

Glucosamine May Reduce Pain in Individuals with Knee Osteoarthritis

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Date: April 2005 (planned review date April 2007)

Clinical Scenario: You are a therapist in an arthritis clinic treating a 75 year old female patient with osteoarthritis of the right knee. She states she has seen several advertisements on television reporting that glucosamine is an effective intervention in osteoarthritis. She wonders if glucosamine actually decreases both the progression of osteoarthritis and its associated pain. She asks you if there is research evidence to support this concept.

Clinical Question:

Does treatment with oral glucosamine reduce the progression of joint structure and symptoms in people with knee osteoarthritis?

Summary of 'Best Evidence' appraised, and Key Finding:

Two articles were indentified that addressed the clinical question:

- The first article selected for review was a meta-analysis of 15 high quality RCTs that assessed the disease-modifying and symptom reducing abilities of glucosamine (Gl) in osteoarthritis (OA) of the hip or knee. Two of the 15 articles assessed the primary end point joint space narrowing and found statistical benefits however this level of evidence is weak due to the limited number of trials. More importantly, the study definitively reported that subjects who took Gl experienced less pain and greater mobility than those taking placebo.
- The second article selected for review was a correlation study that performed sub-group analysis on a previous high quality RCT to determine the relationship between the knee OA severity and future disease progression of subjects taking oral Gl. The study found that in the placebo group, joint space width was significantly and negatively correlated with joint space narrowing after 3 years. In subjects with mild OA, Gl use was associated with a trend towards a significant reduction in joint space narrowing.

Clinical Bottom Line:

The effectiveness of oral glucosamine in reducing the progression of joint space narrowing has not yet been definitively established due to the small numbers of long term clinical trials and weak statistical evidence. However, the evidence from these studies suggests that oral glucosamine is effective in reducing symptomatic pain in subjects with knee osteoarthritis.

Limitation of this CAT: This CAT was prepared by a single reviewer and has not been externally peer-reviewed.

Search Strategy:

Databases & Sites Searched	Search Terms	Limits Used
- Medline - CINAHL - Cochrane Databases of Systematic Reviews - Cochrane Central - EMBASE - PEDro - AMED - Cochrane Register of Controlled Trials	- Glucosamine - Chondroitin - Drug therapy - Drug administration - Knee Arthritis - Arthritis - pain, swelling, ROM - Joint space narrowing/width - Knee/ knee joint	- Drug administration → oral - Arthritis → osteoarthritis - Human studies - English Language Articles - 2002 to present - Systematic reviews

Inclusion and Exclusion Criteria

Inclusion:

Osteoarthritis of the knee/hip
 Primary & secondary studies
 Oral administration
 Single intervention studies

Exclusion:

Rheumatoid Arthritis or other rheumatic diseases
 Topical/ intramuscular/ intrarticular administration
 Multiple intervention studies
 Non-English studies
 Unpublished literature

Results of Search

Sixteen studies were located within the available databases at Queen's University. From these results, 3 articles were related to the topic and 2 articles directly answered the clinical question.

Table 1: Summary of Designs of Articles Retrieved

Level of evidence	Study design	Number located	Source
I	Meta-analysis	1	Cochrane Databases of Systematic Reviews (reference 1)
Level IV	Correlation	1	CINAHL (reference 2)
Level Ib	Randomized Controlled Trial	3	Cochrane Central Register of Controlled Trials (references 3-5)

Best Evidence

The following articles were identified as the 'best' evidence and selected for critical appraisal. Reasons for selecting these papers were:

- The meta-analysis included only high quality RCTs and is the highest level of evidence
- Although the correlation study has a lower level of evidence this article directly related to the clinical question
- Both studies involved the target population of interest (subjects with osteoarthritis of the knee)

Summary of Best Evidence

Table 2: Description and Appraisal of the Meta-analysis by Richy et al. (2002)

Purpose of the Study: The primary purpose of the article was the analysis of the potential effectiveness of the oral administration of glucosamine and chondroitin on knee joint space narrowing. The second purpose was the assessment of the symptomatic efficacy of these two compounds by subgroup analyses of the currently recommended outcomes for symptomatic efficacy based on pain and function.

Methods/design: A meta-analysis that analyzed 15 prospective, randomized, double blind, placebo controlled, parallel group trials that assessed the effects of glucosamine and Chondroitin in human subjects with knee or hip arthritis was used.

Outcome Measures: The primary outcome measure was radiological evolution assessed by joint space narrowing. The secondary outcome measures were evaluation of pain by visual analog scale (VAS pain); joint mobility (VAS mobility); Lequesne Index and Western Ontario McMaster University Osteoarthritis Index (WOMAC).

Results: Patients taking oral glucosamine 1500 mg/d for 3 years demonstrated 0.27 mm less joint space narrowing (95% confidence interval [CI], 0.13–0.41 mm) than those taking placebo. Patients taking either glucosamine (1500 mg/d) or chondroitin (at doses ranging from 200–2000 mg/day) experienced less pain and greater mobility than those taking placebo at 4 weeks. Combined outcomes in the Lequesne Index produced a global effect size of 0.43 (95% CI, 0.32–0.54); the WOMAC revealed a common effect size of 0.30 (95% CI, 0.11–0.49). The effect sizes for visual analog pain scale (0.45; 95% CI, 0.33–0.57) and mobility (0.59; 95% CI, 0.25–0.92) also demonstrated improvement.

