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REVIEW

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Access to highly purified chondroitin sulfate for appropriate treatment of osteoarthritis: a review

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ABSTRACT

Current pharmacological therapies for osteoarthritis are symptom-focused and aimed at controlling pain. However, currently approved symptom-modifying agents do not restore the structure and function of damaged joints. Symptomatic slow-acting drugs in osteoarthritis (SySADOAs), including the sulfated glycosaminoglycan, chondroitin sulfate, have shown promising beneficial effects on the pain and other symptoms of osteoarthritis, and some may also have a positive effect on cartilage, slowing the progression of joint deterioration in osteoarthritis. A highly-purified, standardized, pharmaceutical-grade preparation of chondroitin sulfate has shown activity in osteoarthritis and has become one of the most prescribed SySADOAs. However, in many countries, formulations of chondroitin sulfate of various sources and purity are available as food supplements or nutraceuticals. As the effects of chondroitin sulfate could vary according to the characteristics of the chondroitin sulfate employed, including source, purity, or structural organization, clinical data from well-designed studies of pharmaceutical-grade chondroitin sulfate should not be extrapolated to support clinical efficacy claims of food supplements; nor should results from trials of chondroitin sulfate-containing food supplements be used to draw conclusions about the efficacy of pharmaceutical-grade chondroitin sulfate. This article reviews the evidence for the role of highly-purified pharmaceutical-grade chondroitin sulfate in the treatment of osteoarthritis and examines the efficacy and safety concerns of other formulations of chondroitin sulfate. Highly-purified pharmaceutical-grade chondroitin sulfate has mild-to-moderate efficacy in the treatment of symptomatic osteoarthritis, with clinically meaningful efficacy.

Keywords: Chondroitin sulfate, DMOADs, Nutraceuticals, Osteoarthritis, Pharmaceuticals, SySADOA

Introduction

Osteoarthritis has the highest prevalence of the musculoskeletal conditions, is a leading cause of chronic pain and disability in older adults and represents a major public health burden (1-6). Systematic review of prevalence and incidence estimates of osteoarthritis suggests a prevalence of osteoarthritis in the adult population as high as 23.9% for osteoarthritis of the knee, 10.9% for hip osteoarthritis and 43.3% for osteoarthritis of the hand (1, 7). Data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2015 show a significant increase in the burden and healthcare demand of osteoarthritis between 1990 and 2015, with total disability-adjusted life-years (DALYs) rising by 35% in line with the aging population and increasing rates of obesity, and age-standardized rates increasing by 4% (6). Over that time, rates of primary hip and knee arthroplasty, the majority performed for osteoarthritis, have risen considerably in high-income countries, further adding to the healthcare burden of osteoarthritis (8-12). Conservative estimates now put the total and indirect costs of osteoarthritis at between 0.25% and 0.50% of the gross domestic product in high-income countries (13, 14).

Although once viewed as a disease solely of mechanical degradation of cartilage within synovial joints, associated with hypertrophy of bone (formation of osteophytes and sclerosis of subchondral bone sclerosis) and thickening of the capsule, osteoarthritis is now understood to be a much more complex condition that affects the whole joint, involving activation of cartilage matrix molecules and cell signaling, inflammatory, and catabolic pathways (4, 5). The complex and multifactorial etiology of osteoarthritis can be considered as an interplay between genetic, biological, and biomechanical components; established risk factors include aging, obesity, female gender, a history of high-intensity repetitive joint activity, bone mineral density, and congenital anomalies such as hip dysplasia (5).

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The most commonly affected joints are the knees, hips, hands, feet, and spine. Joint pain may be symptomatic of osteoarthritis, or the signs of osteoarthritis may be diagnosed radiologically (5). Clinical features include joint pain that is worse on activity, joint dysfunction, tenderness, pain and stiffness with rest, varying degrees of local inflammation, and deformity accompanying the progressive degeneration of articular cartilage and the remodeling of underlying bone in the synovial joints (4, 5, 15).

The prevention or alleviation of symptoms is the primary focus of treatment. However, by the time symptoms prompt a patient to seek treatment, the disease is usually advanced, and preventing, slowing, or reversing progression may be difficult or unachievable (5). Therefore, early identification and appropriate management is a desirable strategy to minimize the long-term effects of osteoarthritis; modifying the risk factors may provide new opportunities for prevention and interventions to reduce the risk of osteoarthritis and minimize subsequent pain and disability.

Current pharmacological therapies for osteoarthritis are symptom-focused and aimed at controlling pain. Osteoarthritis medications include topical or systemic nonsteroidal anti-inflammatory drugs (NSAIDs), topical capsaicin, analgesics, SySADOAs (symptomatic slow-acting drugs in osteoarthritis), locally-administered corticosteroids and intra-articular visco-supplementation with hyaluronic acid (16-21). However, currently approved symptom-modifying agents do not restore the structure and function of damaged joints (22).

In the absence of effective disease-modifying osteoarthritis drugs (DMOADs), osteoarthritis can result in progressive cartilage damage that ultimately necessitates joint replacement (18, 21, 23).

Among the different products available for the treatment of osteoarthritis, SySADOAs have shown promising beneficial effects on symptoms, such as pain, and some of them have also demonstrated a positive effect on cartilage (i.e., can be classified as DMOADs) (24, 25).

