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The use of glucosamine for chronic back pain: A systematic review of randomised control trials

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Abstract

Background: The use of glucosamine as a treatment for symptomatic osteoarthritis (OA) remains controversial. The aim of this review is to ascertain whether the use of oral glucosamine influences symptoms or functional outcomes in patients with back pain thought to be related to spinal OA.

Data Sources: Searches were performed by two reviewers independently up to March 2011 on Medline, AMED, CINHAL, Cochrane and EMBASE with subsequent reference screening of retrieved studies. In addition grey literature was searched via opensigle.

Methods: Included studies were required to incorporate at least one of the Cochrane Back Pain Review Group's (CBRG) outcome measures as part of their design. Trials with participants over 18 years with a minimum of 3 months of back pain, in combination with radiographic changes of OA in the spine were included. Studies were rated for risk-of-bias and graded for quality.

Results:148 studies were identified, after screening and meeting eligibility requirements 3 RCTs (n=309) were included in the quantitative synthesis. The review found there was low quality but generally no evidence of an effect from glucosamine on function, with no change on the Roland Morris Disability Questionnaire (RMDQ) score in all studies. Conflicting evidence was demonstrated with pain scores with 2 studies showing no difference and one study with a high risk-of-bias showing both a statistically and clinically significant improvement from taking glucosamine.

Conclusion: Based on current research, there is insufficient evidence to recommend the use of oral glucosamine for spinal OA, however any effect glucosamine may exert cannot be completely excluded due to the low quality of existing research.

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Introduction

Rationale

Low back pain (LBP) affects around one-third of UK adults each year.[1 2] Around 20% will consult their general practitioner (GP), making it one of the commonest presentations seen in primary care.[3] Additionally, there are considerable financial consequences associated with back pain with previous estimates of direct healthcare costs in the UK amounting to over £1.6 billion and indirect costs from informal care and loss of productivity to the economy, of £10.7 billion.[4]

Osteoarthritis (OA) is a highly prevalent degenerative joint condition that the World Health Organisation (WHO) Scientific Group on Rheumatic Diseases estimates is the cause of significant clinical problems in at least 10% of patients who are 60 years or older.[5]

OA can affect several parts of the body including the spine. Within the spine, OA affects the vertebral facet joints[6] and may occur with or without the presence of LBP.[7]

Borenstein suggested that OA may cause LBP [8] however; this relationship is complex and controversial. Some of the evidence supporting a link between spinal OA and LBP comes from early studies which showed improved back pain following intra-articular or peri-artciular joint injections. [9 10 11] However it is apparent that not all patients with LBP will have symptoms that correlate with severity of radiographic OA changes on imaging.[7]

A further degenerative process can be found in the spine in the form of intervertebral degenerative disc disease (DDD). A recent twin study demonstrated the presence of lumbar degenerative discs on MRI to be a major determinate feature of patients with LBP.[12] Although the prevalence of DDD and facet joint OA correlate[13], it is unclear with they are

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independent of one another or whether they are different ends of the spectrum of the same pathological process.

Pharmacological therapies are the most frequently used intervention for LBP,[14] however serious side effects associated with long term use of some medications such as non-steroidal anti-inflammatory drugs (NSAIDS), has led patients to seek alternative medicines such as glucosamine.

Glucosamine is available to purchase as a food supplement and is gaining popularity amongst patients in the UK for the relief of knee and hip pain associated with osteoarthritis, however more than 25% of patients have tried glucosamine for LBP. [15]

Glucosamine is a naturally occurring amino monosaccharide and is a precursor for glycosaminoglycans, a major component of joint cartilage and synovial fluid[16] and this forms the basis of the rationale for its use in OA. Glucosamine is available in over fifty different preparations most commonly in the form of glucosamine sulphate and hydrochloride.[17]

Glucosamine Hydrochorlide (Alateris®) is the only preparation licensed for medical use in the UK and the license is restricted to the symptomatic relief of mild to moderate knee OA. Despite its license there is less evidence for its use compared with glucosamine sulphate and neither are currently recommended by the National Institute for Health and Clinical Excellence (NICE).[18]

Several trials and systematic reviews have looked into the use of glucosamine in knee and hip arthritis. A Cochrane review identified 16 double-blind randomised controlled trials (RCTs) and concluded that there was good evidence that glucosamine is both effective and safe in treating OA, but this did not assess spinal OA[19] This review was updated and failed to show a uniformly positive conclusion, if only high quality studies were included[20]. Analysis

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restricted to studies with adequate allocation concealment failed to show any benefit of glucosamine for pain, function and stiffness based on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) used to assess pain, stiffness and function in patients with hip and knee OA. However the review also assessed pain and function on the Lequesne index which did reveal an improvement after glucosamine when compared to placebo. The disparity between these findings remains unexplained by the authors, however a study that compared and tested the validity of WOMAC and Lequense index found that although both measures show internal validity when assessing function in hip and knee OA, only the WOMAC is consistently reliable when assessing symptoms such as pain.[21]

Given the lack of conclusive evidence regarding an improvement in LBP from glucosamine and at present no recommendations from NICE, the indications for using glucosamine remain controversial for clinicians and patients.

Reviews so far have focused on trials looking at the use of glucosamine in hip and knee OA.[22] The current study has been undertaken to provide an up to date systematic review of the evidence for the use of glucosamine in LBP.

