PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The use of glucosamine for chronic low back pain: A systematic review of randomised control trials
AUTHORS	Sivanadarajah, Naveethan; Sodha, Reena; Alam, Mahbub

VERSION 1 - REVIEW

REVIEWER	Lauren Griffith Assistant Professor Department of Clinical Epidemiology and Biostatistics McMaster University Canada
REVIEW RETURNED	22-Jun-2012

THE STUDY	I believe the reporting of the methods needs to be improved. This would only require a bit more detail and should be easily accomplished by the authors.
RESULTS & CONCLUSIONS	I think the authors should consider a "best evidence" review.
GENERAL COMMENTS	This is an interesting paper that addresses a topic of importance. The authors conducted a systematic review of RCTs examining the use of glucosamine for chronic back pain. Comments and suggestions for the authors' consideration are below. **Major comments**: Although the authors conducted a rigorous systematic review, the only papers identified, other than Wilkens (2010), were 2 of the 3 papers mentioned in the introduction of the Wilkens paper. It is not clear whether this third paper by Drovanti was found and excluded or not found in the systematic search. Drovanti was published in 1980 - was there a date restriction on the search? In general, the methods regarding the search need to be better described. It sounds like the two searches were independently developed and undertaken. This is not likely the case as on set of search terms is presented in Appendix 1. In the text it states that no language restriction was applied, but in the discussion it states that bias may have been introduced because studies published in

	languages other than English were excluded. The dates searched for each of the databases should also be explicitly stated. In the text it states that “searches and subsequent data synthesis” was performed by two reviewers independently. I am assuming that this means that screening, risk of bias assessment, and data extraction were all done independently, but it should be stated explicitly as well as the qualifications of the screeners/data extractors. Was there any assessment of inter-rater reliability? The authors used appropriate tools to assess risk of bias and quality. The grade table is somewhat deceiving, You have a recent, high quality trial and two additional RCTs that are older and not as high quality. The results of the higher quality study (of the two additional studies) are based on a subgroup analysis as both OA knee and OA spine patients were randomized. The overall results, however, are all considered low quality or very low quality due to the combining the high quality study evidence with the lower quality studies. Would it be better focus on the recent, high quality study? The authors should consider a “best evidence” synthesis. I’m not sure that I agree with the authors’ suggestion that patients may experience some benefit from taking glucosamine albeit only due to the placebo effect. Do you think this effect would be experiences outside of the trial situation? Could it be somehow the participants had better care by just being part of a trial? **Minor comments**: In the abstract the authors state that the trial participants had a minimum of 3 months of back pain and in the text they define chronic back pain as 12 weeks or more.

REVIEWER	Irina Melnik, M.D. (on behalf of Dr. Richard Derby) Spinal Diagnostics Clinic, Daly City. No disclosures. No competing interests.
REVIEW RETURNED	20-Aug-2012

THE STUDY	Need to use clinically acceptable terminology to identify the goal of the study: treatment of what condition? Chronic low back pain? Symptomatic OA? Non-symptomatic Facets atrhrosis (MRI images

	based diagnosis)? All of these terms where used interchangeable in the paper, which doesn't make clinical sense. Symptomatic (!) OA of the lumbar facet joints is determined by a positive result of a Diagnostic Comparative Medial Branch Block, or less standart positive Diagnostic Intraarticular Facet Join injections, or positive Imaging Spectroscopy tests.
GENERAL COMMENTS	The prevalence of chronic back pain due to facet joints disease increases with age from 15% in younger patients to 40% in older. The (positive)Tant paper reported mean age of patients 64, while two others (with negative results) reported 43 and 48 mean age. This is an internal flaw based on the patients demographics included in this study and inappropriate comparison. The younger patients have more predominant discogenic pathology, which would be unlikely affected by glucosamine, while older patients tend to have truly symptomatic facet joint related pain, that seemed to be improved with glucosamine (per Tant). It is unclear why would one expect a positive result while taking glucosamine for a discogenic pathology (with possibly herniations, given a description of leg pain symptoms in included patients) , if you are mentioning in the introduction of the paper that "Glucosamine is a naturally occurring amino monosaccharide and is a precursor for glycosoaminoglycans, a major component of joint cartilage and synovial fluid". In your paper you might need to consider using term "Non-specific chronic back pain".

