

# Chondroitins 4 and 6 Sulfate in Osteoarthritis of the Knee

## A Randomized, Controlled Trial

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**Objective.** To determine whether chondroitin sulfate (CS) is effective in inhibiting cartilage loss in knee osteoarthritis (OA).

**Methods.** In this randomized, double-blind, placebo-controlled trial, 300 patients with knee OA were recruited from an outpatient clinic, from private practices, and through advertisements. Study patients were randomly assigned to receive either 800 mg CS or placebo once daily for 2 years. The primary outcome was joint space loss over 2 years as assessed by a posteroanterior radiograph of the knee in flexion; secondary outcomes included pain and function.

**Results.** Of 341 patients screened, 300 entered the study and were included in the intent-to-treat analysis. The 150 patients receiving placebo had progressive joint space narrowing, with a mean  $\pm$  SD joint space loss of  $0.14 \pm 0.61$  mm after 2 years ( $P = 0.001$  compared with baseline). In contrast, there was no change in mean joint space width for the 150 patients receiving CS ( $0.00 \pm 0.53$  mm;  $P$  not significant compared with baseline). Similar results were found for minimum joint space narrowing. The differences in loss of joint space width between the two groups were significant for mean joint space width ( $0.14 \pm 0.57$  mm;  $P = 0.04$ ) and for minimum joint space width ( $0.12 \pm 0.52$  mm;  $P = 0.05$ ). CS was well tolerated, with no significant differences in rates of adverse events between the two groups.

**Conclusion.** While there was no significant symptomatic effect in this study, long-term treatment with CS may retard radiographic progression in patients with OA of the knee. However, the clinical relevance of the observed structural results has to be further evaluated, and further studies are needed to confirm the structural effects of CS.

Osteoarthritis (OA) is a major public health problem (1) and the leading cause of disability in developed countries, particularly in the elderly (2). The prevalence of symptomatic OA has been assessed at 12% in the US population of persons ages 25–75 years (3). Direct and indirect costs for OA of the knee and hip in the US in 1994 were \$15.5 billion (4) and account for a substantial proportion of costs in managed care plans (5).

Current treatment options for OA include pain relief with analgesics (acetaminophen, opioids), non-steroidal antiinflammatory drugs (NSAIDs), exercise, patient education, and joint arthroplasty (6). The recommendations of the European League Against Rheumatism (7) and the guidelines of the American College of Rheumatology (ACR) (8) include these treatment options. In two recent meta-analyses, chondroitin sulfate (CS) and glucosamine were found to be probably effective for reducing pain and improving function in OA of the knee (9,10), although likely publication bias has been suggested (9).

However, the ultimate goal of treating OA is not only to relieve symptoms, but also to halt disease progression. Based on limited preliminary evidence, it has therefore been suggested that a number of drugs, including glucosamine and CS, should be formally tested for their disease-modifying properties (11). The main evaluation criterion for disease-modifying drugs is the

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prospective evaluation of radiographic changes by analysis of joint space narrowing (12,13).

Structure-modifying effects have been suggested by the results of 3 large randomized clinical trials, 1 of diacerein for hip OA (14) and 2 of glucosamine sulfate for knee OA (15,16). Another constituent of human cartilage, similar to glucosamine, is CS. Both compounds are absorbed from the gut (17,18) and appear to be capable of increasing proteoglycan synthesis in articular cartilage (19,20).

The specific aims of this study were 1) to determine whether CS can delay or halt structural changes in OA of the knee, as assessed by radiographic followup over 2 years, and 2) to determine whether this translates in terms of reduced pain and improved physical function.

## PATIENTS AND METHODS

**Study design and patients.** This randomized, double-blind, placebo-controlled study on patients with knee OA was conducted from March 1996 to May 2001. Patients were recruited from the Outpatient Clinic of Rheumatology of the University Hospital Zurich, Switzerland; from rheumatology practices in the Zurich area; and through advertisements.

