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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Is chondroitin sulfate effective for osteoarthritis?

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Abstract

Osteoarthritis is the most prevalent chronic articular disease, in which pain is one of the main symptoms and the major determinant of functional loss. Several therapeutic options have been proposed, including chondroitin sulfate, but its actual usefulness has not yet been established. To answer this question we searched in Epistemonikos database, which is maintained by screening multiple information sources. We identified 13 systematic reviews including 50 randomized trials overall. We extracted data, conducted a meta-analysis and generated a summary of findings table using the GRADE approach. We concluded it is not clear whether the use of chondroitin sulfate leads to an improvement in pain or functionality in osteoarthritis because the certainty of the evidence is very low.

Problem

Osteoarthritis is the most prevalent chronic joint disease in the world, and is associated with progressive and chronic joint cartilage damage, producing pain and limiting the functionality of patients.

One of the drugs available for the management of osteoarthritis is chondroitin sulfate, which in *in vitro*models has beneficial effects in the metabolism of chondrocytes, synoviocytes and subchondral bone cells, increasing the synthesis of type II collagen and proteoglycan, decreasing the production of inflammatory mediators and proteases, slowing cell death and improving the anabolic-catabolic balance of the cartilage extracellular matrix. Even so, results of its effects differ in clinical trials. Chondroitin sulfate is recommended as a slow-acting drug for osteoarthritis in some international guidelines, while other guidelines do not recommend it or just for certain conditions.

Methods

We used Epistemonikos database, which is maintained by screening multiple information sources, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- It is not clear whether the use of chondroitin sulfate leads to an improvement in pain or functionality in osteoarthritis because the certainty of the evidence is very low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We identified 13 systematic reviews [1],[2],[3],[4],[5],[6],[7],[8],[9],[10],[11],[12],[13] that included 50 randomized controlled trials reported in 53 references [14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66].
What types of patients were included	Four trials included outpatients [21],[52],[54],[66]. The rest of the trials did not provide this information. Thirty eight trials included patients with knee osteoarthritis [14],[15],[17],[19],[20],[21],[22],[24],[25],[26],[27],[28],[29],[31],[38],[39],[41],[42],[43],[44],[45],[46],[48],[50],[51],[52],[53],[54],[55],[56],[57],[60],[61],[62],[63],[64],[65],[66]. Two trials included hip osteoarthritis [16] and [23], four included hand osteoarthiritis [35],[37],[40],[58], three trials included osteoarthritis in more than one joint [18],[32],[33] an three trials did not provide this information [30],[36],[59].
What types of interventions were included	All of the trials used chondroitin sulfate. Twenty seven trials used only chondroitin sulfate: [14],[15],[16],[17],[18],[20],[21],[22],[23],[24],[26],[27],[28],[31],[37],[41],[46],[48],[50],[54],[55],[56],[58],[61],[63],[65],[66], eleven trials used chondroitin sulfate and glucosamine [30],[34],[39],[42],[43],[44],[45],[51],[52],[53],[57], five trials used chondroitin sulfate, glucosamine and other components [29],[38],[59],[60],[62], four trials used chondroitin sulfate versus nonsteroidal anti-inflammatory drugs [18],[25],[35],[40] and three trials used chondroitin and did not inform the comparator (no placebo) [33],[36],[64]. Twenty trials used a daily dose of chondroitin sulfate greater than 1000 mg (between 1000 mg and 2000 mg) [16],[17],[18],[19],[21],[25],[28],[31],[36],[37],[48],[50],[51],[53],[56],[57],[59],[63],[64],[66], nineteen trials used a daily dose of chondroitin sulfate lesser than 1000 mg (between 60 mg and 800 mg) [20],[22],[23],[24],[26],[29],[34],[35],[39],[40],[41],[46],[54],[55],[58],[60],[61],[62],[65], seven trials used a dose scheme with more than one dose of chondroitin sulfate [27],[30],[33],[42],[43],[44],[45] and four trials did not provide this data [14],[15],[38],[52]. Forty seven trials used oral administration of chondroitin sulfate [16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[33],[34],[35],[36],[37],[39],[40],[41],[42],[43],[44],[45],[46],[48],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66], two trials used intramuscular administration [14],[15] and one trial used topical administration [38]. Nine trials reported that patients received coadjuvant therapy with acetaminophen [17],[19],[20],[26],[27],[28],[48],[56],[66]. Fourteen trials used ibuprofen, diclofenac or other nonsteroidal anti-inflammatory drugs [14],[25],[35],[36],[38],[40],[42],[43],[44],[52],[59],[60],[62],[63]. The rest of the trials did not provide information on the use of other drugs besides chondroitin sulfate. The treatment mean time of duration was 7 months, with a minimum of 1 month and a maximum of 2 years. Eight trials did not report this data [25],[26],[27], [29],[35],[36],[40],[56]. Thirty-seven trials compared against placebo: [14],[15],[16],[17],[18],[20],[21],[22],[23],[24],[26],[27],[28], [29],[30],[31],[34],[37],[38],[39],[41],[46],[48],[50], [51],[52],[54],[55],[56],[58],[59],[60],[61],[62],[63],[65],[66]. Ten trials compared against nonsteroidal anti-inflammatory drugs [19],[25],[35],[40],[42],[43],[44], [45],[53],[57]. Three trials did not provide this information (no placebo) [33],[36],[64].