Objective

To systematically search and assess the quality of the evidence of the efficacy of glucosamine on low back pain symptoms in patients diagnosed with spinal facet joint OA or degenerative disc disease.

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Methods

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were considered for this review as randomisation ensures that patients in the treatment and control groups are comparable from the start. In the hierarchy of study designs, RCTs and systematic reviews are considered the highest level of evidence.[23] At least one day of follow-up was required to ascertain any effect of an intervention. RCTs were included if they: 1) evaluated the efficacy and toxicity of glucosamine in OA, 2) were placebo-based or comparative studies, 3) were open-label, single-blinded or double-blinded, 4) evaluated glucosamine-only or combination preparations**,** 5) utilised oral administration of glucosamine as this is the route which will be used by the majority of patients.

Types of participants

Participant inclusion criteria for this review included: adult subjects (≥18 years), with chronic back pain (≥12 weeks) with a diagnosis of spinal OA. As there are no consensus guidelines about constitutes a diagnosis of OA in the spine any radiographic changes consistent with OA were included. A variety of radiographic grading systems have been proposed but there is no single global staging system suitable for the assessment of OA at all sites. [24]

The exclusion criteria were: trials that included subjects with specific LBP caused by other pathologies such as vertebral canal stenosis, ankylosing spondylitis, scoliosis and coccycydinia and trials that looked at OA at multiple sites but did not separate the data from the different sites making conclusions regarding changes in spinal symptoms difficult.

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Types of Interventions

Both placebo-controlled trials and comparative studies were eligible. Types of comparison considered appropriate were conventional therapies used for OA such as physical therapy, analgesics and anti-inflammatories.

Types of Outcome Measures

For inclusion, at least one of the following outcome measures, recommended by the Cochrane Back Review Group (CBRG), had to be observed: 1) pain intensity, for example visual analogue scale, 2) reliable and valid measure of functional status or disability for example, the Roland-Morris Disability Questionnaire (RMDQ)[25 26] 3) perceived recovery, 4) return-to-work status 5) structural benefits measured by radiography 6) adverse effects. The primary outcomes for this review were pain and functional status. The timing of measured outcomes had to be explicitly described.

Search methods for identification of studies

Searches and subsequent data synthesis were performed by two reviewers independently. Differences were resolved after discussion with a third reviewer. The search was conducted up to March 2011 and included grey literature, searched via opensigle. No language restriction was applied. By searching MEDLINE (medical, nursing and biomedical journals), it was anticipated that approximately half of available RCTs would be identified, therefore a subsequent search of EMBASE (biochemical and pharmaceutical journals) would ensure a comprehensive search as there is little overlap between these databases and in the field of LBP, EMBASE has been shown to retrieve more clinical trials.[27] Searching AMED and CINHAL would cover complementary medicine and allied health journals, whilst including

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Cochrane enabled high quality evidence from RCTs and systematic reviews to be included. References of relevant studies were screened to identify additional studies.

The electronic search strategy outlined in Appendix 1 was developed in MEDLINE and adapted for the other databases. The search was developed by reviewing relevant articles in the area of back pain and OA and combining search terms used in these studies.

Risk-of-bias assessment and quality

The risk of bias was assessed using the criteria advised by the CBRG.[27] Each criterion was scored as yes, unclear or no, where yes indicated the criterion had been met. Studies are rated as having a low 'risk of bias' when at least 6 of the 12 CBRG criteria have been met with no serious flaws.

Data Extraction

Data was recorded onto a standardised form and described the main trial characteristics, patient demographics, interventions, comparisons, outcomes, analysis, results and assessment of trial quality (tables 1 and 2).

Quality of the Evidence

Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria were used to evaluate the overall quality of the evidence. This is recommended by the Cochrane Handbook to rate the quality of evidence for each important patient-centred outcome as it goes beyond the reporting of quantitative analysis. The quality of evidence was based on 5 domains: limitations of the study design, inconsistency, indirectness (inability to

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generalise), imprecision (insufficient or imprecise data) of results and publication bias across all studies that measure that particular outcome.[28] The overall quality was considered to be high when at least 75% of the RCTs with no limitations of study design had consistent findings, direct and precise data and no known or suspected publication biases.[27] The grades of quality of evidence are outlined in Appendix 2. [29]

Results

Description of studies

Study selection

Studies were identified through the following databases: Medline (11), Embase (53), Cochrane library (84) (Cochrane reviews (10), other reviews (7), clinical trials (67)). Three studies were included (Table 1). Reasons for exclusion are outlined in Figure 1. Due to differences in the study design of included trials, metanalysis was not attempted.

Risk of bias in included studies

The risk-of-bias assessment is shown in table 2. Although all studies were described as randomised, only two described adequate randomisation.[30 31] One trial was open-label and did not report compliance.[31] One trial had a 20% drop-out rate.[32] All trials had similar groups at baseline, timings of outcome assessments and co-interventions in both groups.

From this assessment two studies have been rated as having a low risk of bias. The one study rated as a high risk of bias scored six, but its open-label design was considered to be a significant methodological flaw.

