role for the recommendation of vitamin E.

## Avocado-soybean Unsaponifiables

ASU refers to extracts derived from one third avocado oil and two thirds soybean oil after hydrolysis. This mixture is thought to both interfere with interleukins, thus preventing deterioration of synovial cells, and stimulate collagen synthesis in culture. Four double-blind, placebo-controlled trials have evaluated the effectiveness of ASU in patients with at least moderate intensity knee and/or hip OA of at least 6 months duration. All trials used recommended standards for OA trials. Ernst [46] performed a meta-analysis of these trials, which included a total of 751 patients who received ASU, either 300 mg or 600 mg (in one trial) once a day, compared with placebo. Three trials had better pain and functional ability with ASU and NSAID compared with placebo and NSAID over 3 to 6 months. Additionally, better pain relief was achieved with a lower dose of NSAID. The one trial looking at dose of ASU showed no difference between 300 mg or 600 mg per day. The fourth trial which showed no difference in pain, functional ability, or daily NSAID use over 24 months examined only patients with OA of the hip, with a low initial daily use of NSAID. In this trial, a significant reduction in narrowing was seen in those patients whose initial joint space was below the median [47]. No serious adverse effects of ASU were reported. Though three high-quality studies found a potential role for ASU, additional studies must be done to determine its longitudinal effect before firm recommendations can be made.

## Conclusions

The current therapeutic approach to OA focuses on symptomatic relief. Some symptomatic relief is provided by attaining and maintaining ideal body weight, graded exercise, and the use of analgesic agents. The ability to modify the incidence or progression of the disease remains a goal of the prescribing physician. Clinical data suggest a potential role for glucosamine/CS (in moderate-severe osteoarthritis), vitamin C, and ASU for treatment of pain in selected patients. However, the ability of these nutraceuticals to change disease outcome remains, like the pathophysiology of OA, in need of clearer elucidation. Although safety profiles are reassuring, until there is better efficacy data, the cost of nutraceuticals remains possibly the most significant limiting factor for their initiation.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance


1. Lawrence RC, Helmick CG, Arnett FC, et al.: **Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States.** *Arthritis Rheum* 1998, **41:**778–799.

2.•• 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.

This is the first multicenter randomized, placebo-controlled trial that rigorously examined glucosamine, CS, and the two in combination for efficacy in pain relief.

3. McAlindon TE, Cooper C, Kirwan JR, Dieppe PA: **Determinants of disability in osteoarthritis of the knee.** *Ann Rheum Dis* 1993, **52:**258–262.

4. Altman R, Asch E, Bloch D, et al.: **Development of criteria for the classification and reporting of OA. Classification of Osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association.** *Arthritis Rheum* 1986, **29:**1039–1049.

5. Goldring MB: **Anticytokine therapy for osteoarthritis.** *Expert Opin Biol Ther* 2001, **1:**817–829.

6. Aigner T, Kurz B, Fukui N, Sandell L: **Roles of chondrocytes in the pathogenesis of osteoarthritis.** *Curr Opin Rheumatol* 2002, **14:**578–584.

7.• Goggs R, Vaughan-Thomas A, Clegg P: **Nutraceutical Therapies for Degenerative Joint Diseases: A critical review.** *Crit Rev Food Sci Nutr* 2005, **45:**145–164.

A comprehensive review of mechanism of action of nutraceuticals.

8. Laufer S: **Role of eicosanoids in structural degradation in osteoarthritis.** *Curr Opin Rheumatol* 2003, **15:**623–627.

9. Henrotin Y, Deby-Dupont G, Deby C, et al.: **Production of active oxygen species by isolated human chondrocytes.** *Br J Rheumatol* 1993, **32:**562–567.

10. Sato H, Takahashi T, Ide H, et al.: **Antioxidant activity of synovial fluid, hyaluronic acid, and two subcomponents of hyaluronic acid. Synovial fluid scavenging effect is enhanced in rheumatoid arthritis patients.** *Arthritis Rheum* 1988, **31:**63–71.
11. **Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines.** *Arthritis Rheum* 2000, **43:**1905–1915.
12. Hochberg MC, Altman RD, Brandt KD, et al.: **Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. American College of Rheumatology.** *Arthritis Rheum* 1995, **38:**1541–1546.
13. Jordan KM, Arden NK, Doherty M, et al.: **EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT).** *Ann Rheum Dis* 2003, **62:**1145–1155.
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.•• Towheed TE, Maxwell L, Anastassiades TP, et al.: **Glucosamine therapy for treating osteoarthritis.** *Cochrane Database Syst Rev* 2005, **2:**CD002946.

This meta-analysis reviews 20 glucosamine trials to date and highlights how functional outcome measures greatly influence results.