What types of outcomes were measured	Among the outcomes measured by the systematic reviews were pain in the visual analogue scale (VAS) from 0 to 10 or from 0 to 100 mm, the Western Ontario and McMaster Universities Total Arthritis Index (WOMAC), WOMAC stiffness, Physical Function from 0 to 100 (adapted WOMAC scale), Lequesne Index, reduction of joint space in the radiography, adverse effects, total knee arthroplasty requirement, among others.

Summary of findings

The effects of chondroitin sulfate are based on 18 randomized trials that, in total, included 2188 patients. The rest of the trials did not report the outcomes of interest, or the identified reviews do not provide data suitable for meta-analysis. Eighteen trials [14],[16],[17],[18],[21],[22],[23],[24],[27],[31],[32],[41],[46],[50],[56],[61],[63],[66] measured pain using the visual analogue scale (2188 patients). Only two trials [24],[26] evaluated functionality using the WOMAC scale (403 patients). Adverse effects were obtained directly from one of the systematic reviews identified [13], since it was not possible to extract more information from the other reviews. The summary of findings is as follows:

- It is not clear whether chondroitin sulfate decreases pain in osteoarthritis because the certainty of the evidence is very low.
- It is not clear whether chondroitin sulfate improves functionality in osteoarthritis because the certainty of the evidence is very low.
- Chondroitin sulfate has no adverse effects or they are minimal. The certainty of the evidence is high.

Chondroitin sulfate for osteoarthritis			
Patients	Osteoarthritis		
Intervention	Chondroitin sulfate		
Comparison	Placebo		
Outcomes	**Absolut effect***	**Relative effect (95% CI)**	**Certainty of the evidence (GRADE)**
Pain	The pain scale was on average 0.36 standard deviations lower than in the group without chondroitin sulfate SMD: -0.36 (-0.69 to -0.02)	--	⊕◯◯◯[1,2,3] Very low
Functionality	The functionality scale was on average 0.41 standard deviations lower than in the group without chondroitin sulfate SMD: -0.41 (-1.34 to 0.53)	--	⊕◯◯◯[1,2] Very low
Adverse effects	No difference between chondroitin sulfate and placebo	RR 0,97 (0,83 a 1,14)	⊕⊕⊕⊕ High

SMD= Standardize mean difference
RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article)

* Standardized mean difference is calculated when the outcome is measured using different scales, and its clinical interpretation is difficult. A rule of thumb is a value of 0.2 SD represents a small, 0.5 a moderate, and 0.8 a large difference.