Effects of intervention

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Tables 3, 4 and 5 summarise the findings with respect to the main outcomes measured. For pain, the two studies with a low risk of bias failed to show any significant improvement with glucosamine compared with placebo, whilst the one study with a high risk-of-bias did show a significant difference with glucosamine compared to no glucosamine.

Back function/disability was measured by Owestry Disability Index (ODI) and RMDQ, both validated tools[26 33]; there was no significant difference in the RMDQ scores with glucosamine as an intervention. The study with a high risk of bias demonstrated a statistically significant difference in the ODI score reduction for the glucosamine group, although this difference was small.[31]

With respect to adverse effects, one trial revealed ~ 30% of participants experienced adverse effects irrespective of whether they were in the placebo or glucosamine group.[30]

Other outcomes that were considered but not across all trials included an assessment of quality of life measured by the Euro-Qol-5 Dimensions (EQ-5D) index and overall health status measured by EQ-VAS.[30] There was no significant difference found between glucosamine and placebo with these outcomes.

One study used several assessments which were totalled to provide an overall summary score.[32] In addition to measuring pain and function, physical examination scores and running times were assessed. There were no statistically significant changes in the LBP group when considering the overall summary score or individual outcome measures.

None of the studies looked at radiographic changes in association with glucosamine use.

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Discussion

In this review three RCTs were included that evaluated the effectiveness of glucosamine as an intervention for chronic low back pain associated with spinal OA. [30 31 32]

Overall, the review found the limited number of studies had methodological deficiencies. The studies did not demonstrate a clear beneficial effect of using glucosamine for LBP due to OA[30 32]. One study however showed a statistically significant difference in the ODI score reduction for the glucosamine group [31], although this difference was small and does not appear to reach the minimally clinical important difference (MCID) alluded to in previous research.[34]

There was conflicting evidence regarding the effect of glucosamine on pain scores. Two studies showed no statistically significant difference on pain scores between the intervention and placebo group. [30 32] One study did show a statistical and clinically significant reduction in pain scores for those taking glucosamine.[31] Quality and methodological differences may account for the discrepancies between these studies and this is discussed below.

Methodological considerations

There were several factors that contributed to the very low or low quality assessment for the main outcomes measured in the trials. The results of one study [31] in particular which found positive effects of glucosamine on both pain and function appears to contradict the findings of the other two, however, this may be partly explained by its limitations. A key limitation was its open-label design. Since participants and clinicians were aware of group allocation, bias was introduced.

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Another study had unclear details about its randomisation.[32] Blinding and randomisation decrease the likelihood of selection and performance bias which would affect the internal validity of the study.[35] This same RCT employed a cross-over design, which may intrinsically have introduced bias if the 5 week wash-out period employed was too short.

To minimize attrition bias, the drop-out rate should be described and acceptable with all the randomised patients analysed in the group to which they were allocated, by an intention to treat analysis (ITT) [35]. One trial did not employ an ITT analysis and compliance was unclear.[31]

There are difficulties in how the trials can be directly applied to the general population and this adversely affects their relevance to practice and external validity. One trial used patients from US Navy diving and special warfare community who have a history of high activity levels and unique occupational exposures. They were also all male; hence the results may not be generalisable.[32] This study used a mixed population of both knee and back pain patients, with some participants having both knee and back pain. The proportion of patients in each group was described and the data was separated.

Despite the fact that the risk of bias was low in two studies, the studies collectively showed flaws regarding concealment of treatment allocation, adequate randomisation, compliance and drop-out rates. The review findings were significantly influenced by these shortcomings despite the fact that the study by Wilkens et al was of a high quality and well designed. The quality of future RCTs needs to be improved to reduce bias in future reviews.

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Review Strengths and Limitations

The selection procedure and literature search utilised in this review may have introduced bias. Relevant, unpublished trials may have been omitted and as these are likely to be small studies without positive results this may lead to publication bias. Studies not published in English were excluded and may also have introduced bias. Utilsing references of the included trials to identify other studies may have also led to an over-representation of positive studies.

The search strategy was however vigorous with several databases utilised, in addition to reference screening of included studies which ensured that the omission of relevant studies was minimised.

Implications for Health Practice

LBP is extremely prevalent with considerable financial consequences.[4] OA accounts for a significant proportion of LBP seen by GPs and secondary care clinicians. Current treatment options such as NSAIDs and surgery have some potentially serious adverse effects .Therefore alternative treatments such as glucosamine which may provide a possible solution to this problem seem attractive.

Global sales of glucosamine reached almost £1.3billion in 2008.[36] Currently in the UK, glucosamine is available as a food supplement and can be prescribed for knee OA. The evidence for its use in back pain is conflicting, it is therefore imperative that a consensus based on sound clinical evidence is reached to justify this immense cost to the public.

This review helps clarify the existing evidence for the use of glucosamine in back pain which will be of particular relevance to patients and clinicians considering using glucosamine.

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The current review has demonstrated that if only the studies with a low risk of bias are considered, there is no evidence of a significant difference between glucosamine and placebo for pain or pain-related disability associated with OA in the lower back.