Chondroitin sulfate, a natural component of proteoglycans of the extracellular matrix of a number of connective tissues, including cartilage, bone, ligaments, tendons, and skin, is a sulfated glycosaminoglycan (GAG) consisting of a long unbranched polysaccharide chain composed of a repeating disaccharide structure of D-glucuronic acid and *N*-acetylgalactosamine residues (26, 27). The chemical structure of chondroitin sulfate is shown in Figure 1. A highly purified, pharmaceutical-grade preparation of chondroitin sulfate developed by IBSA Institut Biochimique S.A., Pambio-Noranco, Switzerland has shown activity in osteoarthritis and has become one of the most prescribed SySADOAs. The formulation has a consolidated benefit/risk profile and a long history in the successful treatment of different forms of osteoarthritis supported by numerous published data.

However, in many countries, particularly the United States, other products containing chondroitin sulfate are available as food supplements or nutraceuticals, which in general cannot claim the same level of purity and quality as highly-purified pharmaceutical-grade, standardized chondroitin sulfate formulations. Therefore, clinical data cannot and should not be extrapolated to support the clinical efficacy of food supplements (28, 29). Nor should results from trials of chondroitin sulfate-containing food supplements be used to draw conclusions about the efficacy of pharmaceutical-grade chondroitin sulfate.

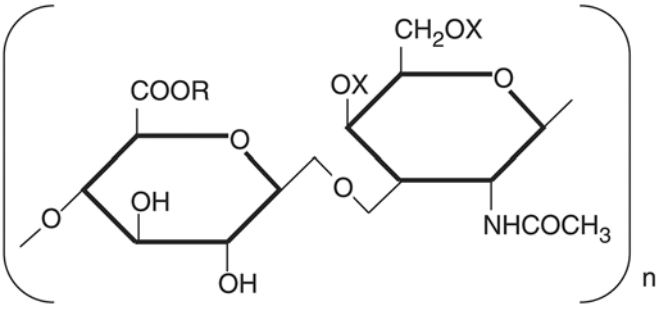

Fig. 1 - Structure of chondroitin sulfate. R represents Na or H; X represents SO_3R or H.

Indeed, there is a specific need to better understand and differentiate the role and clinical efficacy of highly-purified pharmaceutical-grade chondroitin sulfate from that of chondroitin sulfate used in preparations marketed as food supplements and nutraceuticals for musculoskeletal conditions. Therefore, we undertook to review the evidence for the role of highly-purified pharmaceutical-grade chondroitin sulfate in the treatment of osteoarthritis and to examine the efficacy and safety concerns of other formulations of chondroitin sulfate.

Search strategy

The MEDLINE and PubMed databases were searched for all randomized controlled trials, systematic reviews, meta-analyses, and review articles of chondroitin sulfate in osteoarthritis published between January 1990 and October 2017. The literature searches performed included the search terms 'chondroitin sulfate', 'chondroitins 4 & 6 sulfate', 'pharmaceutical-grade', 'highly-purified', 'nutraceutical', 'food supplement', 'osteoarthritis', 'humans'. The bibliographies of retrieved papers identified in the search were manually searched for additional relevant articles, and recent recommendations and treatment guidelines were also considered for inclusion. Relevant articles describing the mechanisms of action of chondroitin sulfate that may explain the potential beneficial effects of the agent in the management of patients with osteoarthritis were also selected and evaluated.

Biological basis for the effect of chondroitin

Although the degeneration of articular cartilage is a defining characteristic of osteoarthritis, the pathophysiology of osteoarthritis is heterogeneous and complex, affecting the entire joint structure, including the subchondral bone and the synovium, and can be further characterized by synovial activation, osteophyte formation, and abnormalities in subchondral bone (5, 15, 30-35). The underlying etiology of osteoarthritis represents a complex and dynamic interaction of biological, biomechanical, and genetic components (5, 22, 36-38). Figure 2 illustrates some of the pathophysiological pathways in chondrocytes.