[1] The certainty of the evidence was downgraded for risk of bias of the primary studies.
[2] The certainity of the evidence was downgraded for imprecision for pain since it has a wide confidence interval that includes both the possibility of clinically insignificant benefit and clinically important benefit. In the case of functionality, it was decreased in two levels, since the interval is very wide and would lead to very different decisions in both ends of the interval.
[3] The certainty of the evidence was downgraded for inconsistency with I^2 of 93%.

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- Although the intention of this summary was to encompass all possible joints that suffer from osteoarthritis and the respective treatment outcome with chondroitin sulfate, most of the primary studies focus on knee osteoarthritis. However, in the absence of direct evidence for other joints, it is reasonable to extrapolate the conclusions of this summary. Therefore, we think the evidence presented in this summary is broadly applicable to patients with all types of osteoarthritis.

About the outcomes included in this summary

- The chosen outcomes were pain and functionality because they are critical outcomes for decision-making on the use of chondroitin sulfate. This selection is based on the opinion of the authors of this summary, but it agrees in general with the outcomes mentioned by the systematic reviews and clinical guidelines.
- No radiological outcomes were selected because they are surrogate outcomes and do not necessarily predict clinical outcomes.

Balance between benefits and risks, and certainty of the evidence

- It is not possible to make an appropriate balance between benefits and risks because of the uncertainty about benefits.

What would patients and their doctors think about this intervention

- Faced with the evidence presented in this summary, most patients and clinicians should lean against the use of this intervention.
- However, in the absence of clearly effective therapeutic alternatives, there may be variability in clinical decisions made by individual patients. Those who put more value on the possible benefit, even if it is not proven, could lean in favor of the intervention. Those who privilege the certainty of the evidence or the costs, would possibly lean against.
- There should be less variability in the decisions made by clinicians given the recommendations against the use of this intervention in the main guidelines.

Resource considerations

- It is not possible to make an appropriate balance between benefits and costs because of the uncertainty about benefits.

Differences between this summary and other sources

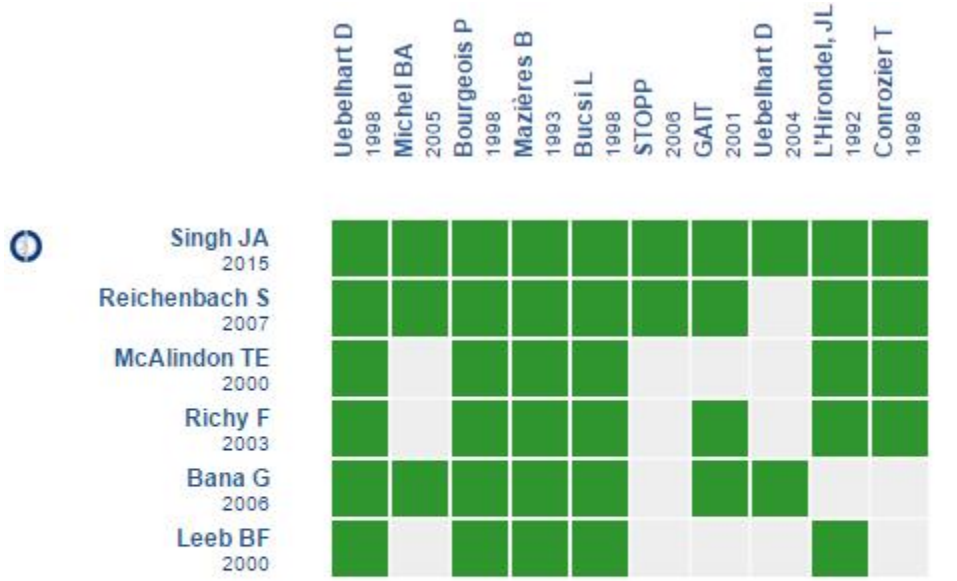
- On the matter of the information given by the systematic reviews, four of them [1],[3],[4],[11] report that chondroitin sulfate would be beneficial for either of the two critical outcomes (pain and functionality), although some highlight the high risk of bias. In contrast, two reviews [5],[6] indicate that it would not be beneficial for any of the aforementioned outcomes. On the other hand, five systematic reviews [7],[8],[9],[10],[12] did not explore clinically relevant outcomes, instead only analysed surrogate outcomes.
- Finally, our summary leads to a conclusion slightly different from that of the Cochrane review [13], which is the most recent and complete of the reviews identified. This indicates that chondroitin sulfate has a small to moderate positive effect compared to placebo in reducing pain, and that it has a low risk of serious adverse effects.
- In respect to the international guidelines for osteoarthritis, the one from the Osteoarthritis Research Society International (OARSI) [67] states that the use of chondroitin sulfate for symptom management has an uncertain result and that its use is not appropriate to modify the disease, which is consistent with the results of this summary. The guidelines of the American Academy of Orthopedic Surgeons (AAOS) [68] do not recommend the use of chondroitin sulfate for patients with symptomatic knee osteoarthritis.