The mechanism by which glucosamine may exert its effect is poorly understood. Wilkens et al, previously proposed that glucosamine may reduce LBP by inhibiting interleukin (IL)-1β which is present in lumbar discs and facet joints. This mechanism is purely theoretical with no conclusive evidence demonstrating a direct pharmacological effect on the spine. The lack of a sound scientific rationale for the use of glucosamine in LBP makes it difficult to successfully design a study to prove any clinical benefit it may have. In addition, there is much debate as to the relationship between LBP and spinal OA findings. Not all patients with LBP have spinal OA and vice versa, however most studies assume they are correlated.

All of the studies included in the review had limitations. All were single centre trials and two had small sample sizes. There were methodological differences in randomisation, blinding, allocation concealment and varying outcome measures. Inclusion criteria varied between trials some looked at both facet joint OA and degenerative disc disease. These two conditions do not necessarily represent the same pathological process. In addition the method for diagnosing the OA differed as there is no existing consensus or criteria for diagnosis. Back pain is complex and whilst spinal OA may cause low back pain, several other structures may be responsible and pathologies may co-exist.

It is possible that glucosamine may work better in more severe disease as has been suggested with knee OA.[37] The studies reviewed all had varying severities of OA symptoms required for inclusion. This limits the conclusions that can be made as the studies did not separate out the data for different levels of severity in the analysis.

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OA is a chronic disease and patients taking supplements such as glucosamine may do so for several years. Follow-up periods for the trials varied from eight weeks to one year. Glucosamine may take longer than this to have an apparent affect. A case report revealed an improvement in the structural quality of disc cartilage on MRI in a patient taking glucosamine over a two year period.[38] The patient's symptoms only began to improve at six months and continued until the end of the study period. None of the studies in this review looked at objective radiographic changes as an outcome and whilst there are obvious limitations to drawing any broad conclusions form a single case report, this provides an argument for a longer follow-up RCT and more objective outcome measures.

A strength of this review is that it contained several placebo-controlled RCTs. One especially well-designed study clearly showed that patients treated with glucosamine for one year who had a combination of chronic LBP and either or both facet joint OA and degenerative disc disease, had no difference in pain or disability when compared to placebo.

An important factor to consider when assessing the relevance of trial data to everyday practice is the generalisability or external validity of the studies. The current review included one study which used a relatively young cohort of male patients who were from a US Navy diving and special warfare community who had a history of high activity levels and unique occupational exposures. This is not the profile of a typical OA patient a doctor would see in general practice.

An important distinction is between statistical significance and clinical relevance of findings. One study showed a statistically significant difference in pain related disability on the ODI, however the difference was very small and may not have represented a clinically relevant change.[31] Currently there is consensus regarding minimal clinically important changes for pain and function (measured by RMDQ not ODI) in back pain.[27] For LBP, 30% on

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VAS/NRS for pain is considered as clinically significant and 2 to 3 points (8 -12%) on the RMDQ for function is considered as clinically significant.[39]

Although some of the trials showed no difference between glucosamine and placebo, there was an overall reduction in pain and disability scores across both groups. This may provide a justification for advising patients that they may experience some benefit from taking glucosamine albeit only due to the 'placebo-effect'. However the review showed a high incidence of adverse effects and although these were mild, it is an important consideration when recommending it.

Based on the current evidence explored in this review, there is not sufficient evidence to either demonstrate or exclude a clinical benefit of glucosamine for spinal OA. Using more objective measures such as radiography to look at any change in OA progression, refining study inclusion criteria, providing longer follow-up periods and trying to establish a clear biochemical model for glucosamine may enable more definitive conclusions to be drawn so that clinicians can confidently advise their patients based on the best available evidence.

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APPENDICES

Appendix 1. Electronic search strategy

1. exp osteoarthritis, spine
2. degenerative arthritis. mp. or exp osteoarthritis
3. osteoarthr*
4. degenerative joint disease. Mp.
5. degenerative disc disease
6. exp low back pain
7. exp back pain
8. exp spine
9. exp lumbar vertebrae
10. chronic back pain. mp.
11. exp glucosamine/ or glucosamine. mp.
12. glucosamine sulphate. mp.
13.exp acetylglucosamine/ or acetylglucosamine. mp.
14. glucosamine hydrochloride. mp.
15. n-acetyl-d-glucosamine.tw.
16. or/1-5
17. or/6-10
18. or/11-15
19. 16 and 17 and 18

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Appendix 2: Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria

High quality (at least 75% of the RCTs with no limitations of study design have consistent findings, direct and precise data and no known or suspected publication biases)	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality 1 of the domains are not met	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality 2 of the domains are not met	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality 3 of the domains are not met	Any estimate of effect is very uncertain

5 Domains:

Limitations of the study design, inconsistency, indirectness (inability to generalise), imprecision (insufficient or imprecise data) and publication bias.