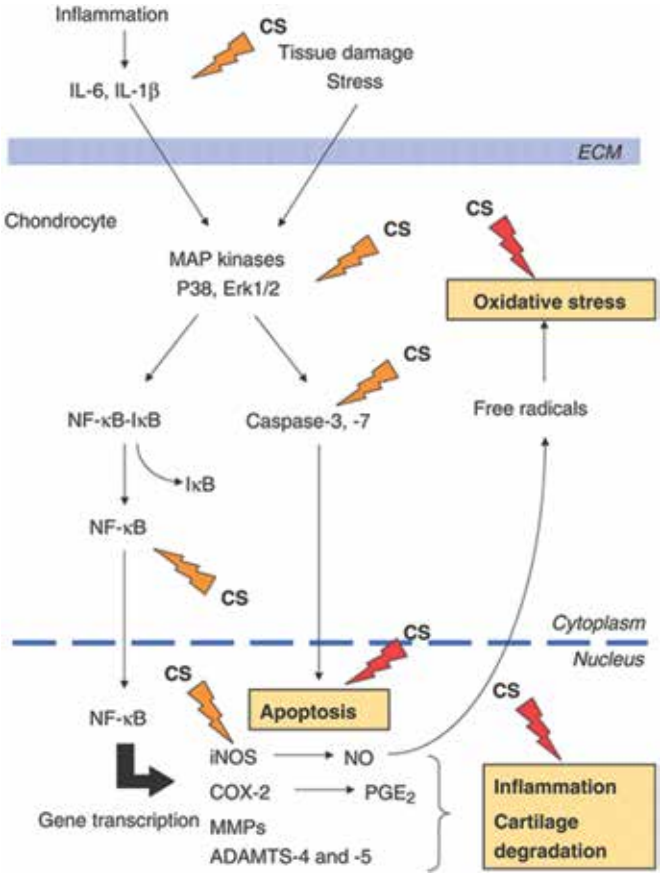

Fig. 2 - Proposed pathophysiological targets of chondroitin sulfate in chondrocytes during osteoarthritis. *In vitro* studies show chondroitin sulfate acts on cell signaling, inflammatory and catabolic pathways and oxidative stress (black arrows), targeting different intermediates in these pathways (grey arrows). CS = chondroitin sulfate; IL = interleukin; ECM = extracellular matrix; PGE_2 = prostaglandin E_2; PG = proteoglycan; MMP = matrix metalloproteinase; NO = nitric oxide; ADAMTS = a disintegrin and metalloproteinase with thrombospondin motifs; NF-kB = nuclear factor kB; COX = cyclooxygenase = iNOS = inducible Nitric Oxide Synthase. Adapted from Henrotin Y, Mathy M, Sanchez C, et al. Ther Adv Musculoskelet Dis, Vol. 2, Issue 6, pp. 335-348, copyright © 2010 by SAGE Publications. Reprinted by Permission of SAGE Publications, Ltd.

Low-grade systemic inflammation is increasingly recognized as having a critical role in the pathogenesis of osteoarthritis (5, 15, 26, 39, 40). Overuse of joints, acute trauma, or altered joint mechanics may cause the destruction of chondrocytes and disruption of the extracellular matrix, leading to the depletion of proteoglycans essential in maintaining the load-bearing capacity of cartilage (5), initiating the detrimental changes in cartilage function that ultimately leads to osteoarthritis.

Aggrecan, a major structural component of cartilage, is a large aggregating proteoglycan containing chondroitin sulfate and keratan sulfate chains and hyaluronic acid attached to a multi-domain protein core (5, 26). Chondroitin sulfate chains attached to the chondroitin sulfate domain form a hydrated, viscous gel that provides compressive resistance to cartilage tissue, counteracting the impact of forces applied across the joint during activity. Activation of chondrocytes in response to chemical and mechanical stimulus results in the production of pro-inflammatory cytokines, including interleukins (Ils), tumor necrosis factor (TNF)-α, metalloproteinases, and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) (5). These compounds appear to have important pathogenic roles in osteoarthritis, suggesting potential targets for intervention.

Chondroitin sulfate has been shown to have a number of *in vitro* beneficial effects in osteoarthritis and on the metabolism of different cell lines, including chondrocytes, synoviocytes and cells from subchondral bone, all of which are involved in the pathophysiology of the disease (24). Specifically, although this compound is not considered *per se* an anti-inflammatory drug, it has been shown to exert a range of immunomodulatory and anti-inflammatory effects, including the reduction of NF-κB nuclear translocation and decreased production of pro-inflammatory cytokines such as Il-1β, interferon (IFN)-γ, and TNF-α, and to reduce the expression of nitric oxide synthase (NOS)-2 and cyclooxygenase (COX)-2 (40, 41). A schematic representation of potential intervention points of chondroitin sulfate in the pathophysiology of osteoarthritis is presented in Figure 2.

Preclinical evidence suggests that chondroitin sulfate has pro-anabolic effects (increased proteoglycan and type II collagen synthesis) and anti-catabolic effects (inhibited degradation of the hyaluronic acid component and core protein of the aggrecan) on articular chondrocytes, inhibiting the cellular death process and restoring the anabolic/catabolic balance of the extracellular matrix (24, 42-45). Beneficial effects on the synovial membrane and subchondral bone osteoblasts have also been demonstrated *in vitro* (42, 46-48); reviewed in Volpi 2011 (41). As chondrocytes, the synovial membrane, and subchondral bone are all negatively affected in osteoarthritis, these properties suggest a potential chondroprotective effect for chondroitin sulfate in osteoarthritis. However, it should be stressed that caution is required in extrapolating from *in vitro* results to *in vivo* results in humans.

Exogenous chondroitin sulfate has a molecular weight of 50-100 kDa, whereas, after extraction from bovine, porcine, or marine cartilage sources chondroitin sulfate has a molecular weight of between 10 and 40 kDa, depending on source and extraction process (49). Pharmacokinetic studies in healthy human volunteers show that exogenous chondroitin sulfate is rapidly absorbed after oral administration (despite a low level of absorption and local degradation), reported to reach peak plasma concentration (mean 12.7 µg/mL) after 2.4 hours in a study by Volpi using chondroitins 4 & 6 sulfate (50). This plasma level is in line with the *in vitro* concentration used to demonstrate the cellular effects of highly purified chondroitin sulfate. Plasma chondroitin sulfate levels increased by over 200% from baseline endogenous values and were detectable for 8 to 16 hours. Analysis of the composition of disaccharides in plasma suggests that exogenous chondroitin sulfate is absorbed as high molecular weight polysaccharide alongside derivatives from partial depolymerization or desulfation (50). Plasma concentrations of endogenous chondroitin sulfate remained constant during the sampling period. Administration of radiolabeled chondroitin sulfate in animal studies shows that a significant proportion of chondroitin sulfate reaches the synovial fluid and cartilage (51, 52).