Could this evidence change in the future?

- The probability that future research changes the conclusions of this summary is very high, due to the uncertainty of the current evidence.
- There are at least ten ongoing randomized trials [69],[70],[71],[72][73],[74],[75],[76],[77],[78] evaluating the use of chondroitin sulfate in osteoarthritis compared to placebo according to the International Clinical Trials Registry Platform of the World Health Organization.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

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Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears. The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

References

1. Leeb BF, Schweitzer H, Montag K, Smolen JS. A metaanalysis of chondroitin sulfate in the treatment of osteoarthritis. J Rheumatol. 2000 Jan;27(1):205-11 | PubMed |
2. McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. JAMA. 2000 Mar 15;283(11):1469-75 | PubMed |

3. Richy F, Bruyere O, Ethgen O, Cucherat M, Henrotin Y, Reginster JY. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. Arch Intern Med. 2003 Jul14;163(13):1514-22 | PubMed |
4. Bana G, Jamard B, Verrouil E, Mazières B. Chondroitin sulfate in the management of hip and knee osteoarthritis: an overview. Adv Pharmacol. 2006;53:507-22 | PubMed |
5. Bjordal JM, Klovning A, Ljunggren AE, Slørdal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials. Eur J Pain. 2007 Feb;11(2):125-38 | PubMed |
6. Reichenbach S, Sterchi R, Scherer M, Trelle S, Bürgi E, Bürgi U, et al. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. Ann Intern Med. 2007 Apr 17;146(8):580-90 | PubMed |
7. Hochberg MC, Zhan M, Langenberg P. The rate of decline of joint space width in patients with osteoarthritis of the knee: a systematic review and meta-analysis of randomized placebo-controlled trials of chondroitin sulfate . Curr Med Res Opin. 2008 Nov;24(11):3029-35 | CrossRef | PubMed |
8. Hochberg MC. Structure-modifying effects of chondroitin sulfate in knee osteoarthritis: an updated meta-analysis of randomized placebo-controlled trials of 2-year duration. Osteoarthritis Cartilage. 2010 Jun;18 Suppl 1:S28-31 | CrossRef | PubMed |
9. Lee YH, Woo JH, Choi SJ, Ji JD, Song GG. Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. Rheumatol Int. 2010 Jan;30(3):357-63 | CrossRef | PubMed |
10. Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ. 2010 Sep 16;341:c4675 | CrossRef | PubMed |
11. Schneider H, Maheu E, Cucherat M. Symptom-modifying effect of chondroitin sulfate in knee osteoarthritis: a meta-analysis of randomized placebo-controlled trials performed with structum(®). Open Rheumatol J. 2012;6:183-9 | CrossRef | PubMed |
12. Gallagher B, Tjoumakaris FP, Harwood MI, Good RP, Ciccotti MG, Freedman KB. Chondroprotection and the prevention of osteoarthritis progression of the knee: a systematic review of treatment agents. Am J Sports Med. 2015 Mar;43(3):734-44 | CrossRef | PubMed |
13. Singh JA, Noorbaloochi S, MacDonald R, Maxwell LJ. Chondroitin for osteoarthritis. Cochrane Database Syst Rev. 2015 Jan 28;1:CD005614 | CrossRef | PubMed |
14. Kerzberg EM, Roldán EJ, Castelli G, Huberman ED. Combination of glycosaminoglycans and acetylsalicylic acid in knee osteoarthrosis. Scand J Rheumatol. 1987;16(5):377-80 | PubMed |