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References:

1. Macfarlane GJ, Beasley M, Jones EA, Prescott GJ, Docking R, Keeley P, McBeth J, Jones GT. The prevalence and management of low back pain across adulthood: Results from a population-based cross-sectional study (the MUSICIAN study). *Pain* 2012; 153(1):27-32.
2. Papageorgiou AC, Croft PR, Thomas E, Ferry S, Jayson MI, Silman AJ. Influence of previous pain experience on the episode incidence of low back pain: results from the South Manchester Back Pain Study. *Pain* 1996; 66(2-3):181-5.
3. Papageorgiou AC, Rigby AS. Review of UK data on the rheumatic diseases--7. Low back pain. *Br J Rheumatol*. 1991; 30(3):208-10.
4. Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain* 2000; 84 (1):95-103.
5. Murray CJL, Lopez AD. The global burden of disease. A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge (MA): Harvard School of Public Health on behalf of the *World Health Organization* and *The World Bank*; 1996.
6. Kalichman L, Hunter DJ. Lumbar facet joint osteoarthritis: a review. *Semin Arthritis Rheum*. 2007; 37(2):69-80.
7. Kalichman L, Li L, Kim D, Guermazi A, Berkin V, O'Donnell C, Hoffmann U, Cole R, Hunter D. Facet joint osteoarthritis and low back pain in the community-based population. *Spine* 2008;33(23): 2560–2565.
8. Borenstein D. Does osteoarthritis of the lumbar spine cause chronic low back pain? *Curr Pain Headache Rep*. 2004;8(6):512-517.
9. Goldthwait J. The lumbosacral articulation. An explanation of many cases of lumbago, sciatica, and paraplegia. *Boston Med and Surg J*. 1911;164:365–372.
10. Schwarzer AC, Aprill C, Derby R. Clinical features of patients with pain stemming from the lumbar zygapophyseal joints. Is the lumbar facet syndrome a clinical entity? *Spine* 1994;10:1132–1137.
11. Dreyer SJ, Dreyfuss PH. Low back pain and the zygapophysial (facet) joints. *Arch Phys Med Rehabil*. 1996;77:290–300.
12. Livshits G, Popham M, Malkin I, Sambrook PN, Macgregor AJ, Spector T, Williams FM. Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study. *Ann Rheum Dis.* 2011;70(10):1740-5.
13. Li J, Muehleman C, Abe Y, Masuda K. Prevalence of facet joint degeneration in association with intervertebral joint degeneration in a sample of organ donors. *J Orthop Res*. 2011;29(8):1267-74.
14. Kuijpers T, Van Middelkoop M, Rbinstein S, Ostelo R, Verhagen A, Koes B, Van Turner M. A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. *Eur Spine J*. 2011; 20:40-50.
15. Avins A. Glucosamine and the ongoing enigma of chronic low back pain *JAMA* 2010;304:1.
16. Arendt-Nielsen L, Weidner M, Bartholin D, Rosetzsky. A double- blind randomized placebo controlled parallel group study evaluation the effects of Ibuprofen and

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glucosamine sulphate on exercise induced muscle soreness. *Journal of Musculoskeletal Pain*. 2007; 15(1):21-28

17. C+D Data, 2008. *The Product File* [online]. Available: http://www.cddata.co.uk [Product search for "glucosamine": 20 October 2008].
18. NICE Guideline CG59 Osteoarthritis the care and management of osteoarthritis in adults http://www.nice.org.uk/guidance/index Feb 2008.
19. Towheed TE, Anastassiades TP, Shea B, Houpt J, Welch V, Hochberg MC. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2001;(1):CD002946.
20. Towheed T, Maxwell L, Anastassiades T, Shea B, Houpt J, Welch V, Hochberg M, Wells G. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2009, Issue 4. Oxford: Update Software.
21. Stucki G, Sangha O, Stucki S, Michel BA, Tyndall A, Dick W, Theiler R. Comparison of the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index and a self-report format of the self-administered Lequesne-Algofunctional index in patients with knee and hip osteoarthritis. *Osteoarthritis Cartilage*. 1998;6(2):79-86.
22. Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ*. 2010; 16:341.
23. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines for the Scottish Intercollegiate Guidelines Network Grading Review Group. (SIGN) *BMJ* 2001;323:334-336.
24. Roland W. Moskowitz M., Roy D. Altman, M, . Hochberg M. Osteoarthrits: Diagnosis and medical /surgical management *Lippincott,Willliams and Wilkens* 4th Ed 2006.
25. Roland M, Morris R A study of the natural history of backpain: Development of a reliable and sensitive measure of disability in low-back pain. *Spine* 1983;8:141–144
26. Stratford PW, Binkley JM, Riddle DL, Guyatt GH Sensitivity to change the Roland–Morris back pain Questionnaire:Part 1. *Phys Ther* 1998;78:1186–1196.
27. Furlan A, Pennick V, Bombardier C, van Tulder M Updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine* 2009;34(18):1929-1941
28. Atkins D, Best D, Briss P. GRADE Working group. Grading quality of evidence and strength of recommendations. *BMJ* 2006; 328:1490
29. Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, for the GRADE Working Group**.** Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations**.** *BMJ* 2008;336:924-926
30. Wilkens P, Scheel I, Grundes O, Hellum C, Storheim K. Effect of Glucosamine on Pain-Related Disability in Patients with Chronic Low Back Pain and Degenerative Lumbar Osteoarthritis. *JAMA*. 2010;304(1):45-52