Clinical efficacy and safety of highly-purified chondroitin sulfate

A number of placebo- and active comparator-controlled trials of highly-purified chondroitin 4 & 6 sulfate in patients with osteoarthritis have shown that pharmaceutical-grade chondroitin sulfate is more effective than placebo in reducing pain and improving articular function. This effect was confirmed in a recent Cochrane Collaboration systematic review (53). Although the beneficial differences with chondroitin sulfate were small-to-moderate compared with placebo, they were clinically meaningful. Furthermore, there was no increased risk of serious adverse events (AEs) with chondroitin sulfate, compared with control (53). Another effect is to prevent joint space narrowing, a measure of structural progression of knee osteoarthritis. As a result, pharmaceutical-grade chondroitin sulfate has been classified as a both a SySADOA and a DMOAD (40).

Clinical studies in osteoarthritis

Effects on symptoms and function

Published results from clinical trials of chondroitin sulfate in osteoarthritis have shown inconsistent outcomes, including the large GAIT study (54). However, not all trials were using highly purified chondroitin sulfate. Table I summarizes controlled clinical trials of pharmaceutical-grade chondroitin sulfate in patients with osteoarthritis, selected on the basis of the use of highly-purified chondroitins 4 & 6 sulfate. A 6-month double-blind, placebo-controlled study in France in 56 patients (mean age 61.4 years) with hip osteoarthritis

TABLE I - Summary of randomized controlled clinical trials of highly-purified chondroitin sulfate in patients with osteoarthritis

Study	Patient population	Intervention	Variables	Results	Safety
Conrozier and Vignon (55)	56 pts with symptomatic grade 1-3 radiologically-confirmed hip OA	CS 3 × 400 mg or placebo od for 6 mo	LI score Huskisson VAS pain scale	Significant improvement in LI and VAS, reduced consumption of NSAIDs and analgesics (all p<0.001 vs placebo)	Well tolerated
Gabay et al (56)	162 pts with symptomatic ACR-defined and radiographically-confirmed hand OA	CS 800 mg or placebo od for 6 mo	FIHOA score at 6 mo Pt and investigator Global assessment	Difference of -8.7 mm in VAS pain score vs placebo (p = 0.016) Mean difference in FIHOA of -2.14 vs placebo (p = 0.008) Pt and investigator global efficacy in favor of CS	No SAEs Similar frequency and spectrum of AEs in each group
Michel et al (60)	300 pts with ACR-defined symptomatic knee OA and grade1-3 KL disease	CS 800 mg or placebo od for 2 yrs	Change in minimum and mean JSW WOMAC measure of symptoms of OA	No change in mean JSW with CS vs -0.14 mm with placebo (p = 0.04 vs CS) Improvements in all WOMAC subscales with CS	No significant between-group difference in frequency of AEs
Kahan et al (62)	622 pts with ACR-defined knee OA and VAS pain score ≥30 mm	CS 800 mg or placebo od for 2 yrs	Loss of minimum JSW at 2 yrs	Significant reduction in minimum JSW with CS (-0.07 ± 0.03 vs -0.31 ± 0.04 mm; p<0.0001) Radiographic progression ≥0.25 mm 28% vs 41%, respectively, p<0.0005 Improved global efficacy with CS	Tolerability similar between groups; most AEs were transient and mild
Zegels et al (58)	353 pts with ACR-defined knee OA, LI ≥7, VAS pain score ≥40 mm	CS 1200 mg od CS 400 mg tid Placebo (3 mo)	LI score VAS pain scale	Single-dose CS was non-inferior to CS tid Both CS groups superior to placebo in improving OA symptoms and function	No significant difference in safety/tolerability between the 3 groups
Hochberg meta-analysis (63)	1179 pts with ACR-defined knee OA	CS 800 mg or placebo od for 2 yrs (n = 922) CS 400 mg or placebo tid for 2 yrs (n = 257)	Change in minimum JSW at 2 years	Difference in mean decline in minimum JSW 0.13 mm with CS vs placebo (p = 0.0002; effect size of 0.23)	Not reported

ACR = American College of Rheumatology; AE = adverse event; CS = chondroitin sulfate; FIHOA = Functional Index for Hand OA; JSW = joint space width; KL = Kellgren-Lawrence; LI = Lequense score of joint function; mo = months; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; od = once daily; pts = patients; SAE = serious adverse event; tid = three times daily; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; yr = year.

requiring regular use of analgesics or NSAIDs and with narrowing of the intra-articular space showed significant improvement in the primary outcome measures (Lesquense score of joint function, pain relief on the Huskisson visual analogue scale [VAS] scale, and consumption of analgesics or NSAIDs; all p<0.001) with prescription-grade chondroitin 4 & 6 sulfate, 3 × 400 mg daily, compared with placebo (55). Chondroitin sulfate was well tolerated.