15. Rovetta G. Galactosaminoglycuronoglycan sulfate (matrix) in therapy of tibiofibular osteoarthritis of the knee. Drugs Exp Clin Res. 1991;17(1):53-7 | PubMed |
16. Conrozier T, Vignon E. The efficacy of chondroitin sulfate in the treatment of the arthrosis of the hip joint. A double-blind study versus placebo [Die Wirkung von Chondroitinsulfat bei der Behandlungder Huftgelenksarthrose: eine Doppelblindstudie gegen Placebo]. Litera Rheumatoiogica 1992;14:69–75. | Link |
17. L'Hirondel JL. Clinical double-blinded study with orally administered chondroitin sulfate versus placebo in patients with tibiofemoral gonarthrosis (125 patients) [Klinische Doppelblind–Studie mit oral verabreichtem Chondroitinsulfatgegen Placebo bei der tibiofemoralen Gonarthrose (125 patients)]. Litera Rheumatologica 1992; 14:77–84. | Link |
18. Mazieres B, Loyau G, Menkes CJ, Valat JP, Dreiser RL, Charlot J, et al. Chondroitin sulfate in the treatment of gonarthrosis and coxarthrosis. 5-months result of a multicenter double-blind controlled prospective study using placebo. Rev Rhum Mal Osteoartic 1992;59(7-8):466–72. | Link |
19. Morreale P, Manopulo R, Galati M, Boccanera L, Saponati G, Bocchi L. Comparison of the antiinflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. J Rheumatol. 1996 Aug;23(8):1385-91 | PubMed |
20. Fleisch AM, Merlin C, Imhoff A, Hodler J, Kissling R. A one-year randomized, double-blind, placebo-controlled study with oral chondroitin sulfate in patients with knee osteoarthritis. Osteoarthritis Cartilage. 1997;5 Suppl A:S70. | Link |
21. Bourgeois P, Chales G, Dehais J, Delcambre B, Kuntz JL, Rozenberg S. Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3 x 400 mg/day vs placebo. Osteoarthritis Cartilage. 1998 May;6 Suppl A:25-30. | PubMed |
22. Bucsi L, Poór G. Efficacy and tolerability of oral chondroitin sulfate as a symptomatic slow-acting drug for osteoarthritis (SYSADOA) in the treatment of knee osteoarthritis. Osteoarthritis Cartilage. 1998 May;6 Suppl A:31-6 | PubMed |
23. Conrozier T. [Anti-arthrosis treatments: efficacy and tolerance of chondroitin sulfates (CS 4&6)]. Presse Med. 1998 Nov 21;27(36):1862-5 | PubMed |
24. Uebelhart D, Thonar EJ, Delmas PD, Chantraine A, Vignon E. Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study. Osteoarthritis Cartilage. 1998 May;6 Suppl A:39-46 | PubMed |
25. Alekseeva LI, Benevolenskaia LI, Nasonov EL, Chichasova NV, Kariakin AN. [Structum (chondroitin sulfate)--a new agent for the treatment of osteoarthrosis]. Ter Arkh. 1999;71(5):51-3 | PubMed |
26. Malaise M, Marcolongo R, Uebelhart D, Vignon E. Efficacy and tolerability of 800 mg oral chondroitin 4&6 sulfate in the treatment of knee osteoarthritis: a randomised, double-blind, multicentre study versus placebo. Litera Rheumatologica 1999;24:31–42 | Link |
27. Pavelka K, Manopulo R, Busci L. Double-blind, dose-effect study of oral chondroitin 4 & 6 sulfate 1200 mg, 800 mg, 200 mg, and placebo in the treatment of knee osteoarthritis. Litera Rhumatologica 1999;24:21–30. | Link |
28. Uebelhart D, Knussel O, Theiler R. Efficacy and tolerability of oral avian chondroitin sulfate in painful knee osteoarthritis. Schweiz Med Wochenschr. 1999;129:1174. | Link |