16. Reichelt A, Forster KK, Fischer M, et al.: **Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee. A randomised, placebo-controlled, double-blind study.** *Arzneimittelforschung* 1994, **44:**75–80.
17. Vajaradul Y: **Double-blind clinical evaluation of intra-articular glucosamine in outpatients with gonarthrosis.** *Clin Ther* 1981, **3:**336–343.
18. Pujalte JM, Llavore EP, Ylescupidez FR: **Double-blind clinical evaluation of oral glucosamine sulphate in the basic treatment of osteoarthrosis.** *Curr Med Res Opin* 1980, **7:**110–114.
19. Houpt JB, McMillan R, Wein C, Paget-Dellio SD: **Effect of glucosamine hydrochloride in the treatment of pain of osteoarthritis of the knee.** *J Rheumatol* 1999, **26:**2423–2430.
20. Noack W, Fischer M, Forster KK, et al.: **Glucosamine sulfate in osteoarthritis of the knee.** *Osteoarthritis Cartilage* 1994, **2:**51–59.
21. 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.
22. 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.
23. Pavelka K, Gatterova J, Olejarova M, et al.: **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.
24. 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.
25. 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:**S460.
26. Lequesne MG, 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.
27. Mazieres B, Loyau G, Menkes CJ, et al.: **Chondroitin sulfate in the treatment of gonarthrosis and coxarthrosis. 5-months result of a multicenter double-blind controlled prospective study using placebo** [in French]. *Rev Rhum Mal Osteoartic* 1992, **59:**466–472.
28. L'Hirondel JL: **Double-blind clinical study with oral administration of chondroitin sulphate versus placebo for tibiofemoral gonarthrosis (125 patients) [in German].** *Litera Rheumatol* 1992, **14:**77–84.
29. Bucsi L, Poor G: **Efficacy and tolerability of oral chondroitin sulfate as a symptomatic slow-acting drug for osteoarthritis (SYSADOA) in the treatment of knee osteoarthritis.** *Osteoarthritis Cartilage* 1998, **6(Suppl A):**31–36.
30. Conrozier T: **Anti-arthrosis treatments: efficacy and tolerance of chondroitin sulfates (CS 4&6)** [in French]. *Presse Med* 1998, **27:**1862–1865.
31. Bourgeois P, Chales G, Dehais J, et al.: **Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3 x 400 mg/day vs placebo.** *Osteoarthritis Cartilage* 1998, **6(Suppl A):**25–30.
32. Pavelka K, Bucsi L, Manopulo R: **Double-blind, dose effect study of oral CS 4&6 1200mg, 800mg, 200mg against placebo in the treatment of femorotibial osteoarthritis.** *Eular Rheumatol Litera* 1998, **(Suppl 2):**63.
33. Uebelhart D, Thonar EJ, Delmas PD, et al.: **Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study.** *Osteoarthritis Cartilage* 1998, **6(Suppl A):**39–46.
34. Mazieres B, Combe B, Phan Van A, et al.: **Chondroitin sulfate in osteoarthritis of the knee: a prospective, double blind, placebo controlled multicenter clinical study.** *J Rheumatol* 2001, **28:**173–181.
35. McAlindon TE, LaValley MP, Felson DT: **Efficacy of glucosamine and chondroitin for treatment of osteoarthritis.** *JAMA* 2000, **284:**1241.
36. 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:**1514–1522.
37. Michel BA, Stucki G, Frey D, et al.: **Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial.** *Arthritis Rheum* 2005, **52:**779–786.
38. Morreale P, Manopulo R, Galati M, et al.: **Comparison of the antiinflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis.** *J Rheumatol* 1996, **23:**1385–1391.
39. Leffler CT, Philippi AF, Leffler SG, et al.: **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.
40. Cohen M, Wolfe R, Mai T, et al.: **A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate and camphor for osteoarthritis of the knee.** *J Rheumatol* 2003, **30:**523–528.
41.• Pham T, van der Heijde D, Altman RD, et al.: **OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited.** *Osteoarthritis Cartilage* 2004, **12:**389–399.

Defines responder criteria.

42. Clegg DO, Reda DJ, Shi H, et al.: **Chondroitin sulfate may have differential effects on OA symptoms related to degree of radiographic involvement.** *Osteoarthritis Cartilage* 2005, **13(Suppl 1):**S76–S77.
43. McAlindon TE, Jaques P, Zhang T, et al.: **Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis?** *Arthritis Rheum* 1996, **39:**648–656.
44. Baker K, Niu J, Goggins J, et al.: **The effects of vitamin C intake on pain in knee osteoarthritis (OA).** *Arthritis Rheum* 2003, **48:**S422.
45. Wluka AE, Stuckey S, Brand C, Cicuttini FM: **Supplementary Vitamin E does not affect the loss of cartilage volume in knee osteoarthritis: a 2 year double blind placebo controlled study.** *J Rheumatol* 2002, **29:**2585–2591.
46. Ernst E: **Avocado-soybean unsaponifiables (ASU) for osteoarthritis—a systematic review.** *Clin Rheumatol* 2003, **22:**285–288.
47. Lequesne M, Maheu E, Cadet C, et al.: **Structural effect of avocado/soybean unsaponifiables on joint space loss in osteoarthritis of the hip.** *Arthritis Care Res* 2002, **47:**50–58.