Inclusion criteria were age 40–85 years with clinically symptomatic knee OA (knee pain while standing, walking, and/or on motion for at least 25 of the 30 days prior to study entry, with no required minimum level of pain on the day of entry) diagnosed according to the ACR clinical and radiographic criteria for OA of the knee (21). Patients with OA of grade 1, 2, or 3 according to the Kellgren/Lawrence (K/L) scoring system were eligible for study entry (22). Patients with OA of K/L grade 4, indicating a greatly narrowed joint space with sclerosis of subchondral bone, were excluded. The target knee was defined as the most symptomatic knee at study entry.

Exclusion criteria were as follows: the presence of any causes of secondary OA including calcium pyrophosphate deposition disease (12); traumatic knee lesions; severe comorbidity (specifically, severe renal, heart, lung, or neurologic disease); previous joint surgery; intraarticular medications, including corticosteroids, in the past month; and the foreseeable prospect of major surgery during the 2-year study period. For potentially longer-acting substances such as CS and glucosamine, a washout period of 3 months was required. The trial was approved by the Ethics Committee of the University Hospital Zurich.

**Intervention.** All patients who provided written informed consent and met the study criteria were randomly assigned to receive either an 800-mg tablet of chondroitins 4 and 6 sulfate (CS [Condrosulf]; IBSA, Lugano, Switzerland) or an identical tablet of placebo daily for 2 years. Both active-agent and placebo pills contained magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide.

Condrosulf is a prescription drug containing highly

purified CS of fish origin in a concentration not <95%. It has an average molecular weight of ~45–55 kd and a nonsulfated disaccharide of chondroitin 4-sulfate to nonsulfated disaccharide of chondroitin 6-sulfate ratio of ~0.5. This product has been approved as a prescription treatment for OA at a daily dosage of 800 mg in many countries throughout Europe.

The randomization was done by computer in blocks of 4. Each patient received a randomization number. Individual envelopes containing the patient's code according to the treatment assignment were stored and at the end of the study, were given to the statistician (FDV), who was blinded to patients' treatment assignments.

For rescue analgesia, patients were allowed to take acetaminophen in 500-mg tablets at a maximum dosage of 3 gm/day. For secondary rescue, NSAIDs were allowed up to a maximum period of 5 consecutive days if the primary rescue analgesia with acetaminophen was insufficient. Physical therapy was limited to application of warmth and strengthening exercises when deemed necessary by the patient. No other interventions were allowed, including steroid injections.

**Data collection procedures.** At the baseline visit, patients were evaluated for inclusion and exclusion criteria based on the results of a clinical examination and a standing antero-posterior radiograph of the knee in extension. Patients included in the study had an additional radiograph of both knees using a partial flexion view as described by Dieppe et al (23). The radiograph was a single, posteroanterior, weight-bearing view of both knees flexed to ~20° (partial flexion view [23]). Patients were positioned with the toes up, directly under the edge of the cassette, and the knees bent to lie against the cassette. The x-ray beam was directed 5° downward at a site midway between the popliteal spaces. A foot map was drawn for each patient in order to reproduce the position when radiographed after 24 months. All radiographs were performed at a single unit of the Department of Radiology at the University Hospital Zurich. The radiographs were transferred to the Centre Hospitalier Lyon Sud in France, and then digitized. The digitized images were analyzed by a single reader (EV) who was unaware of the treatment assignment and time sequence of the radiographs. To limit x-ray exposure, the extended-view radiograph was not repeated at the end of the study.

Blood samples for routine laboratory tests were obtained from the patients who were included in the study. Patients completed a questionnaire that included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (24). The clinical examination by the trained research assistant included measurements of body weight, height, blood pressure, and 50-foot walking time.

