Effect of chondroitin sulfate on cartilage volume loss and subchondral bone marrow lesions in osteoarthritis knee

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Background
Chondroitin sulfate (CS) is a major component of the extracellular matrix of many connective tissues, including cartilage, bone, skin, ligaments, and tendons.

Objective
The aim of this work was to study the effect of CS treatment for short time (6 months) clinically and using MRI on cartilage volume loss, subchondral bone marrow lesions (BMLs), and synovitis in patients with primary knee osteoarthritis (OA).

Patients and methods
A total of 50 patients with primary knee OA and clinical signs of synovitis were included in this study. They were divided into two treatment groups. Group 1 included 30 patients who received two capsules of CS (structum capsule 500 mg) once daily for 6 months. Group 2 included 20 patients who received placebo once daily for 6 months. Clinical, radiological, and laboratory assessments were performed for all patients. Cartilage volume loss, subchondral BMLs, and synovial membrane thickness were assessed with MRI at baseline and after 6 months for both groups.

Results
The CS group showed significantly less cartilage volume loss compared with the placebo group after 6 months for the global knee, lateral compartment and tibial plateaus. However, there were no significant differences in the medial compartment and trochlea between the two groups. Significantly lower BML scores were found for the CS group compared with the placebo group after 6 months, and there were no significant differences in synovial membrane thickness between the two groups. Disease symptoms were similar in both groups.

Conclusion
CS treatment significantly reduces the cartilage volume loss and subchondral BMLs in primary knee OA after 6 months of treatment. These findings suggested a joint structure-protective effect of CS.

Keywords:
chondroitin sulfate, MRI knee joint, primary knee osteoarthritis, structum

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Introduction

Of all the musculoskeletal conditions, osteoarthritis (OA) has the highest prevalence, affecting a significant percentage of the aging population [1]. The main features of OA include articular cartilage degeneration, subchondral bone abnormal remodeling, and synovial membrane inflammation, leading to joint swelling, synovitis, and pain [2]. Management of OA requires a long-standing combination of pharmacological and nonpharmacological treatment modalities to relieve pain and to maintain joint mobility in daily life [3]. Chondroitin sulfate (CS) is a major component of the extracellular matrix of cartilage implicated in its elasticity and its resistance to loading. It consists of repeated chains of sulfated and/or unsulfated d-glucuronic acid and N-acetyl-d-galactosamine residues [4]. CS is one of the most used molecules in the management of OA, and numerous clinical trials have shown its clinical benefits in decreasing pain, improving functional disability, and reducing NSAIDs or acetaminophen consumption [5]. Although its mechanisms of action remain unclear, in-vitro experiments suggest that CS stimulates the production of proteoglycans by chondrocytes and synoviocytes and inhibits the expression of interleukin-1-induced metalloproteinases and prostaglandin E2, thus preventing cartilage damage [6]. At the same time, CS has shown to have a positive effect on some of the OA-related pathological processes involving the synovial tissue and subchondral bone [7]. However, all other previous studies on disease-modifying OA

drugs have used conventional radiographs, which, although recognized by the authorities, might not have fully explored the drugs' protective effect, as this technique allows for only an indirect assessment of the cartilage [8]. Recent advances in MRI have enabled investigators to quantitatively assess cartilage volume, as well as the other joint structural changes occurring in the subchondral bone, menisci, and synovium. MRI also has the benefit of providing a multiplanar image of the whole joint and is the only imaging modality that can demonstrate subchondral BMLs [9,10].

Objective

The aim of this work was to study the effect of CS treatment for short time (6 months) clinically and using MRI on cartilage volume loss, subchondral BMLs, and synovitis in patients with primary knee OA.

