Meta-analysis: chondroitin for osteoarthritis of the knee or hip

CRD summary
This well-conducted and reliable review concluded that evidence from large and methodologically sound trials suggests that the symptomatic benefit of chondroitin is minimal or non-existent. However, it should be noted that the majority of the included studies showed favourable effects of chondroitin.

Authors' objectives
To evaluate the effects of chondroitin on pain in patients with osteoarthritis of the knee or hip.

Searching
MEDLINE, EMBASE, CINHAL and the Cochrane CENTRAL Register were searched from inception to November 2006 without any language restrictions; the search terms were reported. The reported search strategy applied a filter for controlled clinical trials; systematic reviews and meta-analyses were also sought and a citation search was used to identify further studies. In addition, conference proceedings, textbooks and references of all papers were screened, trial authors and content experts were contacted, and clinical trial registries were searched.

Study selection
Study designs of evaluations included in the review
Randomised or quasi-randomised controlled trials were eligible for inclusion.

Specific interventions included in the review
Studies comparing chondroitin with placebo or no intervention were eligible for inclusion. Studies where patients were given oral doses of less than 400 mg/day were excluded. The majority of the included studies administered chondroitin orally on consecutive days using doses ranging from 800 to 2,000 mg/day (median 1,000). Treatment duration ranged from 6 to 132 weeks (median 31).

Participants included in the review
Studies in patients with osteoarthritis of the knee or hip were eligible. Most of the included patients had osteoarthritis of the knee; in one trial patients had only osteoarthritis of the hip. Where reported, the median duration of symptoms was 5 years and the proportion of patients with low-grade osteoarthritis ranged from 0 to 100% (median 73). The average age of the included participants ranged from 50 to 67 years (median 61) and the median percentage of women was 62.

Outcomes assessed in the review
The primary outcome was pain at the end of the trial or at a maximum of 3 months after the termination of therapy (whichever came first). The reviewers applied a published hierarchy to select outcomes when more than one pain measure was reported. Adverse events were also recorded.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened the publications; any disagreements were resolved through discussion.

Assessment of study quality
Two reviewers independently assessed allocation concealment, blinding, withdrawal rates and the use of an intention-to-treat (ITT) analysis. Concealment of allocation was considered adequate if the person responsible for patient selection was unable to suspect before allocation which treatment was next. The method used to handle missing data was also recorded, but not assessed in terms of its appropriateness. Any disagreements were resolved through discussion with a third reviewer.
Data extraction
The data were extracted in duplicate; any disagreements were resolved through discussion with a third reviewer. Effect sizes were calculated from the difference in means of pain-related outcomes between treatment and control at the end of the trial divided by the pooled standard deviation (SD). Where necessary, means and measures of dispersion were estimated from figures and authors were contacted when effect sizes could not be calculated. Only the data from the first phase of crossover trials were used, and ITT analyses were selected where possible.

Methods of synthesis
How were the studies combined?
The data were combined in a random-effects model and the pooled effect sizes reported, together with 95% confidence intervals (CIs). Weighted mean differences were used for continuous outcomes and adverse events were expressed as relative risks. Funnel plots were used to assess publication bias.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the I-squared statistic; values of 25, 50 and 75% were rated as low, moderate and high heterogeneity, respectively. Meta-regression investigated effects of allocation concealment, placebo control, patient blinding, ITT analysis, trial size, funding, route of administration, length of follow-up and cointerventions. Further analyses were reported.

Results of the review
Twenty-two studies (n=4,056) were included in the review. All but one study (n=100) were reported as being randomised (n=3,956).

The allocation sequence was judged to be adequately generated in one trial and adequately concealed in two trials. Three trials used ITT analyses and most trials did not describe the method used to handle missing data.

Pain scores of the intervention groups were significantly lower in the chondroitin group (effect size -0.75, 95% CI: -0.99, -0.50; 20 studies) and there was evidence of significant statistical heterogeneity (I-squared 92%).

Small trials, trials with unclear concealment of allocation and trials not using ITT analyses showed larger effects. Three large trials (equivalent to 40% of the total number of participants) using an ITT analysis showed an effect size of -0.03 (95% CI: -0.13, 0.07; 3 trials; I-squared 0%).

Chondroitin showed favourable results for minimum joint space width (0.16 mm, 95% CI: 0.08, 0.24) and mean joint space width (0.23 mm, 95% CI: 0.09, 0.37), corresponding to effect sizes of 0.12 and 0.18 SD units; there was no evidence of heterogeneity.

The relative risk of experiencing any adverse event (12 studies) was 0.99% (95% CI: 0.76, 1.31).

Authors' conclusions
Large and methodologically sound trials suggest that the symptomatic benefit of chondroitin is minimal or non-existent.

CRD commentary
This was a well-conducted and well-reported review with clear inclusion criteria. The search was thorough, applied no language restrictions and included methods to identify unpublished studies, thus reducing the risk of language and publication bias. Methods to minimise reviewer error and bias were reported for all critical stages of the review. The quality of the included studies was assessed and taken into account during the evidence synthesis. The statistical analyses were comprehensive and accounted for potential confounders. The authors' decision to concentrate on the highest quality studies, which incidentally showed little effect of chondroitin, is justifiable. However, it should be noted that 18 out of 20 available data sets showed favourable results for chondroitin and two studies showed no effect (rather than showing a mixed evidence base). Overall, the authors' cautious conclusions are likely to be reliable.
Implications of the review for practice and research
Practice: The authors stated that the use of chondroitin in routine clinical practice should be discouraged.

Research: The authors stated that studies should adhere to methodological standards regarding allocation concealment, blinding, withdrawals and ITT analysis; reporting standards should also be followed. A rigorously designed, adequately powered, randomised placebo-controlled trial that is restricted to patients with low-grade osteoarthritis is needed.

Funding
Swiss National Science Foundation, grant numbers 4053-40-104762/3, 3200-066378 and 3233-066377; Swiss Society of Internal Medicine; German Ministry of Education and Research, grant number 01 GK0516.

Bibliographic details

PubMedID
17438317

Original Paper URL
http://www.annals.org/cgi/content/full/146/8/580

Other publications of related interest
This additional published commentary may also be of interest. Lane N. Review: based on evidence from higher-quality trials, chondroitin does not reduce pain in knee or hip osteoarthritis. ACP J Club 2007;147:44.

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Chondroitin Sulfates /adverse effects /therapeutic use; Female; Hip Joint /radiography; Humans; Knee Joint /radiography; Male; Middle Aged; Osteoarthritis, Hip /drug therapy /physiopathology /radiography; Osteoarthritis, Knee /drug therapy /physiopathology /radiography; Pain /drug therapy /etiology; Randomized Controlled Trials as Topic /standards

AccessionNumber
12007008116

Date bibliographic record published
30/04/2008

Date abstract record published
16/05/2008

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.