Followup assessments were conducted by mail every 3 months over the 2-year study period. At each assessment, patients were asked to complete the WOMAC and to mail back the completed form along with their treatment diary for the previous 3-month period. The diaries were examined for entries about study drug use, adverse events experienced, and rescue medications taken. Compliance with study treatment was also assessed by pill counts when the patients returned to the clinic for the 12-month and 24-month evaluations. The followup visits at 12 and 24 months also included a clinical

**Table 1.** Baseline characteristics of the patients\*

	Intent-to-treat analysis (n = 300)		All patients completing the 2-year study (n = 219)	
	Chondroitins 4 and 6 sulfate (n = 150)	Placebo (n = 150)	Chondroitins 4 and 6 sulfate (n = 110)	Placebo (n = 109)
Women, no. (%)	76 (51)	78 (52)	55 (50)	55 (50)
Age, years	62.5 ± 9.1 (61, 64)/63	63.1 ± 10.7 (61, 65)/64	62.4 ± 9.0 (61, 64)/63	62.6 ± 10.6 (61, 65)/64
Body mass index, kg/m <sup>2</sup>	27.7 ± 5.2 (27, 29)/26.8	28.1 ± 5.5 (27, 29)/27.3	27.4 ± 4.9 (26, 28)/27	28.1 ± 5.7 (27, 29)/27
Minimum joint space width, mm	2.41 ± 0.14 (2.1, 2.7)/2.7	2.35 ± 0.14 (2.1, 2.6)/2.4	2.37 ± 0.17 (2.0, 2.7)/2.7	2.45 ± 0.17 (2.0, 2.7)/2.4
Mean joint space width, mm	3.04 ± 0.14 (2.8, 3.3)/3.3	3.00 ± 0.15 (2.7, 3.3)/3.3	3.05 ± 0.18 (2.8, 3.4)/3.4	3.10 ± 0.17 (2.7, 3.4)/3.3
50-foot walking time, seconds	15.2 ± 3.2 (15, 16)/15	15.6 ± 3.4 (15, 16)/15	15.0 ± 3.1 (15, 16)/14	15.1 ± 2.7 (14, 16)/15
Time to climb 4 stairs, seconds	33.3 ± 10.8 (32, 35)/31	35.5 ± 15.8 (33, 38)/31	32.8 ± 11.6 (31, 35)/30	33.5 ± 9.9 (32, 35)/31
WOMAC score, range 0–10				
Total	2.3 ± 1.6 (2.0, 2.5)/2.0	2.6 ± 1.7 (2.3, 2.9)/2.2	2.2 ± 1.5 (1.9, 2.5)/1.9	2.4 ± 1.5 (2.1, 2.7)/2.2
Pain	2.5 ± 1.6 (2.3, 2.8)/2.2	2.7 ± 1.8 (2.5, 3.0)/2.6	2.4 ± 1.5 (2.1, 2.7)/2.2	2.5 ± 1.6 (2.2, 2.8)/2.4
Function	2.1 ± 1.6 (1.8, 2.4)/1.7	2.5 ± 1.8 (2.2, 2.7)/2.0	2.0 ± 1.6 (1.7, 2.3)/1.7	2.3 ± 1.6 (2.0, 2.6)/1.9
Stiffness	3.0 ± 2.3 (2.6, 3.4)/2.5	3.5 ± 2.5 (3.0, 3.9)/3.0	3.0 ± 2.2 (2.6, 3.4)/2.5	3.2 ± 2.3 (2.8, 3.7)/2.5

\* Except where indicated otherwise, values are the mean ± SD (95% confidence interval)/median. There were no statistically significant differences between the study groups. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

examination and routine laboratory tests, and a second partial flexion view radiograph of the knees was obtained at the 24-month visit.

**Measures.** The primary study end points were the minimum and mean joint space width of the more severely affected compartment of the target knee. The minimum and mean joint space width was measured on digitized radiographs using an image analysis system (Acticiel, Lyon, France) (25). The outer limit of the measured region was delineated by the nonosteophytic edge of the femorotibial compartment. The inner limit of the measured region was then delineated at a constant distance from the outer limit by the computer. The distance was fixed to represent 20% of the length of the tibial plateaus. Afterward, the measurements were automatically calculated by the computer (25). Measurement of both the minimum and the mean joint space width of the femorotibial compartment yielded an intraclass correlation coefficient (ICC) of 0.98, based on 2 evaluations of the digitized radiograph. The ICC was unrelated to the medial or lateral location of the measurements.

The secondary outcome measures, individual symptoms of OA, were assessed by the WOMAC, a validated, disease-specific, self-administered instrument for evaluating joint pain (5 questions), stiffness (2 questions), and limitation of physical function (17 questions) (24). Numerical rating scales ranging from 1 to 10 were used as reported for the German version (26).

