Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis

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CRD summary

This review concluded that chondroitin or glucosamine, alone or in combination, did not have a clinically relevant effect on perceived joint pain or on joint space narrowing. This was a well-conducted piece of research and the authors' conclusions seem appropriate. However, uncertainties regarding indirect rather than head-to-head comparisons should be borne in mind.

Authors' objectives

To assess the effects of glucosamine and/or chondroitin supplements on joint pain and radiological progression of disease in patients with osteoarthritis of the hip or knee.

Searching

MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to June 2010; Science Citation Index was also searched between 1981 and 2008. Search terms were not reported. In addition, conference proceedings, text books, and reference lists of retrieved articles were searched manually, and experts in the field were contacted.

Study selection

Randomised controlled trials (RCTs) that compared chondroitin sulphate and/or glucosamine (sulphate or hydrochloride) versus placebo or each other (head to head), in patients (at least 100 per treatment arm) with knee or hip osteoarthritis, were eligible for inclusion. Trials with treatment arms that administered sub-therapeutic doses (less than 800mg/day of chondroitin and less than 1,500mg/day of glucosamine) were excluded.

The primary outcome was absolute pain intensity at any of nine time points (up to three months, six, nine, 12, 15, 18 and 21 months, then 22 months or more). Secondary outcomes were: changes in the minimum radiographic joint space between baseline and last follow-up; the number of patients withdrawn or dropped out; and adverse events.

In the included trials, participants were aged between 58 to 66 years, with the majority being women. Symptom duration ranged from 0.5 to 10.6 years (where reported). Treatment duration ranged from one to 156 weeks, with most patients treated for osteoarthritis of the knee. Most trials compared glucosamine with placebo. Outcomes were measured at one month up to 36 months.

Two of four reviewers independently screened studies for inclusion, with disagreements resolved by consensus.

Assessment of study quality

Two of four reviewers independently assessed the quality of the trials based on allocation concealment, blinding, and adequacy of analyses. Trials were also assessed on an intention-to-treat basis, and whether experimental preparations had undergone quality control. Disagreements were resolved by consensus.

Data extraction

One reviewer extracted means and standard deviations (SDs) for pain, joint space narrowing, and adverse events, on an intention-to-treat basis, where possible. A second reviewer checked the data extraction for accuracy. Where necessary, means and measures of dispersion were estimated from figures in the articles, and standard deviations were calculated from standard errors or confidence intervals. Where data [A: for joint space narrowing] were reported for multiple outcome time points, the longest follow-up data were extracted. [A: Where pain data were reported for multiple timepoints, outcome data from all timepoints were extracted.] Where trials used more than one pain scale, the outcome rating highest on a previously described hierarchy of pain related outcomes was extracted.

Methods of synthesis

A multivariable Bayesian random-effects model was used to calculate pooled mean differences (MDs) and 95% credible intervals (CrI), and corresponding effect sizes. The model took into account multiple treatment comparisons within trials and correlation of outcome data reported at different time points within a trial. Effect sizes for pain were back transformed to differences on a 10cm visual analogue scale. Heterogeneity was estimated from the median variance of treatment effects between trials (τ^2). A linear term for time was included as a covariate to investigate possible time trends (p value) [A: in an additional exploratory analysis] . Subgroup analyses were undertaken to take into account individual quality criterion, source of funding (industry independent versus other), type of glucosamine supplement used (sulphate versus hydrochlorides), and type of joint affected (knee versus hip).

Consistency of the meta-analysis network was assessed to identify the contribution of indirect evidence from the direct evidence between RCTs with one intervention in common. Goodness of fit was assessed by the median variance between trials (r^2) and through visual inspection of Q-Q plots.

Odds ratios (ORs) and 95% credible intervals were calculated for adverse events and withdrawals/drop-outs due to adverse events.

Results of the review

Ten RCTs were included in the review (n=3,803 patients, range 202 to 1,265; there was some discrepancy in the number of patients reported in the tables, and the number calculated from the web appendix table was n=3,786 patients - see URL for Additional Data). Six trials adequately described allocation concealment, nine trials reported adequate blinding of patients, and seven trials used intention-to-treat analysis. In eight trials, the experimental preparations had undergone quality control. Seven trials were funded by supplement manufacturers.

Joint pain (10 RCTs): Supplements compared to placebo showed some statistically significant reduction in pain intensity across all time points: glucosamine mean difference -0.4cm (95% CrI -0.7 to -0.1; seven RCTs), chondroitin mean difference -0.3cm (95% CrI -0.7 to 0.0), and glucosamine and chondroitin combined mean difference -0.5 cm (95% CrI -0.9 to 0.0). Corresponding effect sizes were small. There was no evidence of statistically significant variation across time points and no significant interaction between treatment effect and time. There was no evidence of significant heterogeneity between trials and no evidence for inconsistency. The goodness of fit of the model was deemed excellent (data not presented). Subgroup analysis by source of funding showed that differences between supplements and placebo were less significant in industry independent trials compared with industry sponsored trials (p=0.02 for interaction), but no other variables were statistically significant.

Radiological joint space (six RCTs): There were no statistically significant differences between supplements and placebo in changes in minimal joint space narrowing. There was some evidence of heterogeneity (r^2=0.02), but no evidence for inconsistency and the goodness of fit of the model was deemed excellent.

Safety (five RCTs): There were no statistically significant differences in the number of adverse events for glucosamine or chondroitin versus placebo, and no differences between glucosamine and/or chondroitin versus placebo for patient withdrawal or drop-out due to adverse events. There was some evidence of heterogeneity (glucosamine r^2=0.02 and chondroitin r^2=0.03). There was some evidence of inconsistency for patient drop-out due to adverse events, but this was not statistically significant (p=0.22).

Authors' conclusions

Chondroitin or glucosamine alone or combined did not have a clinically relevant effect on perceived joint pain or on joint space narrowing.

CRD commentary

The review question and corresponding inclusion criteria were clearly defined. A comprehensive search of the literature was undertaken, including attempts to locate unpublished data. However, search terms were not reported and it was unclear whether language restrictions were imposed. Each stage of the review process was undertaken in duplicate, minimising the potential for reviewer error and bias.

The authors assessed the quality of the trials using appropriate criteria, with most trials adequately fulfilling the criteria. The network analysis was well-conducted; it took into consideration both direct and indirect evidence, and investigated potential sources of bias and inconsistency.

This was a well-conducted piece of research and the authors' conclusions seem appropriate. However, uncertainties regarding indirect rather than head-to-head comparisons should be borne in mind.

Implications of the review for practice and research

Practice: The authors stated that supplements are not harmful and can be given to patients as long as the patients perceive a benefit and pay for their own treatment.

Research: The authors stated that an additional industry independent trial may be needed to include only patients (150 to 200 in each comparison group) with baseline pain intensity of at least 4cm on a 10cm visual analogue scale, and moderate osteoarthritis. The trial should have adequate treatment allocation concealment and blinding, should be carefully controlled and monitor analgesic cointerventions, and adhere to intention-to-treat analysis.

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