Patients and methods

A total of 50 patients with primary knee OA and clinical signs of synovitis were recruited from private outpatient Rheumatology and Rehabilitation Clinics (Faisal and Boushahri polyclinics, Kuwait city, Kuwait). They were diagnosed according to the European League Against Rheumatism (EULAR) OA Task Force [11]. A guideline mainly for the clinical diagnosis of knee OA was published in 2010. It stated that the diagnosis should be based on three key symptoms (persistent knee pain, morning stiffness, and functional impairment) and three typical clinical signs (crepitus, restricted movement, and bony enlargement). There were 38 female and 12 male patients between 55 and 75 years of age who presented with medial or, with the less common, lateral tibiofemoral OA of the knee, and 25 patients (50%) had bilateral knee involvement. If both knees were affected by OA, the knee with more pronounced symptoms was selected if within the inclusion criteria.

Inclusion criteria

Patients who were symptomatic for more than 6 months with a baseline level of global pain score of at least 40 mm on a Visual Analog Scale (VAS) of 0–100 and all patients with radiographic OA knee as defined by Kellgren–Lawrence grades II or III [12] on an anteroposterior weight-bearing view taken at baseline were included in the study.

Radiologically, OA was divided into five grades as follows: 0, none; 1, doubtful; 2, minimal; 3, moderate; and 4, severe. Grade 0 indicated a definite absence of radiographic changes of OA and grade 2, in our opinion, indicated that OA was definitely present, although of minimal severity.

Exclusion criteria

Exclusion criteria were as follows: the presence of another rheumatic condition leading to secondary OA (rheumatoid arthritis or calcium pyrophosphate deposition disease), traumatic synovitis, allergy to CS, contraindications to MRI, and progressive serious medical conditions (cancer or end-stage renal disease). Patients were also excluded if they were being treated with corticosteroids (systemic or intra-articular), glucosamine, CS, or within the 6 months preceding selection they were treated with intra-articular hyaluronic acid.

The study was approved by the ethics committee of the Ministry of Health, State of Kuwait and the patients were included in the study after giving their informed consent after explanation of the purpose and procedures of the study.

All patients were subjected to the following:

(1) Complete history taking, including the duration of disease and drug therapy.
(2) Complete general and musculoskeletal examinations.
(3) Complete local knee examination, including the ligaments and menisci.
(4) VAS (0–100 mm).
(5) Lequesne algo function index (LFI).
(6) Radiography of both knees in the anteroposterior weight-bearing view.
(7) Laboratory investigations to exclude secondary OA (complete blood count, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, serum uric acid, and liver and renal function tests).

Treatment groups

Group 1: Thirty patients received two capsules of CS (structum capsule 500 mg, Avian CS, sodium salt; MA holder Pierre Fabre Médicament, Boulogne, France) once daily for 6 months (the CS group).

Group 2: Twenty patients received placebo once daily for 6 months (the placebo group). During the study, in case of pain flare, a rescue medication was allowed, starting as recommended by all international guidelines [3] with paracetamol, which was allowed up to 4 g/day for a maximum of 4 days. In case paracetamol was ineffective to relieve pain, a NSAID could be used.

Lequesne algo function index

This score was used to assess the effectiveness of therapeutic interventions for OA knee. It consists of a 10-question survey given to patients with knee OA, five questions relating to pain or discomfort, one question dealing with the maximum distance walked,

and four questions about activities of daily living. The total questionnaire is scored on a scale from 0 to 24. Higher scores indicate that there is greater functional impairment. The classification is as follows: more than 13, extremely severe; 11–13, very severe; 8–10, severe; 5–7, moderate; 1–4, mild; and 0, none [13].

Knee MRI

MRI was performed using a 1.5 T and 3 T GE system (General Electric Healthcare scanner units, Florida, USA) to the target knee for both groups at baseline and after 6 months for assessment of cartilage volume loss, synovial membrane thickness, and subchondral BML score.