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

31. Tant L, Gillard B, Appelboom T. (2005) Open-label, randomized, controlled pilot study of the effects of a glucosamine complex on low back pain. *Current Therapeutic Res.* 2005;66(6):511-521
32. Leffler C, Philippi A, Leffler S, Mosure J, Kim P. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo controlled pilot study. *Mil Med.* 1999;164(2):85-91.
33. Fairbank J, Couper J, Davies J, O'Brien J The Owestry low back pain disability questionnaire. *Physiotherapy* 1980;66: 271-273.
34. Lauridsen HH, Manniche C, Korsholm L, Grunnet-Nilsson N, Hartvigsen J. What is an acceptable outcome of treatment before it begins? Methodological considerations and implications for patients with chronic low back pain. *Eur Spine J.* 2009 Dec;18(12):1858-66.
35. Hart A. Making sense of statistics in health care *Radcliffe Medical Press* 2001.
36. Heller L. US glucosamine grows slow, lags global sales. 2009. www.nutraingredients-usa.com/Consumer-Trends/US-glucosamine-grows-slow-lags-global-sales.
37. Clegg D, Reda D, Harris C. Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis. *New England Journal of Medicine*, 2006; 354:795-808.
38. Van Blitterswijk W, van de Nes J, Wuisman P. Glucosamine and chondroitin sulphate supplementation to treat symptomatic disc degeneration: Biochemical rationale and case report. *BMC Complementary and Alternative Medicine* 2003;3:2 ;1-8
39. Ostelo R, Deyo R. Stratford P Interpreting change scores for pain and function status in low back pain: towards international consensus regarding minimal important change. *Spine* 2008;33: 90-94

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Table 1: Characteristics of studies included

	Methods	Participants	Interventions	Outcome measures	Notes
Wilkens 2010	RCT Double-blind Single centre	Outpatients (N=250) Country – Norway Mean age 48.5, 48.4% female Inclusion criteria: Chronic LBP > 6 months, MRI findings indicating degenerative lumbar OA, age >25	1500mg glucosamine sulphate versus placebo for 6 months	Primary outcome: disability – RMDQ Secondary outcomes: pain at rest and during activity (11-point scale), quality of life (QOL): EQ-5D and EQ-VAS, global perception of effect (7 point scale) Adverse effects	Sponsored by Pharma Nord.
Tant 2005	RCT Open-label Single centre	Outpatients (N=36) Country – Belgium Mean age 64, 43.8% female Inclusion criteria: LBP > 12 weeks with associated signs of lumbar arthrosis on radiography, pain score on VAS >3mm	Conventional treatment (CT) (anti-inflammatory and physical therapy) plus glucosamine complex (containing equivalent :1500mg glucosamine, 200mg of Ribes nigrum, 2000mg methylsulfonylmethane and 100mg colloidal silicon) for 12 weeks versus CT alone	Primary outcome: pain at rest on VAS Secondary outcomes: lumbar stiffness on VAS, 2 QOL questionnaires – ODI and RMDQ, global assessment of treatment (satisfied or not) Adverse effects	Sponsored by Pierre Fabre Sante
Leffler 1997	RCT (cross-over) Double-blind Single centre	Outpatients (N=34, 23 back patients) Country – USA Mean age 43.5 100%male Inclusion Criteria: chronic knee or low back pain on most days for at least 3 months and radiographic evidence of degenerative joint disease	16 weeks (8 weeks each arm). 1500mg glucosamine hydrochloride, 1200mg chondroitin sulphate, 228g manganese ascorbate versus placebo	Pain (VAS scores), Function: Lequesne Index (knee), RMDQ (back), patient assessment of handicap, physician assessment of severity and physical exam scores	Patients from US Navy diving and special warfare community Mixed population of knee and back pain (21 – knee OA, 23 - spinal degenerative joint disease. Data separated by site for analysis. Sponsored by Nutramax

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Table 2: Methodological quality assessment and risk of bias

	Randomisation adequate?	Allocation concealed?	Groups similar at baseline?	Patient blinded?	Care provider blinded?	Outcome assessor blinded?	Drop-out rate described and acceptable?	Intention to treat analysis?	Co-interventions avoided or similar?	Compliance acceptable?	Timing outcome assessment similar?	Report free of selective outcome reporting	Total
Wilkens 2010	yes	yes	yes	Yes	yes	yes	Yes	yes	Yes	yes	yes	yes	12
Tant 2005	yes	no	yes	No	no	no	Yes	no	Yes	unclear	yes	yes	6
Leffler 1999	unclear	yes	yes	Yes	yes	yes	No	yes	Yes	yes	yes	yes	10

Risk of bias assessed using criteria from the CBRG (Furlan et al, 2009). Studies rated as having a 'low risk of bias' when at least 6 of the 12 CBRG criteria have been met and it has no serious flaws.

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Table 3: Key findings: Effect of glucosamine on back pain outcomes