**Statistical analysis.** We estimated that a total of 160 patients (80 patients in each group) would be necessary to have a power of 80% to show a 0.4-mm difference in the mean reduction in joint space narrowing between the group receiving placebo (expected reduction  $-0.4 \pm 0.9$  mm mean ± SD) (27) and the group receiving CS (expected reduction  $0 \pm 0.9$  mm) with a 5% significance level. The expected difference in the mean reduction of the joint space of 0.4 mm over 2 years was based on a recent report just before initiation of the study in 1994 (27). The strengthened criterion of a joint space loss of 0 mm on average in the group receiving CS was chosen in order

to get a relevant difference between the two study groups. Accounting for an estimated dropout rate of 40%, the minimum number of patients to be included was 266. To be on the safe side, we included 150 patients per group.

Both an intent-to-treat analysis, including all randomized patients, and an analysis limited to those completing the 2 years of the study (per-protocol completer analysis) were performed. The analysis consisted of a comparison of data from the last visit with data from the baseline visit. Patients who dropped out of the study had a second radiographic evaluation at the time they dropped out, with the exception of the 16 patients who dropped out within 1 month of study entry.

Joint space narrowing in the target knee was calculated in each patient. The mean changes were compared in the two study groups using the nonparametric Wilcoxon test (28), because none of the criteria followed a normal distribution (Shapiro and Wilks test [29]).

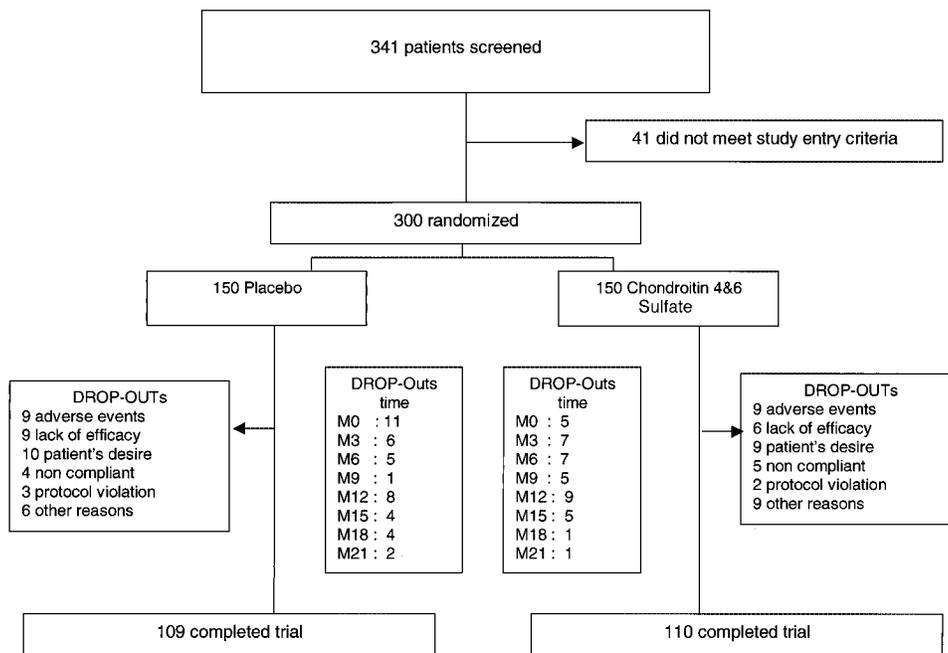
The analysis of the WOMAC score, which was obtained every 3 months, consisted of a repeated-measures analysis of variance and a comparison of the 2-year variations using a Wilcoxon test. Similar analyses were performed for each of the WOMAC subscales.

The total consumption of rescue drugs during the trial and the average number of tablets study drug taken per day were compared between the two study groups using the Wilcoxon test. The correlation between radiographic measures and clinical outcomes was assessed using Spearman's correlation test (28).