Another independent study, a randomized, double-blind, placebo-controlled trial in 162 patients with symptomatic radiographically-confirmed osteoarthritis of the hand evaluated the effects of chondroitins 4 & 6, 800 mg once daily, or placebo on hand pain (change in patient's assessment of global spontaneous hand pain) and function (Functional Index for Hand OA [FIHOA] score) at 6 months (56). Patient's global assessment of hand pain decreased significantly more in the chondroitin sulfate group than with placebo, with a difference in mean VAS score of -8.7 mm (p = 0.016). Hand function also improved significantly more with chondroitin sulfate; the mean difference in FIHOA score was -2.14 (p = 0.008). Reduction in duration of morning stiffness and investigator's global impression of treatment efficacy was also in favor of chondroitin sulfate.

In knee osteoarthritis, an international, multicenter, placebo-controlled dose frequency comparison in 353 patients with clinically and radiologically confirmed (American College of Rheumatology [ACR] criteria) (57) knee osteoarthritis compared chondroitins 4 & 6 sulfate 1200 mg daily as a single versus a 400 mg three times daily dose (58). After 3 months of follow-up, non-inferiority was established between the two chondroitin sulfate formulations; there was no significant difference between once-daily chondroitin sulfate and three-times-daily administration. Both active treatment groups showed significant improvements in osteoarthritis symptoms and function, compared with placebo, as measured by Lequesne Index (59) and a VAS pain scale. There was no significant difference in tolerability between groups. Daily administration of an oral sachet of 1200 mg of chondroitin 4 & 6 sulfate appears to provide significant clinical improvement compared to placebo, and a similar improvement compared to a regimen of three daily capsules of 400 mg of the same active ingredient.

Structure-modifying effects

Evidence from a number of studies suggests that the combined structure-modifying and symptom-modifying effects of pharmaceutical-grade chondroitin sulfate might be classified as a disease-modifying agent in patients with knee osteoarthritis. The activity of chondroitin sulfate as a SYSADOA is supported by the largest number of well conducted studies in knee OA with chondroprotection as the main objective. Michel and colleagues investigated chondroitins 4 & 6 sulfate (800 mg) or placebo daily for 2 years in 300 patients (mean age 62.5 years) with symptomatic knee osteoarthritis (60). In the intent-to-treat analysis, patients receiving placebo had progressive joint space narrowing over the course of the study (mean -0.14 mm; p = 0.001 vs baseline, p = 0.04 vs chondroitin sulfate), whereas there was no change in mean joint space width for patients receiving chondroitin sulfate. Although total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (61) did not significantly change in either group over the study, there were improvements for chondroitin sulfate, but not placebo, recipients for all WOMAC subscales, including pain, stiffness, and function (60). There was no significant between-group difference in the frequency of AEs.

The long-term effects of chondroitins 4 & 6 sulfate on the radiographic progression of knee osteoarthritis were assessed in 622 patients randomly assigned to chondroitin sulfate 800 mg (n = 309) or placebo (n = 313) once daily for 2 years (62). The primary outcome measure was loss in minimum joint space width over 2 years. There was a significant reduction in minimum joint space width loss in the chondroitin sulfate group (mean -0.07 ± 0.03 mm) compared with placebo (mean -0.31 ± 0.04 mm; p<0.0001). The percentage of patients with a radiographic progression ≥0.25 mm was significantly reduced with chondroitin sulfate compared to placebo (28% vs 41%; p<0.0005), with a relative risk reduction of 33%. In addition, there was a significantly faster improvement in pain symptoms in the chondroitin sulfate group (p<0.01), which was notably marked during the first year. Global efficacy assessed by the patient and investigator was significantly better (p<0.02 and p<0.04, respectively) at 6 months with chondroitin sulfate, compared with placebo. Tolerability was similar between groups, and most AEs were transient and mild.

The results of an updated meta-analysis of randomized controlled trials of two-year duration further demonstrated the structure-modifying effects of pharmaceutical-grade chondroitin sulfate, which was effective in reducing the rate of decline in minimum joint space in patients with knee osteoarthritis (63). Three trials met the inclusion criteria and were included in the meta-analysis (60, 62, 64). The dosing varied between studies: in two studies, chondroitin sulfate was administered at a dose of 800 mg once daily (60, 62), and in the third, it was administered at a dose of 400 mg three times daily (64). The Sawitske study, a substudy of the GAIT trial, was negative in terms of chondroprotection while the two others showed a small beneficial effect.

In the pooled analysis, over 2 years chondroitin sulfate was associated with a small but significant mean difference in decline in minimum joint space width of 0.13 mm (95% CI 0.06, 0.19), compared with placebo (p = 0.0002). This corresponded to an effect size of 0.23 (95% CI 0.11, 0.35; p = 0.0001) (63).

Comparative studies with NSAIDS

Chondroitin sulfate has been compared with NSAIDs in several studies. The anti-inflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis was compared in 146 patients with knee osteoarthritis (65). Patients were randomized to 3 × 50 mg diclofenac tablets per day plus 3 × 400 mg placebo sachets for 1 month, or 3 × 50 mg placebo tablets plus 3 × 400 mg sachets of chondroitin sulfate daily for 1 month. From month 2 to month 3, patients in the diclofenac group received placebo sachets only, and patients in the chondroitin sulfate group received only chondroitin sulfate sachets. Thereafter, both groups received 3 × 400 mg placebo sachets from months 4 to 6.