29. Das A Jr, Hammad TA. Efficacy of a combination of FCHG49 glucosamine hydrochloride, TRH122 low molecular weight sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis. Osteoarthritis Cartilage. 2000 Sep;8(5):343-50 | PubMed|
30. Debi R, Robinson D, Agar G, Halperin N. [GAG for osteoarthritis of the knee--a prospective study]. Harefuah. 2000 Mar 15;138(6):451-3, 518 | PubMed |
31. Knüsel O, Theiler R, Uebelhart D. Clinical study report: Double-blind, placebo controlled, multicentre trial assessing the efficacy and safety of chondroitin sulfate, 1 gram per day for 6 months, in patients with painful femorotibial osteoarthritis. Internal document from the Institut de Recherche Pierre Fabre, Centre de Développement Pierre Fabre, Rue Jean Rostand, F-31319 Labège Cedex, September 2000. | Link |
32. Mazieres B, Combe B, Phan Van A, Tondut J, Grynfeltt M. Chondroitin sulfate in osteoarthritis of the knee: a prospective, double blind, placebo controlled multicenter clinical study. J Rheumatol. 2001 Jan;28(1):173-81 | PubMed |
33. Nasonova VA, Alekseeva LI, Arkhangel'skaia GS, Davydova AF, Karmil'tseva EA, Kogan KM, et al. [Results of the multicenter clinical trial of structum preparation in Russia]. Ter Arkh. 2001;73(11):84-7 | PubMed |
34. Nguyen P, Mohamed SE, Gardiner D, Salinas T. A randomized double-blind clinical trial of the effect of chondroitin sulfate and glucosamine hydrochloride on temporomandibular joint disorders: a pilot study. Cranio. 2001 Apr;19(2):130-9 | PubMed |
35. Rovetta G, Monteforte P, Molfetta G, Balestra V. Chondroitin sulfate in erosive osteoarthritis of the hands. Int J Tissue React. 2002;24(1):29-32 | PubMed |
36. Soroka NF, Chyzh KA. Clinical efficiency and pharmacoeconomical evaluation of treatment by chondroitinsulphate (Structumc) in patients with primary osteoarthritis (POA). Ann Rheum Dis. 2002;61 Suppl 1:AB0289 | Link |
37. Verbruggen G, Goemaere S, Veys EM. Systems to assess the progression of finger joint osteoarthritis and the effects of disease modifying osteoarthritis drugs. Clin Rheumatol. 2002 Jun;21(3):231-43 | PubMed |
38. Cohen M, Wolfe R, Mai T, Lewis D. A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. J Rheumatol. 2003 Mar;30(3):523-8. Erratum in: J Rheumatol. 2003 Nov;30(11):2512 | PubMed |
39. Rai J, Pal SK, Gul A, Senthil R, Singh H. Efficacy of chondroitin sulfate and glucosamine sulfate in the progression of symptomatic knee osteoarthritis: a randomized, placebo-controlled, double-blind study. Bulletin PGI 2004;38:18–22. | Link |
40. Rovetta G, Monteforte P, Molfetta G, Balestra V. A two-year study of chondroitin sulfate in erosive osteoarthritis of the hands: behavior of erosions, osteophytes, pain and hand dysfunction. Drugs Exp Clin Res. 2004;30(1):11-6 | PubMed |