(1) Cartilage volume: The change in cartilage volume over time was calculated for the entire knee, tibial plateaus, the medial and lateral compartments, and the trochlea [14]. The trochlea corresponds to the area of the femoral cartilage in contact with the patella [15].
(2) Synovial membrane thickness: The extent of synovitis was assessed by measuring its thickness in mm in four regions: the medial and lateral articular recess and the medial and lateral border of the suprapatellar bursa [16].
(3) Bone marrow lesions (BMLs): The extent of BMLs was assessed for the global knee and the subregions using the following scale: 0 = absence, 1 = <25%, 2 = 25–50%, and 3 = >50% of the surface of the respective region, regardless of the presence of additional smaller lesions [17].

Statistical analysis

IBM SPSS statistics (version 22.0, 2013; IBM Corp., Chicago, Illinois, USA) was used for data analysis. Data were expressed as mean ± SD for quantitative parametric measures. The following tests were carried out: first, comparison between two independent mean groups for parametric data using the Student *t*-test, and, second, comparison between more than two patient groups for parametric data using analysis of variance.

Results

The general characteristics of both groups are shown in Table 1. No significant differences were observed in the MRI between the two groups at baseline (Table 2). As regards the symptoms and function, there was no statistically significant difference between the two groups in terms of pain using the VAS ($P > 0.05$); however, there was highly statistically significant difference between the two groups as regards the LFI score ($P < 0.001$) (Table 3). Our data revealed that patients in the CS group, compared with those in the placebo group, experienced a significant reduction in cartilage volume loss in the global knee after 6 months (Figs 1 and 2); similar significant reduction was seen in the lateral compartment and tibial plateaus. No significant differences were seen in the medial compartment and trochlea (Table 4). Significantly lower subchondral BML scores were found for the CS group after 6 months compared with the placebo group (Table 5). No significant differences were found between the two groups in terms of changes in the mean global synovial membrane thickness. Paracetamol was used by 70% of patients (CS = 22 and placebo = 13) and an NSAID was used by 30% of patients (CS = 8 and placebo = 7). No significant differences in laboratory investigations between the two groups and no adverse effects were detected.

Table 1 General characteristics of both groups at baseline

Characteristics	CS group (*n* = 30)	Placebo group (*n* = 20)	*P*-value
Female/male [*n* (%)]	23 (77)	15 (75)	>0.05
Mean age (years)	62.2 ± 16.8	65.8 ± 18.5	>0.05
Mean duration of symptoms (months)	18.4 ± 8.6	16.9 ± 7.5	>0.05
Number of bilateral knee OA [*n* (%)]	14 (47)	11 (55)	>0.05
VAS (0–100 mm)	66.0 ± 15.9	62.8 ± 17.6	>0.05
LFI score	11.05 ± 2.54	11.03 ± 2.44	>0.05

CS, chondroitin sulfate; LFI, Lequesne algo function index; OA, osteoarthritis; VAS, Visual Analog Scale.

Table 2 Baseline MRI findings in both groups

The findings	CS group	Placebo group	*P*-value
Cartilage volume (mm^3)	6245.2 ± 1712.5	6055.2 ± 1540.3	>0.05
BML score	1.8 ± 2.2	2.1 ± 1.9	>0.05
Synovial membrane thickness	1.9 ± 0.54	1.8 ± 0.75	>0.05

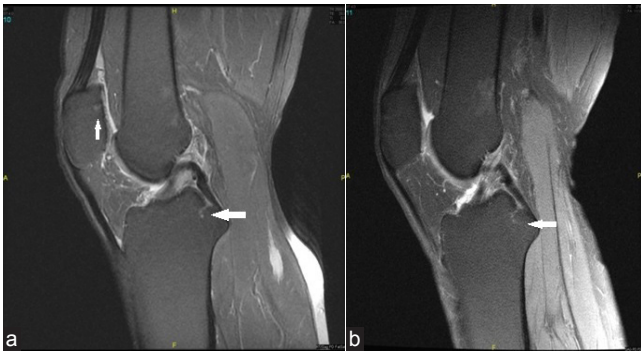
BML, bone marrow lesion; CS, chondroitin sulfate.