The analysis of adverse events, performed with Fisher's exact test (2-tailed), was a comparison of the number of patients in each group who had a specific sign or symptom (29). All statistical tests were 2-sided. *P* values less than or equal to 0.05 were considered significant.

## RESULTS

Of 341 patients screened, 300 fulfilled the inclusion criteria and were randomly assigned to receive



**Figure 1.** Flow of patients enrolled in the study. Dropout times were as follows: M0 = months 0–2; M3 = months 3–5; M6 = months 6–8; M9 = months 9–11; M12 = months 12–14; M15 = months 15–17; M18 = months 18–20; and M21 = months 21–23.

either CS or placebo. At the time of inclusion, patients in the two groups had similar characteristics (Table 1). The severity of initial OA changes was not significantly different between the two groups based on K/L scores of the target knees ( $P > 0.5$ ). Forty patients (27%) in the CS group and 41 patients (27%) in the placebo group did not complete the 2-year treatment course; there were no significant differences in reasons for withdrawal (Figure 1). The proportion of patients who reported taking more than 70% of the tablets during the clinical trial was 69% in the CS group and 72% in the placebo group, with no significant difference between the groups.

**Radiographic measures.** The left side of Table 2 shows the change in tibiofemoral joint space width for all randomized patients. Patients who received placebo experienced significant reductions in the mean joint space width ( $-0.14 \pm 0.61$  mm mean  $\pm$  SD;  $P = 0.001$  compared with baseline) and minimum joint space width ( $-0.07 \pm 0.56$  mm;  $P = 0.05$  compared with baseline). In contrast, the loss of joint space was null in the CS group. The difference in loss between the two groups was significant for the mean joint space width ( $0.14 \pm 0.57$  mm;  $P = 0.04$ ) and for the minimum joint space width ( $0.12 \pm 0.52$  mm;  $P = 0.05$ ). Similar results, with greater

**Table 2.** Comparison of joint space changes over 2 years in patients treated with chondroitin sulfate and placebo (intent-to-treat analyses)\*

Joint space narrowing, mm	All patients (n = 300)				All patients with minimum joint space width $\geq 1$ mm at entry (n = 225)			
	Chondroitins 4 and 6 sulfate (n = 150)	Placebo (n = 150)	Difference	$P^\dagger$	Chondroitins 4 and 6 sulfate (n = 114)	Placebo (n = 111)	Difference	$P^\dagger$
Minimum	$0.045 \pm 0.48$ (-0.03, 0.12)/0.0	$-0.07 \pm 0.56$ (-0.16, 0.02)/0.0	$0.12 \pm 0.52$ (0.00, 0.24)/0.0	0.05	$0.05 \pm 0.53$ (-0.05, 0.14)/0.0	$-0.14 \pm 0.57$ (-0.25, -0.03)/0.0	$0.19 \pm 0.55$ (0.04, 0.33)/0.0	0.01
Mean	$0.00 \pm 0.53$ (-0.08, 0.09)/0.0	$-0.14 \pm 0.61$ (-0.24, -0.04)/0.0	$0.14 \pm 0.57$ (0.01, 0.27)/0.0	0.04	$0.01 \pm 0.54$ (-0.09, 0.11)/0.0	$-0.20 \pm 0.58$ (-0.31, -0.09)/0.0	$0.21 \pm 0.56$ (0.06, 0.36)/0.0	0.006

\* Values are the mean  $\pm$  SD (95% confidence interval)/median.

† By the nonparametric Wilcoxon test.

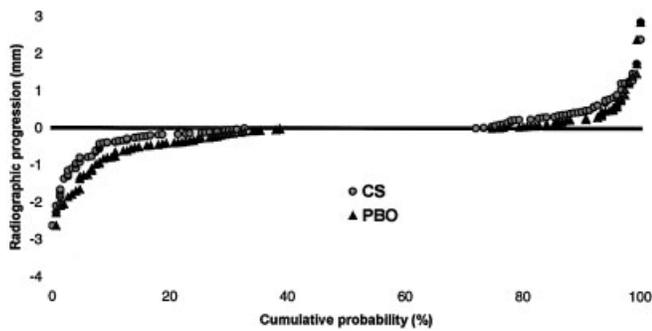


Figure 2. Cumulative probability plots of individual 2-year radiographic progression scores (mean joint space narrowing in mm) for the chondroitin sulfate (CS) and placebo (PBO) groups.

differences between the two groups, were obtained in the 219 patients who completed the 2-year study (per-protocol patients) (data not shown). The cumulative probability plots of individual 2-year radiographic progression scores are shown in Figure 2, presented according to the recommendations by Landewé and van der Heijde (30).