41. Uebelhart D, Malaise M, Marcolongo R, de Vathaire F, Piperno M, Mailleux E, et al. Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomized, double-blind, multicenter study versus placebo. Osteoarthritis Cartilage. 2004 Apr;12(4):269-76. Erratum in: Osteoarthritis Cartilage. 2007 Aug;15(8):979. DeVathaire, Florent [corrected to de Vathaire, Florent] | PubMed |
42. Alekseeva LI, Chichasova NV, Benevolenskaia LI, Nasonov EL, Mendel' OI. Combined medication ARTRA in the treatment of osteoarthrosis]. Ter Arkh. 2005;77(11):69-75 | PubMed|
43. Alekseeva LI, Artemenko NA, Zotkin EG, Kudryavtceva NV, Lesnyak OM, Mendel OI, et al. Rational selection of basal therapy in osteoarthritis. Results of the open randomized multicenter clinical trial of ARTRA preparation in Russia. Russkiy Meditsinskiy Journal 2005;13(24):1637. | Link |
44. Artemenko NA, Chvamaniya NA. [Features of the progression and treatment of osteoarthritis]. Регулярные выпуски «РМЖ». 2005;(7):p.403 | Link |
45. Lila AM, Mazurov VI, Shidlovskaya OV, Shostak MS. THERAFLEX in comprehensive therapy of knee steoarthrosis and spinal osteochondrosis (results of a clinical trial). Russkiy Meditsinskiy Journal 2005;13(24): 1618. | Link |
46. Michel BA, Stucki G, Frey D, De Vathaire F, Vignon E, Bruehlmann P, et al. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. Arthritis Rheum. 2005 Mar;52(3):779-86 | PubMed |
47. Clegg DO, Reda DJ, Harris CL, Klein MA, O'Dell JR, Hooper MM, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med. 2006 Feb 23;354(8):795-808 | PubMed |
48. Mazières B, Hucher MMH, Zam MMZ. Chondroitin sulfate in the treatment for knee osteoarthritis: a randomized, double blind, multicenter, placebo controlled trial. Ann Rheum Dis. 2006;65(Suppl II):398. | Link |
49. Reginster JY, Kahan A, Uebelhart D, et al. A two-year prospective, randomized, double-blind, controlled study assessing the effect of chondroitin 4 & 6 sulfate (CS) on the structural progression of knee osteoarthritis: STOPP (Study on Osteoarthritis Progression Prevention). [Presented at 2006 annual scientific meeting of the American College of Rheumatology (abstract L42)] | Link |
50. Mazières B, Hucher M, Zaïm M, Garnero P. Effect of chondroitin sulphate in symptomatic knee osteoarthritis: a multicentre, randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2007 May;66(5):639-45 | PubMed |
51. Messier SP, Mihalko S, Loeser RF, Legault C, Jolla J, Pfruender J, et al. Glucosamine/chondroitin combined with exercise for the treatment of knee osteoarthritis: a preliminary study. Osteoarthritis Cartilage. 2007 Nov;15(11):1256-66 | PubMed |
52. Alekseeva LI. Results of an open comparative randomized clinical trial to assess efficacy and safety of two regimens of treatment with Theraflex preparation