Study	Risk of bias	Method of assessment	Key findings	Notes
Wilkens, 2010	Low	Low back and leg pain intensities during activity and rest measured by 11-point numeric pain rating scale (NRS) Patients assessed at baseline, 6 weeks, 3 months, 6 months, 1 year.	Baseline NRS LBP at rest for the glucosamine group was 3.7 (95% CI 3.3-4.1) and 3.9 (95% CI 3.5-4.3) for placebo. The 6-month NRS score was 2.5 (95% CI 2.1-2.9) for glucosamine and 2.4 (95% CI 2.0-2.8) for placebo. No statistical difference in change between the two groups found at 6 months (P =0.91) for LBP at rest and (P= 0.97) for LBP during activity.	No significant difference between glucosamine and placebo
Tant 2005	High	VAS for pain at rest and on movement (0-10cm) measured every 4 weeks	At week 4, mean change from baseline VAS scores for pain at rest was significantly greater in the glucosamine group compared with control group (-2.18 vs +0.13, P<0.001). Difference also significant at 8 and 12 weeks (both P<0.01). The between-group difference in mean VAS scores for pain on movement was only significant at week 12 (2.08) in glucosamine group versus (4.00) in control group; (P=0.029)	Significant difference between CT+glucosamine and CT
Leffler 1997	Low	VAS for pain recorded at clinic visits (0-10cm) VAS for pain recorded in a daily diary by patients (VAS 0-7cm). Assessed after weeks 7&8 Knee and back data were separated in later analysis.	Back: The VAS for pain showed a mean change of -28.0% when medication was compared to placebo during the clinic visit (p>0.06) and -21.0% in the diary data (p>0.06). No CI.	No significant effect on back pain between glucosamine and placebo.

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Table 4 Key findings: Effect of Glucosamine on function outcomes

Study	Risk of bias	Method of function assessment	Key findings	Notes
Wilkens, 2010	Low	RMDQ	At baseline, mean RMDQ scores were 9.2 (95% CI 8.4-10.0) for glucosamine and 9.7 (95% CI 8.9-10.5) for the placebo group. At 6 months, the mean RMDQ score was the same for the glucosamine and placebo groups (5.0; 95% CI 4.2-5.8). No statistically significant difference in change between the groups found when assessed at 6 months and 1 year (P=0.72).	No significant difference between placebo and glucosamine
Tant 2005	High	RMDQ and ODI	Mean score on the ODI significantly improved from baseline at weeks 4, 8 and 12 in the glucosamine group (all P<0.001). In the control group no significant improvement in score until week 12 (p<0.001). At 12 weeks: significant difference in ODI score between the 2 groups (P=0.028) At baseline, mean RMDQ scores were 9.76 for glucosamine and 7.86 for placebo group. Mean RMDQ scores significantly improved from baseline at weeks 4, 8 and 12 in both groups (all P<0.001) but no significant between-group differences found.	No significant difference between CT+glucosamine and CT for RMDQ but significant difference for ODI.
Leffler 1997	Low	RMDQ	Back: Mean baseline RMDQ score was 6.9 with a mean change of -13.7% when medication was compared to placebo (p>0.06) No CI.	No significance difference between placebo and glucosamine.

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Table 5 Key findings: Adverse Effects

Study	Risk of bias	Monitoring	Adverse effects	Notes
Wilkens, 2010	Low	Adverse events, blood pressure (bp) monitored every visit. Fasting blood glucose, cholesterol levels before and following intervention.	Adverse events (n=86), 40 in glucosamine group, 46 in placebo group. ~ 30% of patients had adverse events. 10 patients withdrew due to adverse events. Adverse events: mild gastrointestinal and dermatological symptoms. All self-limiting. Fasting blood glucose, cholesterol and bp did not alter.	1 patient died in glucosamine group 1 participant in each group developed a disc herniation requiring surgery, events not considered study related.
Tant 2005	High	Patients interviewed at clinic visit regarding undesirable effects	Abdominal discomfort reported at 8 weeks by 1 patient in the glucosamine group and 1in the control group. None of the patients discontinued treatment due to an adverse event.	Adverse effect may have been due to analgesic/anti-inflammatory treatment instead of glucosamine as abdominal discomfort also occurred in 1 patient not receiving glucosamine.
Leffler 1997	Low	Patient survey of toxicity symptoms and faecal occult blood testing at end of each phase. Bp and pulse measured 21 patients had blood count and coagulation studies done.	No patients reported symptoms requiring termination of the study. Symptom frequency on medication was similar to that at baseline. Vital signs, occult blood testing and haematological parameters did not change significantly from placebo to medication.	

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Table 6: GRADE evidence profile

Quality Assessment							
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Pain measured on VAS, follow up (4weeks – 1year)							
3	Randomised trials	Serious[1]	Serious[2]	Serious[3]	No serious imprecision	None	Very low
Function/disability measured on RMDQ, Follow up (4weeks – 1year)							
3	Randomised trials	Serious[1]	No serious inconsistency	Serious[3]	No serious imprecision	None	Low
Adverse effects							
3	Randomised trials	Serious[1]	No serious inconsistency	Serious[3]	No serious imprecision	None	Low

[1]One study was open-label (Tant, 2005). There were limitations regarding unclear randomisation in another trial (Leffler, 1999). One trial did not clearly employ an intention to treat analysis and compliance was also unclear (Tant 2005).

[2]Two trials with a low risk of bias failed to show any significant decrease in pain levels (Wilkens, 2005 and Leffler, 1999), whereas one trial with a high risk of bias (Tant 2005) showed a significant effect of glucosamine on back pain.

[3]One trial used male patients from US Navy special warfare community with a history of high activity levels and unique occupational exposures; hence the results may not be generalisable (Leffler, 1999). One study used a mixed population of both knee and back pain patients and some patients had both, although data was separated by site (Leffler, 1999).