Table 3 Differences in both groups as regards VAS and LFI at baseline and after 6 months

Variant	CS group		Placebo group		*P*-value
	At baseline	After 6 months	At baseline	After 6 months	
VAS (0–100 mm)	66.0 ± 15.9	38.4 ± 13.4	62.8 ± 17.6	36.5 ± 16.7	>0.05
LFI score (0–24)	11.05 ± 2.54	7.01 ± 3.2	11.03 ± 2.44	10.07 ± 4.2	<0.001

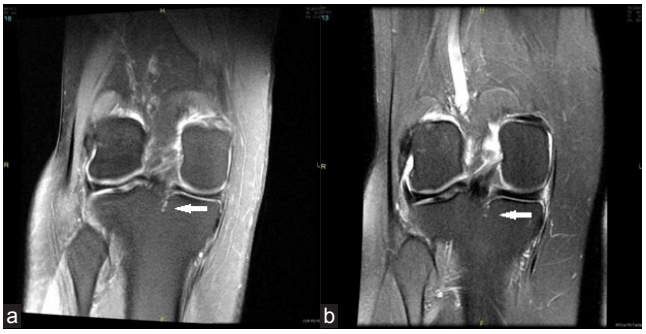
CS, chondroitin sulfate; LFI, Lequesne algo function index; VAS, Visual analog scale.

Figure 1



Sagittal proton density fat-saturated MRI images. (a) Osteoarthritic changes in a 58-year-old female patient showing thinning of patellar cartilage and multiple subchondral cystic lesions in the patella and lateral tibial plateau. (b) Image of the same patient after chondrotin sulfate treatment showing resolution of the patellar bone marrow lesions and regression of the tibial plateau lesion.

Figure 2



Coronal proton density fat-saturated MRI images.(a) Osteoarthritic changes in a 64-year-old female patient showing cartilage loss of the tibial medial compartment of the left knee joint with subchondral bone marrow lesions. (b) Image of the same patient after chondrotin sulfate treatment showing regression of the subchondral bone marrow lesions and stationary course of the cartilage loss of medial tibial plateau.

Table 4 Cartilage volume loss (%) after 6 months versus baseline in both groups

Anatomical site	CS group	Placebo group	*P*-value
Global knee	−2.62 ± 1.2	−4.75 ± 1.6	<0.001
Medial compartment	−4.57 ± 1.4	−5.22 ± 1.6	>0.05
Lateral compartment	−1.77 ± 0.6	−3.92 ± 1.2	<0.001
Tibial plateau	−0.43 ± 0.14	−2.54 ± 0.9	<0.001
Trochlea	−1.15 ± 1.5	−1.48 ± 1.6	>0.05

CS, chondroitin sulfate.

Table 5 Changes in BML scores in both groups after 6 months

Anatomical site	CS group	Placebo group	*P*-value
Global knee	0.13 ± 0.04	0.80 ± 0.01	<0.001
Medial compartment	0.43 ± 0.12	1.01 ± 0.3	<0.001
Lateral compartment	0.43 ± 0.01	1.27 ± 0.4	<0.001
Tibial plateau	0.15 ± 0.02	1.17 ± 0.02	<0.001
Trochlea	0.16 ± 0.04	1.25 ± 0.1	<0.001

BML, bone marrow lesion; CS, chondroitin sulfate.

Discussion

CS has been studied extensively to describe its pharmacokinetic effects *in vitro* and *in vivo* and its clinical efficacy. Various results have been reported depending on the system of evaluation, dosage and duration, and the source of CS origin and quality [18].