The responder rate was favorable for active treatment (relative risk=1.60; 95% CI, 1.39–1.83) and produced a number needed to treat of 5. Participants taking glucosamine or chondroitin did not experience more adverse reactions compared with placebo.

Author's Conclusions: The authors concluded their data demonstrated the efficacy of glucosamine on joint space narrowing and WOMAC scores and comparable efficacies of chondroitin and glucosamine on Lequesne Index, VAS pain, and VAS mobility were found. From this they deduced that a structure-modifying effect had been demonstrated for glucosamine and that the administration of glucosamine and chondroitin decreased the symptoms of osteoarthritis.

Critical Appraisal

Validity: The methodology was fairly good. To reduce bias the study included: only high quality RCTs, studies in all languages and unpublished literature. To reduce random error the study involved: a large sample size and was blindly scored by 2 raters using valid instruments. Furthermore, statistical techniques were employed to reduce any publication bias.

Importance of the Results: The results for efficacy of glucosamine on joint space narrowing were weak as only 2 of the 15 trials assessed this endpoint. Furthermore, studies have shown that joint space narrowing does not reliably predict disease progression and the relatively small reduction in joint space narrowing may not actually be clinically significant. Despite these weak findings, there was strong evidence that the administration of glucosamine decreases symptoms of osteoarthritis. This is very clinically important especially for people who cannot tolerate non-steroidal anti-inflammatory drugs (NSAIDs) or for whom NSAIDs are ineffective or contraindicated.

Implication for Practice/Applicability: The results from this study were not strong enough to confirm that glucosamine is a disease modifier. However, oral administration of Glucosamine does appear to decrease the symptoms of OA.

Table 3: Description and Appraisal of the Correlation Study by Bruyer et al (2003)

Purpose of the Study: To investigate whether radiographic knee OA severity, assessed by joint space width measurement was correlated to future structural progression of the disease, over a three year period of follow-up.

Methods/design: Retrospective sub-group analysis was performed on a 3 year randomized, placebo controlled study of 212 patients with knee OA. The original study evaluated the effects of glucosamine sulfate on symptom and structure modification in knee OA.

Outcome measure: Computer-assisted radiographic joint space width (JSW) and joint space narrowing (JSN).

Results: In the placebo group JSW was significantly and negatively correlated with JSN observed after 3 years ($r = -0.34$, $p = 0.003$). In patients with mild OA, glucosamine use was associated with a trend ($P = 0.10$) towards a significant reduction in JSN.

Author's Conclusions: The authors' concluded that patients with the less severe radiographic knee OA will experience, over three years, the most dramatic disease progression in terms of JSN and that such patients may be particularly responsive to structure-modifying drugs.

Critical Appraisal

Validity: To reduce random error in the original study, the researchers' randomly assigned subjects to treatment and control groups which helped account for variations in the sample. The effects of 'maturation' (change as part of normal development) and 'history' (events occurring in the environment at the same time), both forms of systematic error that can affect the final outcome, were reduced in the original study by adding a control group.

Importance of the Results: Despite the efforts to improve validity in the original study, secondary subgroup analysis lowered the statistical power of the second study. Furthermore, the effect of glucosamine on JSN was not statistically significant. Based on the low statistical power and low evidence the results do not support the conclusions of the study.

Implication for Practice/Applicability: The results of this study support the findings of the meta-analysis that the effectiveness of oral glucosamine as a disease modifier has not been determined. Supplying and translating the information from both studies to clients is very feasible as healthcare providers have the skills to relay this information and the cost to do this is minimal.

References

1. Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. (2000). *Evidence-based medicine*. 2nd ed. Edinburgh: Churchill Livingstone. 173-177.

Articles Critically Appraised:

Level 1

2. Richey, F., Bruyere, O., Cucherat, M., Henrotin, Y., & Reginster, J.Y. (2003). Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis. *Arch Intern Med*, 163, 1514–1522.

Level 4

3. Bruyer, O., Honere, A., Ethgen, O., Rovatis, L.C., Giacobellis, G., Henrotin, Y.E., & Seidel, L. (2003). Correlation between radiographic severity of knee osteoarthritis and future disease progression. Results from a three year prospective, placebo-controlled study evaluating the effects of glucosamine sulfate. *Osteoarthritis and Cartilage*, 11, 1-5.

Related Articles (not individually appraised):

4. Matheson, A. J. & Perry, C. M. (2003). Glucosamine: A review of its use in the management of osteoarthritis. *Drugs & Aging*, 20, 1041-1060.

5. Braham, R., Dawson, B., & Goodman, C. (2003). The effects of glucosamine supplementation on people experiencing regular knee pain. *British Journal of Sports Medicine*, 37, 45-49.

6. Nozack, W., Fischer, M., Forester, K.K., Rovati, L.C., & Setnikar, I. (1994). Glucosamine sulfate in osteoarthritis of the knee. *Osteoarthritis & Cartilage*, 2, 51-59.