Although there was a prompt reduction of clinical symptoms in NSAID-treated patients, measured by the Lequesne Index, symptoms reappeared after the end of active treatment. In contrast, the therapeutic response was slower in the chondroitin sulfate group, but a carry-over effect was noted, with the response lasting for up to 3 months after the end of treatment (65). At study end, the Lequesne Index score was 64.4% lower than baseline in the chondroitin sulfate group, compared with 29.7% lower than baseline in the diclofenac group ($p<0.01$) (65).

Pharmaceutical-grade chondroitin sulfate was as effective as celecoxib and superior to placebo in patients (n = 604) with primary symptomatic knee osteoarthritis diagnosed according to ACR criteria in the ChONdroitin versus CElecoxib versus Placebo Trial (CONCEPT) (66). Chondroitins 4 & 6 sulfate 800 mg once daily and celecoxib, a cyclooxygenase (COX)-2 inhibitor, 200 mg once daily showed a greater significant reduction in pain and Lequesne Index than placebo. In the intent-to-treat population, pain reduction at day 182 was significantly greater in the chondroitin sulfate and celecoxib groups than with placebo, while no difference was observed between chondroitin sulfate and celecoxib. All treatments demonstrated excellent safety profiles during the duration of the study. However, long-term treatment with NSAIDS is still of concern because of increased cardiovascular risk. As pharmaceutical-grade chondroitin sulfate (800 mg/day) was superior to placebo and similar to celecoxib in reducing pain and improving function over six months in symptomatic knee osteoarthritis, the researchers considered that this formulation of chondroitin sulfate should be considered a first-line treatment in the medical management of knee osteoarthritis (66).

Pelletier et al compared chondroitins 4 & 6 sulfate 1200 mg (3 × 400 mg capsules) once daily to celecoxib 200 mg (plus 2 placebo capsules) once daily in a randomized, double-blind, double-dummy study in 138 patients with knee osteoarthritis (67). This originality of this study was its focus on cartilage volume measured by magnetic resonance imaging (MRI). Patients had primary symptomatic knee osteoarthritis diagnosed according to ACR criteria (57), with clinical signs of synovitis and grade 2-3 disease severity, according to the Kellgren-Lawrence radiographic scoring scale (68).

In the intent-to-treat analysis at 24 months, chondroitin sulfate- versus celecoxib-treated patients had a significant reduction in cartilage volume loss in the medial tibial plateau (-6.3 ± 3.2% vs -8.1 ± 4.2%; $p = 0.018$) and medial condyle compartments (-5.5 ± 3.9% vs -7.7 ± 4.7%; $p = 0.008$). There was no significant effect seen in the lateral compartment. There was a trend towards a statistically significant reduction in synovial thickness with chondroitin sulfate (-0.66 ± 22.72 mm), but not celecoxib (+17.96 ± 33.73 mm; $p = 0.076$), associated with a significant decrease in cartilage volume loss in the medial compartment ($p = 0.045$). The study demonstrated, for the first time in a 2-year randomized controlled trial using quantitative magnetic resonance imaging, that chondroitin sulfate was superior to celecoxib at reducing cartilage volume loss in patients with knee osteoarthritis. There was a marked reduction in the incidence of joint swelling and/or effusion in both groups, and both treatments were effective in reducing disease symptoms and quality of life over time. Both chondroitin sulfate and celecoxib showed similar favorable tolerability profiles, including cardiovascular events over the 24-month study period (67).

As well as demonstrating the superiority of pharmaceutical-grade chondroitin sulfate in reducing long-term progression of knee osteoarthritis cartilage volume loss, the study also demonstrates the potential NSAID-sparing effect of chondroitin sulfate in patients with osteoarthritis.

This was confirmed by a pharmacy-based observational study, which showed that long-term use of chondroitins 4 & 6 sulfate (at a dosage of 800-1200 mg daily in the majority of patients) reduced the use of NSAIDs in patients with osteoarthritis (69). A total of 844 patients filling a prescription for chondroitins 4 & 6 sulfate 400 mg were included and classified into recent users (≤3 months of continuous use) or long-term users (>3 months of continuous use). Mean treatment duration with chondroitin sulfate was 227 days (range 30-719 days). Compared with recent users, long-term users had significantly lower current (44.4% vs 52.5%; $p<0.05$) and long-term use of NSAIDs (11.8% vs 18.5%; $p<0.05$). Analgesic use was also lower in long-term chondroitin sulfate users (70.3% vs 79.3%; $p<0.01$).

Safety

The safety of highly-purified pharmaceutical-grade chondroitin sulfate has been reviewed by K. D. Rainsford (29). Although the clinical monitoring and reporting of AEs in published trials is variable, and data from long-term studies are limited, the incidence and severity of chondroitin sulfate-related AEs is low and similar to that of placebo at the upper clinical dose limit of chondroitin sulfate 1200 mg/day. The Cochrane Collaboration systematic review of chondroitin for osteoarthritis concluded that chondroitin sulfate appears to be well tolerated, with no major safety issues (53).