in knee osteoarthritis patients. Russkiy Meditsinskiy Journal 2008;16(5):316 | Link |
53. Sawitzke AD, Shi H, Finco MF, Dunlop DD, Bingham CO 3rd, Harris CL, et al. The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the glucosamine/chondroitin arthritis intervention trial. Arthritis Rheum. 2008 Oct;58(10):3183-91 | CrossRef | PubMed |
54. Kahan A, Uebelhart D, De Vathaire F, Delmas PD, Reginster JY. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2009 Feb;60(2):524-33. | CrossRef | PubMed |
55. Möller I, Pérez M, Monfort J, Benito P, Cuevas J, Perna C, et al. Effectiveness of chondroitin sulphate in patients ith concomitant knee osteoarthritis and psoriasis: a randomized, double-blind, placebo-controlled study. Osteoarthritis Cartilage. 2010 Jun;18 Suppl 1:S32-40 | CrossRef | PubMed |
56. Pavelka K, Coste P, Géher P, Krejci G. Efficacy and safety of piascledine 300 versus chondroitin sulfate in a 6 months treatment plus 2 months observation in patients with osteoarthritis of the knee. Clin Rheumatol. 2010 Jun;29(6):659-70 | CrossRef | PubMed |
57. Sawitzke AD, Shi H, Finco MF, Dunlop DD, Harris CL, Singer NG, et al. Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. Ann Rheum Dis. 2010 Aug;69(8):1459-64 | CrossRef | PubMed |
58. Gabay C, Medinger-Sadowski C, Gascon D, Kolo F, Finckh A. Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial at a single center. Arthritis Rheum. 2011 Nov;63(11):3383-91 | CrossRef | PubMed |
59. Magrans-Courtney T, Wilborn C, Rasmussen C, Ferreira M, Greenwood L, Campbell B, et al. Effects of diet type and supplementation of glucosamine, chondroitin, and MSM on body composition, functional status, and markers of health in women with knee osteoarthritis initiating a resistance-based exercise and weight loss program. J Int Soc Sports Nutr. 2011 Jun 20;8(1):8 | CrossRef | PubMed |
60. Nakasone Y, Watabe K, Watanabe K, Tomonaga A, Nagaoka I, Yamamoto T, et al. Effect of a glucosamine-based combination supplement containing chondroitin sulfate and antioxidant micronutrients in subjects with symptomatic knee osteoarthritis: A pilot study. Exp Ther Med. 2011 Sep;2(5):893-899 | PubMed |
61. Wildi LM, Raynauld JP, Martel-Pelletier J, Beaulieu A, Bessette L, Morin F, et al. Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. Ann Rheum Dis. 2011 Jun;70(6):982-9 | CrossRef | PubMed |
62. Kanzaki N, Saito K, Maeda A, Kitagawa Y, Kiso Y, Watanabe K, et al. Effect of a dietary supplement containing glucosamine hydrochloride, chondroitin sulfate and quercetin glycosides on symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled study. J Sci Food Agric. 2012 Mar 15;92(4):862-9 | CrossRef | PubMed |
63. Railhac JJ, Zaim M, Saurel AS, Vial J, Fournie B. Effect of 12 months treatment with chondroitin sulfate on cartilage volume in knee osteoarthritis patients: a randomized, double-blind, placebo-controlled pilot study using MRI. Clin Rheumatol. 2012 Sep;31(9):1347-57 | CrossRef | PubMed |
64. Fardellone P, Zaim M, Saurel AS, Maheu E. Comparative efficacy and safety study of two chondroitin sulfate preparations from different origin (avian and bovine) in symptomatic osteoarthritis of the knee. Open Rheumatol J. 2013;7:1-12 | CrossRef | PubMed |
65. Raynauld JP, Martel-Pelletier J, Dorais M, Haraoui B, Choquette D, Abram F, et al. Total Knee Replacement as a Knee Osteoarthritis Outcome: Predictors Derived from a 4-Year Long-Term Observation following a Randomized Clinical Trial Using Chondroitin Sulfate. Cartilage. 2013 Jul;4(3):219-26 | CrossRef | PubMed |
66. Zegels B, Crozes P, Uebelhart D, Bruyère O, Reginster JY. Equivalence of a single dose (1200 mg) compared to a three-time a day dose (400 mg) of chondroitin 4&6 sulfate in patients with knee osteoarthritis. Results of a randomized double blind placebo controlled study. Osteoarthritis Cartilage. 2013 Jan;21(1):22-7 | CrossRef | PubMed |

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