For 75 patients (36 in the CS group and 39 in the placebo group), the baseline joint space width was <1 mm on the partial flexion view radiographs. It was recently suggested that patients must have a minimum joint space width of at least 1 mm to be included in studies evaluating radiographic progression in OA of the knee (31). When we included only patients fulfilling this criterion, the results were similar in the CS group, but the loss was greater in the placebo group; the difference in change between the groups was  $0.21 \pm 0.56$  mm for the mean joint space width ( $P = 0.006$ ) and  $0.19 \pm 0.55$  mm for the minimum joint space width ( $P = 0.01$ ) (right side of Table 2).

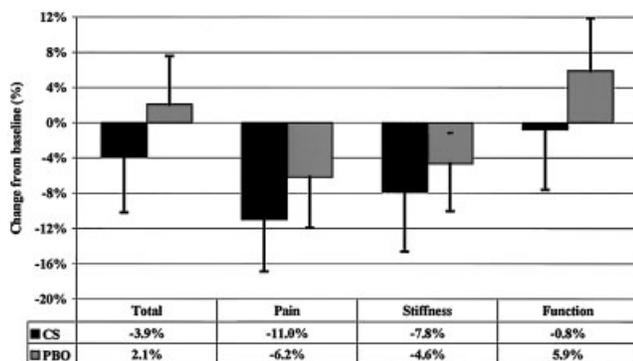


Figure 3. Changes in Western Ontario and McMaster Universities Osteoarthritis Index scores over 2 years. Values are the mean and SEM. Intergroup differences were not statistically significant. CS = chondroitin sulfate; PBO = placebo.

Table 3. Adverse events reported in daily logbooks by patients with knee osteoarthritis treated with chondroitin sulfate or placebo (frequencies of at least 5% with one of the two study groups)\*

	Chondroitins 4 and 6 sulfate (n = 150)	Placebo (n = 150)
Upper respiratory tract infection	44 (29)	46 (31)
Headache	11 (7)	14 (9)
Abdominal pain	6 (4)	17 (11)
Allergic episode	9 (6)	9 (6)
Cardiac problem	9 (6)	8 (5)
Urinary tract infection	8 (5)	7 (5)

\* Values are the number (%) of patients. *P* values for intergroup comparisons were not significant.

The mean joint space width at baseline had no influence on radiographic progression. In addition, baseline pain severity had no influence on radiographic progression, either in the CS group or in the placebo group.

**Symptoms.** Over the 2-year study period, the total WOMAC score did not show a significant improvement, either for study completers analysis or for the intent-to-treat analysis. The intent-to-treat analysis yielded improvement for the CS group on all WOMAC subscales, including pain, stiffness, and function, while the placebo group showed less improvement on the pain and stiffness subscales and some worsening on the function subscale on average. However, there were no statistically significant differences between the two groups (Figure 3). Neither at baseline nor at the end of the study did weight differ statistically between the two groups; furthermore, weight changes in the two groups were similar (mean change  $-0.20$  kg in the CS group versus  $-0.09$  kg in the placebo group) and were not significant. Similar amounts of rescue drugs were taken in both groups over time, without statistically significant differences between groups.

**Adverse events.** Table 3 lists the adverse events reported with a frequency of at least 5% in 1 of the 2 study groups. There was no statistically significant difference in the frequency of any event between the two groups. Adverse events led to the withdrawal of 9 patients from each study group. Only 2 events were judged to be possibly related to CS (abdominal pain and nausea in 1 patient each). All other adverse events were judged to be unrelated to the study drug and were most probably caused by concomitant disorders.