Place of highly-purified chondroitin sulfate within international guidelines

In Europe, where pharmaceutical-grade preparations of highly-purified chondroitin sulfate are available, the European League Against Rheumatism (EULAR) includes chondroitin sulfate in its recommendations for symptomatic pain relief and improving joint function in knee osteoarthritis (evidence grade 1b) (19), and hand (evidence grade 1b) and hip osteoarthritis (evidence grade A) (18, 23). Furthermore, the algorithm for the management of knee osteoarthritis developed by a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) positions long-term SySADOA therapy with chondroitin sulfate as a Step 1 treatment option for patients with symptomatic osteoarthritis (70). The task force also considers that there is evidence to support potential benefits beyond symptom control for the use of long-term administration of pharmaceutical-grade chondroitin 4 & 6 sulfate in the management of knee osteoarthritis, with the potential for clinically relevant delay in joint structure changes. ESCEO cautions that the highly-purified chondroitin sulfate used

in the study on which this recommendation is based (62) should be distinguished from that of low-quality chondroitin sulfate preparations available OTC outside Europe (70).

However, support for the use of chondroitin sulfate in treatment guidelines is inconsistent, and there is a degree of disagreement among guidelines reflecting conflicting evidence in the literature based on trials where patient numbers or flaws in study design may have limited the evaluation of outcome measures, and with mixed endpoints and timescales. This is compounded by the lack of pharmaceutical-grade chondroitin sulfate in preparations available in countries such as the USA and a failure by authors of systematic reviews to differentiate whether trials included have used pharmaceutical-grade chondroitin sulfate or nutritional supplements containing lower-grade chondroitin sulfate.

This is reflected in a recent systematic review of recommendations and guidelines for the management of osteoarthritis by the Chronic Osteoarthritis Management Initiative of the US Bone and Joint initiative which found that, while a number of organizations recommend or conditionally recommend the use of chondroitin sulfate, there remain some organizations that rate supporting evidence for the use of chondroitin sulfate inconclusive, or do not recommend its use (71). These findings were echoed by an earlier critical appraisal of then-current treatment guidelines by the Osteoarthritis Research Society International (OARSI), which found that, despite evidence from systematic reviews of randomized controlled trials of chondroitin sulfate and its own systematic review of the current research evidence, its use was recommended by fewer than 50% of treatment guidelines in which chondroitin was considered (72).

For example, the American College of Rheumatology (ACR) guidelines notes the lack of available pharmaceutical-quality chondroitin sulfate preparations in the US and does not recommend over-the-counter (OTC) nutritional supplement preparations of chondroitin sulfate for knee and hip osteoarthritis (16). Although the 2008 OARSI evidence-based recommendations for the management of hip and knee osteoarthritis (20) recommended chondroitin sulfate for symptomatic relief in knee osteoarthritis and for structure-modifying effects in knee osteoarthritis, a more recent update (2010) of the OARSI recommendations concluded that the heterogeneous results from recent trials weakened the evidence for relief of pain, although still finding evidence for the structure-modifying effects of chondroitin sulfate, based on a small but significant reduction in the rate of decline of joint space narrowing over time (21). The most recent OARSI guidance for knee osteoarthritis assesses chondroitin sulfate of uncertain benefit for symptom relief and does not recommend chondroitin sulfate for disease modification (17), despite the estimated Effect Size for pain ranging from small (0.13) to moderate/large (0.75). These decisions were made on the basis of a high degree of heterogeneity in studies analyzed, and mixed results regarding disease modification.

Finally, the Pan-American League of Associations for Rheumatology (PANLAR) recommendations support chondroitin sulfate for symptomatic pain relief and improving joint function, and notes a number of studies in support of chondroitin sulfate in delaying the progression of osteoarthritis (73).

Pharmaceutical-grade chondroitin sulfate versus food supplements

Chondroitin sulfate is usually derived from bovine, porcine, chicken, or fish cartilage sources by extraction and purification procedures. Unlike in Europe, where standardized, highly-purified pharmaceutical-grade chondroitin has been prescribed for the treatment of osteoarthritis for some years, in a number of countries, including the USA, chondroitin sulfate is available only as a nutraceutical or dietary supplement (74). Pharmaceutical-grade formulations are required by national health regulators to reach strict standards of high and standardized quality and purity and to demonstrate specific characteristics and properties, including structural characterization and parameters such as charge density and molecular mass, designed to protect patients from ineffective or harmful drugs and to ensure safety and therapeutic reproducibility (28).

In contrast, food supplements are not required to reach the same level of purity as pharmaceutical-grade chondroitin sulfate, should not be considered bioequivalent to prescription formulations, and may not even contain the amount of constituent indicated on the label (5, 75-77).

The reference standard for pharmaceutical-grade sodium chondroitin sulfate, as defined by the European Pharmacopoeia monograph (78), is produced from both terrestrial or marine origin. Like other natural polysaccharides, the pharmacological/biological activity of chondroitin sulfate is affected by the source material, manufacturing process, purity of the extract, presence of contaminants, and other factors (28). Species of origin / tissue source or production process may result in substantial differences in the structural organization and disaccharide composition of chondroitin sulfate (28) and modify the way chondroitin sulfate acts on osteoarthritic cartilage (26, 49).

ESCEO has recently completed an evidence-based review of the issue of non-eqivalent medications in osteoarthritis, and has released a position paper advocating that biologically-active complex molecules such as chondroitin sulfate and glucosamine sulfate should be treated as “biosimilars”, and only formulations clearly supported by the evidence base should be used in clinical practice (79). ESCEO therefore recommend only prescription-grade chondroitin sulfate to maximize clinical outcomes; claims of eqivalence from other formulations should be considered inappropriate (79).