VERSION 1 – AUTHOR RESPONSE

Reviewer: Lauren Griffith
Assistant Professor
Department of Clinical Epidemiology and Biostatistics
McMaster University
Canada

I believe the reporting of the methods needs to be improved. This would only require a bit more detail and should be easily accomplished by the authors.

I think the authors should consider a "best evidence" review.

This is an interesting paper that addresses a topic of importance. The authors conducted a systematic review of RCTs examining the use of glucosamine for chronic back pain.

Comments and suggestions for the authors' consideration are below.

Major comments:
Although the authors conducted a rigorous systematic review, the only papers identified, other than Wilkens (2010), were 2 of the 3 papers mentioned in the introduction of the Wilkens paper. It is not clear whether this third paper by Drovanti was found and excluded or not found in the systematic search. Drovanti was published in 1980 - was there a date restriction on the search?

Response; There was no date restriction on the search. The Drovanti paper was considered but subsequently excluded as the participants had OA at multiple sites and the results were not presented in a site specific manner (unlike the Leffler paper), making it impossible to ascertain whether

glucosamine has any affect on LBP. The exclusion of papers which did not attempt to analyse in isolation, patients with low back pain has now been clearly presented in the study methods section (it was previously only displayed on the flow diagram).

In general, the methods regarding the search need to be better described. It sounds like the two searches were independently developed and undertaken. This is not likely the case as on set of search terms is presented in Appendix 1. In the text it states that no language restriction was applied, but in the discussion it states that bias may have been introduced because studies published in languages other than English were excluded. The dates searched for each of the databases should also be explicitly stated. In the text it states that "searches and subsequent data synthesis" was performed by two reviewers independently. I am assuming that this means that screening, risk of bias assessment, and data extraction were all done independently, but it should be stated explicitly as well as the qualifications of the screeners/data extractors. Was there any assessment of inter-rater reliability?

Response; Only papers published in English were considered (thank you for detecting this error).

The authors do agree with the reviewers comments that the description of the methods is ambiguous/needs clarification

The search strategy was formulated jointly by the first two authors and the searches were then independently undertaken including reference searching (and as a result the same initial shortlist of papers was yielded). The subsequent screening/risk of bias assessment was undertaken independently. There was no formal inter-rater reliability assessment performed. However a summary of the disagreements are shown below;

Screening; the first 2 authors initially disagreed as to the inclusion of the Drovanti paper as the aim of the current review was to assess the affect of glucosamine in chronic back pain and just under half of the participants in the paper had cervical spine pain/ and OA 'at other sites'. There were no other screening disagreements between researchers.

Risk of bias assessment; of the 12 areas assessed over 3 papers(36 points in total) the researchers disagreed on 3 points.

Grade profiling of papers; of the 7 areas assessed for 3 outcomes(total 21 points) the authors disagreed on 3 points.

All disagreements were resolved with discussion with the 3rd Author.

The qualifications of the authors are as follows;
Author 1; MBBS, MRCGP, BSc(Hons), current MSc Student-thesis submitted
Author 2; MBBS, MRCS(Eng),BSc(Hons), current MD(Res) Student
Author 3; MBBS, FRCS(Orth), BSc(Hons), MD(Res)

The authors used appropriate tools to assess risk of bias and quality. The grade table is somewhat deceiving; You have a recent, high quality trial and two additional RCTs that are older and not as high quality. The results of the higher quality study (of the two additional studies) are based on a subgroup analysis as both OA knee and OA spine patients were randomized. The overall results, however, are all considered low quality or very low quality due to the combining the high quality study evidence with the lower quality studies. Would it be better focus on the recent, high quality study? The authors should consider a "best evidence" synthesis.