CS has been recommended in the guidelines published by Osteoarthritis Research Society International and the EULAR for the management of knee OA [3]. The Osteoarthritis Research Society International recommends CS for its symptomatic and structure-modifying effect in knee OA, but also recommends discontinuing it after 6 months if no symptomatic response is apparent. Our study revealed that patients in the CS group, compared with those in the placebo group, experienced a significant reduction in the cartilage volume loss, especially for the global knee, lateral tibiofemoral compartment, and tibial plateaus, and a significantly lower subchondral BML scores on MRI after 6 months of treatment compared with baseline. No significant differences were found between the two groups in terms of changes in the mean global synovial membrane thickness after 6 months. The same results were obtained in a study conducted by Wildi *et al.* [8], who reported evidence of the structure-protective effect of CS in knee OA patients as early as within 6 months of treatment. In this randomized, double-blind, controlled trial in primary knee OA, 69 patients with clinical signs of synovitis were randomized to receive CS 800 mg or placebo once daily for 6 months, followed by an open-label phase of 6 months in which patients in both groups received CS 800 mg once daily. Cartilage volume loss and BMLs were assessed with MRI at baseline and at 6 and 12 months, and the thickness of synovial membrane was assessed at baseline and at 6 months. The CS group showed significantly less cartilage volume loss compared with the placebo group as early as within 6 months for the global knee, lateral compartment, and tibial plateaus, with significance persisting at 12 months. In addition, the reduction in cartilage loss was also associated with a reduction in BML scores for the CS group at 12 months. This finding is interesting as BMLs are believed to be associated with the progression of cartilage lesions [9,10]. The positive results were in line with a number of studies using radiographic technology. [19] assessed the long-term effects of CS on the radiographic progression and symptom changes in OA knee. A placebo-controlled trial was conducted, in which 622 patients with knee OA were randomly assigned to receive either 800 mg CS (n = 309 patients) or placebo (n = 313 patients) once

daily for 2 years. Radiographs of the target knee were obtained at the time of enrollment and at 12, 18, and 24 months. The minimum joint space width (JSW) of the medial compartment was assessed using digital image analysis. The trial demonstrated a significant reduction in the minimum JSW loss in the CS group compared with the placebo group. Pain improved significantly faster in the CS group than in the placebo group.

Hochberg [20] assessed the efficacy of CS as a structure-modifying drug for knee OA for 2 years' duration, and the results demonstrated a small significant effect of CS on reduction in the rate of decline in minimum JSW. In contrast to these results, Wandel *et al.* [21] studied the effect of CS, glucosamine, or the two in combination on joint pain and on radiological progression of disease in OA of the hip or knee. They concluded that, compared with placebo, glucosamine, CS, and their combination do not reduce joint pain or have an impact on narrowing of joint space.

However, there were highly significant differences between the two groups as regards the LFI score. The results of our study showed no significant differences in symptoms between the two groups after 6 months of treatment. The absence of differences in disease symptoms could be explained by the use of rescue medication (paracetamol), as well as NSAIDs, which are strong confounding factors, and this may have masked the underlying symptom-relieving effect of CS.

A study conducted by Schneider *et al.* [22] demonstrated that CS, in the form of structum at an oral dose of 1 g/day, has a modest but statistically significant reducing effect of pain intensity and improves functions (algo functional index) and increases the actual numbers of responders in a statistically significant manner in patients with OA of the knee.

Another trial compared the efficacy and safety of two CS of different origin, structum (avian) daily dosages 1 g, 500 mg twice daily and chondrosulf (bovine) 1200, 400 mg three times daily on the clinical symptoms in the treatment of knee OA. The results showed that both products are equally effective on pain relief assessed with VAS and functional improvement assessed with the LFI score over a 6-month period. A clinically relevant improvement is obtained at as early as 6 weeks and persists over 24 weeks [23].

Conclusion

CS treatment could significantly reduce the cartilage volume loss and the subchondral BML scores in knee OA after 6 months of treatment. These findings suggested a joint structure-protective effect of CS.

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Conflicts of interest

There are no conflicts of interest.

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