It is therefore clear that caution should be exercised in interpreting the results of trials of different chondroitin sulfate formulations. Also, differences in pharmaceutical purity, different pharmaceutical formulations, and differences in dose regimen between prescription products and dietary supplements further complicate the interpretation and comparison of efficacy trials of chondroitin sulfate (74).

This is illustrated by recent meta-analysis and results from large-scale clinical trials, which have reported variable and at times conflicting efficacy for chondroitin sulfate in patients with symptomatic osteoarthritis (16, 72, 80-82), probably because of differences in study design, patient populations, investigator bias, or varying drug formulations and level of purity (5, 74, 83). Therefore, it is important in interpreting efficacy and safety data for chondroitin sulfate that the source

and purity of the preparation under investigation are clearly stated, and the implications of differentiating data relating to highly-purified pharmaceutical-grade chondroitin sulfate and food supplement grade chondroitin sulfate are understood.

Efficacy and safety concerns with food supplements

A wide range of beneficial therapeutic activities are claimed for food supplements and nutraceuticals, often with limited or no scientific validation (84, 85). The use in food supplements of extracts of plant or animal origin known to have physiological effects raises important questions about safety and efficacy, as the composition, purity, amount, and origin of active ingredient present in marketed products can be highly variable. Analysis of the quality of a wide range of different commercially available nutraceuticals and food supplements has shown variable quality, not only between different products but within batches, with implications for safety and efficacy when products are noncompliant with label claims or contain contaminants or inappropriate components (84).

With particular regard to chondroitin sulfate, studies of chondroitin sulfate-containing supplements have shown wide variations between the labeled amount and the level present (75-77). Only five of 32 tested supplements in one study in the US contained within ±10% of the labeled amount of chondroitin sulfate, and 17/32 had less than 40% of the stated content (77). The actual chondroitin sulfate content of tested products ranged from 33% to 110% of that claimed on the label. There were also significant variations between products in the structural organization of chondroitin sulfate, and evidence of contamination with hyaluronan.

Such quality and consistency issues have implications for efficacy and safety. Therefore, clinical data from well-designed studies of pharmaceutical-grade chondroitin sulfate should not be extrapolated to support clinical efficacy claims of food supplements; nor should results from trials of chondroitin sulfate-containing food supplements be used to draw conclusions about the efficacy of pharmaceutical-grade chondroitin sulfate.

The disparity in the effects of chondroitin sulfate in the treatment of osteoarthritis could depend on the characteristics of the chondroitin sulfate employed, including source, purity, or structural organization.

Indeed, proteomic analysis of the effects on human intra- and extracellular chondrocyte proteomes of three different brands of chondroitin sulfate with different origins or purity has shown that some chondroitin compounds can induce activation of inflammatory and catabolic (tissue degradation) pathways, in contrast to the anabolic (tissue repair) responses observed with highly-purified pharmaceutical-grade chondroitin sulfate (83). This study emphasizes the importance of the source of origin and purity of chondroitin sulfate for pharmaceutical applications.

Conclusions

Highly-purified pharmaceutical-grade chondroitin sulfate has demonstrated efficacy and a placebo-like tolerability profile in the treatment of symptomatic osteoarthritis, with a well-documented consolidated benefit/risk profile and a long history in the treatment of different forms of osteoarthritis. Although the clinical result is mild-to-moderate, its efficacy in decreasing the pain of osteoarthritis and slowing cartilage destruction is clinically meaningful, and pharmaceutical-grade chondroitin sulfate should be considered as part of the therapeutic arsenal. Furthermore, chondroitin sulfate intake may contribute to decreasing the consumption of other drugs with more harmful side effects, such as NSAIDs. This is particularly important in chronic conditions, such as osteoarthritis, where long-term treatment is necessary.

Chondroitin sulfate acts *in vitro* by several mechanisms that may potentially explain an *in vivo* influence on symptoms and on the course of osteoarthritis Indeed, highly-purified chondroitin sulfate exerts a range of immunomodulatory and anti-inflammatory effects that impart beneficial effects on the chondrocytes, synovial membrane, and subchondral bone, all components involved in osteoarthritis.

The results of trials of highly-purified pharmaceutical-grade chondroitin sulfate are considered to support the inclusion of chondroitin sulfate as a recommended treatment option by some international guidelines for the management of osteoarthritis, while other guideline committees consider that the high degree of heterogeneity in available studies, and mixed results regarding disease modification, currently preclude the addition of chondroitin sulfate as a recommended treatment modality for the management of osteoarthritis. However, in some countries, chondroitin sulfate is available only in food supplements or nutraceutical preparations, which are not required to meet the strict standards of high and standardized quality and purity required by national health regulators for pharmaceutical-grade formulations. Therefore, clinical data from well-designed studies of pharmaceutical-grade chondroitin sulfate should not be extrapolated to support clinical efficacy claims of food supplements; nor should results from trials of chondroitin sulfate-containing food supplements be used to draw conclusions about the efficacy of pharmaceutical-grade chondroitin sulfate.

In conclusion, highly purified pharmaceutical-grade CS is effective and safe in the treatment of patients with OA in different joints (i.e. knee, hand), with a positive benefit/risk profile; for these reasons it should be considered a first-line treatment in the medical management of these patients.

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