Response; there was some debate amongst the authors as to the best way to proceed with this matter. It was decided that as the project was conducted as a systematic review and guidelines were followed in order to evaluate all existing evidence in line with the standards expected of systematic review it should therefore be presented in the same manner. The authors do acknowledge in the text that when only considering studies with a low risk of bias any affect of glucosamine on back pain is currently unfounded.

I'm not sure that I agree with the authors' suggestion that patients may experience some benefit from taking glucosamine albeit only due to the placebo effect. Do you think this effect would be experiences outside of the trial situation? Could it be somehow the participants had better care by just being part of a trial?

This point has subsequently been deleted.

Minor comments:

In the abstract the authors state that the trial participants had a minimum of 3 months of back pain and in the text they define chronic back pain as 12 weeks or more.

This has been amended accordingly.

Reviewer: Irina Melnik, M.D. (on behalf of Dr. Richard Derby)
Spinal Diagnostics Clinic, Daly City.
No disclosures. No competing interests.

Comment: Need to use clinically acceptable terminology to identify the goal of the study: treatment of what condition? Chronic low back pain? Symptomatic OA? Non-symptomatic Facets atrhrosis (MRI images based diagnosis)? All of these terms where used interchangeable in the paper, which doesn't make clinical sense. Symptomatic (!) OA of the lumbar facet joints is determined by a positive result of a Diagnostic Comparative Medial Branch Block, or less standart positive Diagnostic Intraarticular Facet Join injections, or positive Imaging Spectroscopy tests.

Response: some changes in line with your suggestions have been made, we have decided to opt for term "chronic low back pain with associated radiographic signs of spinal OA".

The prevalence of chronic back pain due to facet joints disease increases with age from 15% in younger patients to 40% in older. The (positive)Tant paper reported mean age of patients 64, while two others (with negative results) reported 43 and 48 mean age. This is an internal flaw based on the patients demographics included in this study and inappropriate comparison. The younger patients have more predominant discogenic pathology, which would be unlikely affected by glucosamine, while older patients tend to have truly symptomatic facet joint related pain, that seemed to be improved with glucosamine (per Tant). It is unclear why would one expect a positive result while taking glucosamine for a discogenic pathology (with possibly herniations, given a description of leg pain symptoms in included patients) , if you are mentioning in the introduction of the paper that "Glucosamine is a naturally occurring amino monosaccharide and is a precursor for glycosoaminoglycans, a major component of joint cartilage and synovial fluid". In your paper you might need to consider using term "Non-specific chronic back pain".

Response: The discussion did mention a theoretical biochemical model for why glucosamine may act on discs AND cartilage " glucosamine may reduce LBP by inhibiting interleukin (IL)-1β which is present in lumbar discs and facet joints" . Nonetheless the authors do agree that glucosamine may in theory only work on articular cartilage and therefore studies with a younger cohort of patients with more 'discogenic' pain may underestimate the effect of glucosamine on facet joint OA.
The authors agree that this is a very important point that was overlooked in the initial submission and this is now acknowledged in the discussion as a potential limitation of the review and explanation for the disparity in findings between papers. The point that you have raised is clearly important and in some ways highlights a potentially significant flaw in drawing broader conclusions from both the Wilkins & Leffler papers and therefore the authors feel that keeping the comparison whilst acknowledging the differences in the study demographics will present readers with a balanced view to help interpret with caution the conclusions from the 'high quality' Wilkens study.

VERSION 2 – REVIEW

REVIEWER	Dr. Irina Melnik Dr. Richard Derby Spinal Diagnostics and Treatment Center, Daly City, Ca USA
REVIEW RETURNED	05-Dec-2012

THE STUDY	You have insufficient data to make conclusions you are making in this paper (see abstract page). I recomend to change your Abstract conclusion to the same one you described in the Discussion section: "Based on current research, clinical benefits of oral G for patients with CLBP and R.changes of spinal OA cannot be demonstrated nor excluded based on insufficient data and low quality of existing research." In my opinion, if this section is not changed, your article is insufficient for publication.

VERSION 2 – AUTHOR RESPONSE

The abstract has been changed according to the reviewers comments.