## DISCUSSION

In this randomized, double-blind, placebo-controlled study, CS halted structural changes in OA of

the knee as assessed by radiographic followup over 2 years. While patients in the placebo group lost, on average, 0.07 mm of the mean joint space width per year, patients taking CS did not experience any loss. CS was both safe and well tolerated.

The validity of the study is supported by both the per-protocol and the intent-to-treat analyses as well as by the relatively low dropout rate of 27%. The validity of the results is also supported by the annual average loss of 0.07 mm in mean joint space width in patients receiving placebo; accounting only for those placebo group patients with a baseline joint space width of at least 1 mm, the annual average loss was 0.10 mm. These findings are similar to the annual average loss in joint space width reported in the recent literature (15,16). Investigators in the 2 glucosamine trials reported joint space losses of 0.06 mm (16) and 0.10 mm (15) for the placebo groups.

At the time of initiation of the study, we expected a mean joint space narrowing in the placebo group of ~0.4 mm over 2 years, based on an available report at that time (27). As indicated both by our results and by more recent reports, this estimate turned out to be too large (15,16). In fact, estimates of the annual rate of joint space narrowing in OA knees tended to be larger in earlier studies. A review of 7 studies reported in 1990–1996 yielded a median estimate of 0.26 mm for the annual rate of joint space narrowing (32). Investigators in more recent larger-scale studies reported a natural rate of joint space narrowing of ~0.1 mm/year (15,16,33). Patient characteristics and methodologic features may be partly responsible for such variability (32).

Similar to the finding of the study by Reginster et al (15), the rate of OA progression in this study was not related to baseline pain as measured with the WOMAC pain subscale. This is consistent with the finding that pain is not closely related to radiographic severity in knee OA (34,35); it is also consistent with the suggestion that other factors may be more relevant for pain than radiographically detectable changes of the joint (36).

Important considerations in the measurement of joint space narrowing include radiographic positioning of the joint and the reading methods used. While extended radiographs were the standard technique at the planning and start of the study, we used both extended radiographs and the partial flexion view as described by Dieppe et al in 1995 (23). The partial flexion view is now generally considered to be superior to extended views (37,38), and it has been refined using different specifications for the positioning of the foot (37) and the use of fluoroscopy (25). However, none of

the reported protocols appears to be uniformly superior to the others (39). Therefore, while extended views were used for the inclusion and exclusion of patients, we used the measurements from the partial flexion view for the analysis. Because radiographs of flexed joints show more joint space narrowing compared with standing antero-posterior radiographs (39), a number of patients in this study with a K/L grade of 3 at study inclusion had a baseline minimum joint space width of <1 mm on partial flexion view radiographs. The exclusion of these patients from the analyses did not influence the main finding of the study. For the joint space measurements in this study, we used an independent automated analysis (25), which is considered superior to manual readings (40).

The results of this study suggest that treatment with CS over 2 years may stop the structural progression observed in OA. While the precise mechanism of action of CS has not yet been fully elucidated, the long-term effects could be due to the reported effect of this substance on cartilage metabolism. CS has been found to cause an increase in RNA synthesis by chondrocytes (41), which appears to correlate with an increase in the production of proteoglycans (19,20). Such effects may partly result from the competitive inhibition of degradative enzymes (42). In addition, CS may inhibit leukocyte elastase (43).

In the present study, there was no appreciable change in pain, stiffness, and function over 2 years. This finding is different from the results of previous studies with CS and glucosamine as summarized in 2 meta-analyses (9,10). The most likely reason for this result is the relatively low mean pain score at study entry, which left little room for improvement. The relatively low pain scores may be explained by the recruitment strategies used in this study. Most intervention studies in OA of the knee include patients who seek treatment because of symptoms. Instead, patients in this study were also recruited from a large university registry and through public announcements. These patients were included if they fulfilled the inclusion/exclusion criteria, but independently of an exacerbation of their symptoms.

While no significant symptomatic effect was found in this first randomized, double-blind, placebo-controlled study, CS may be able to halt structural changes in OA of the knee over 2 years. Further research is needed to determine whether this translates into clinically relevant gains in arthroplasty rates, decreased long-term disability, and reduced resource utilization.

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