Glucosamine long-term treatment and the progression of knee osteoarthritis: systematic review of randomized controlled trials

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CRD summary
This review assessed the effects of long-term glucosamine on the symptoms and progression of knee osteoarthritis. The authors concluded that the limited evidence suggests that glucosamine may be safe and effective in delaying structural progression and improving symptoms, but further research is required. The authors’ cautious conclusions reflect the limited data and uncertainties about the influence of high drop-out rates.

Authors' objectives
To assess the effects of long-term glucosamine on the symptoms and progression of knee osteoarthritis (OA).

Searching
MEDLINE, EMBASE, BIOSIS Previews, EMB (Evidence Based Medicine) Reviews and the Cochrane Library were searched from inception to August 2004; the search terms were reported. The reference lists of RCTs and narrative and systematic reviews of glucosamine were checked.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared oral glucosamine, given for at least 1 year, with placebo were eligible for inclusion. The included studies used glucosamine sulphate at a dose of 1,500 mg once daily for 3 years.

Participants included in the review
Studies of patients with primary knee OA were eligible for inclusion. Both included studies were conducted in patients with primary knee OA of the medial femorotibial compartment, according to American College of Rheumatology criteria.

Outcomes assessed in the review
Studies that reported symptom severity and disease progression measured as joint space narrowing were eligible for inclusion. The primary outcome was disease progression, which was defined as a joint space narrowing of greater than 0.5 mm. Symptoms were assessed using the pain and physical function subscales of the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index. The review also assessed adverse effects.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed and scored using the Jadad scale, which considers the reporting and handling of randomisation, blinding and handling of withdrawals. The maximum possible score was 5 points. Drop-outs were also reported. Two reviewers independently assessed validity and reached consensus through discussion.

Data extraction
Two reviewers independently extracted the data and reached consensus through discussion. For each study, the
The proportion of patients with disease progression in each treatment group was extracted and used to calculate the relative risk (RR) and risk difference (RD) with the respective 95% confidence intervals (CIs). Effect sizes (ESs) and 95% CIs were calculated using standardised mean differences for the pain and physical function subscales of the WOMAC Index.

**Methods of synthesis**

How were the studies combined?
The pooled RR and RD with 95% CIs were calculated for disease progression using a random-effects model, weighting by the inverse of the variance. The number-needed-to-treat (NNT) and corresponding 95% CI were also calculated. Pooled ESs with 95% CIs were calculated for pain and physical function.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic.

**Results of the review**

Two RCTs (n=414) were included.

The studies scored 4 and 5 out of 5 on the Jadad scale. The drop-out rates in the two RCTs were high: 36% with glucosamine versus 33% with placebo and 46% with glucosamine versus 35% with placebo.

The risk of disease progression was significantly lower with glucosamine than with placebo; the pooled RR was 0.46 (95% CI: 0.28, 0.73, P<0.0011) and the pooled RD was 0.12 (95% CI: -0.05, -0.19, P=0.0006). No statistically significant heterogeneity was found (P>0.1). The NNT was 9 (95% CI: 6, 20).

In terms of symptoms, glucosamine significantly reduced pain (ES 0.41, 95% CI: 0.21, 0.60, P<0.0001) and significantly improved function (ES 0.46, 95% CI: 0.27, 0.66, P<0.0001) in comparison with placebo. No statistically significant heterogeneity was found for either meta-analysis (P>0.1).

Adverse effects were more common with glucosamine than placebo, but the difference was not statistically significant; the proportions of patients reporting any adverse effect were 94% with glucosamine versus 93% with placebo and 66% with glucosamine versus 64% with placebo. The most common adverse effects with glucosamine were abdominal pain, dyspepsia, diarrhoea, increased blood-pressure, fatigue and rash. The review did not report rates of these adverse effects.

**Authors' conclusions**

Data on the long-term effects of glucosamine were sparse. The evidence suggested that glucosamine may be safe and effective in delaying the structural progression of knee OA and in improving symptoms. Further research is required.

**CRD commentary**

The review addressed a clear question defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched, but no attempt was made to locate any unpublished studies and publication bias was not assessed. It was not stated whether any language restrictions were applied, so the potential for language bias could not be assessed. Methods were used to minimise errors and bias in the extraction of data but, since the methods used to select studies were not described, it is not known whether any efforts were made to reduce errors and bias in the selection process. Validity was assessed using established criteria.

Some information on the included studies was presented, but reasons for the high drop-out rates were not reported. In addition, it was not stated whether the data were analysed on an intention-to-treat basis, so the influence of drop-outs on the results is therefore uncertain. In view of these uncertainties and the limited information, the authors’ cautious conclusion seems appropriate.
Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further high-quality placebo-controlled, long-term studies examining different forms of glucosamine are required.

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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.