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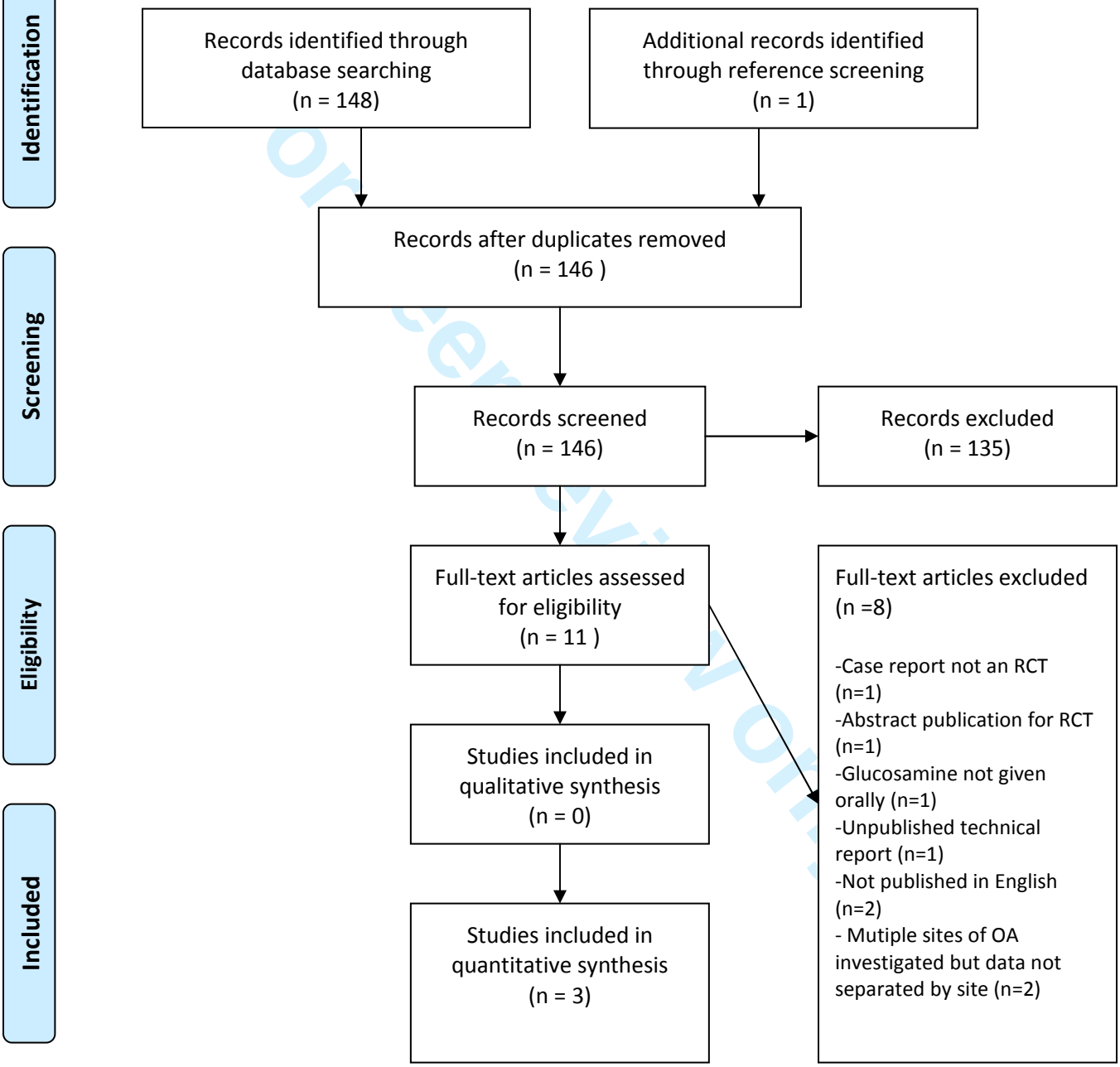
Figure 1: Flow diagram of inclusion and exclusion of articles for glucosamine use in spinal OA (PRISMA 2009 Flow Diagram) (Moher et al)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Appendix 3 – Prisma 2009 Checklist (Moher et al)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	-
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6,7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	-
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7,8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	-

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Appendix 3 – Prisma 2009 Checklist (Moher et al)

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	-

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2&6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 3,4,5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10,11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10,11,12,part B
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

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Appendix 3 – Prisma 2009 Checklist (Moher et al)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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The use of glucosamine for chronic low back pain: A systematic review of randomised control trials

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Abstract

Background: The use of glucosamine as a treatment for osteoarthritis (OA) remains controversial. The aim of this review is to ascertain whether the use of oral glucosamine influences symptoms or functional outcomes in patients with chronic low back pain (LBP) thought to be related to spinal OA.

Data Sources: Searches were performed up to March 2011 on Medline, AMED, CINHAL, Cochrane and EMBASE with subsequent reference screening of retrieved studies. In addition grey literature was searched via opensigle.

Methods: Included studies were required to incorporate at least one of the Cochrane Back Pain Review Group's (CBRG) outcome measures as part of their design. Trials with participants over 18 years with a minimum of 12 weeks of back pain, in combination with radiographic changes of OA in the spine were included. Studies were rated for risk-of-bias and graded for quality.

Results:148 studies were identified, after screening and meeting eligibility requirements 3 RCTs (n=309) were included in the quantitative synthesis. The review found there was low quality but generally no evidence of an effect from glucosamine on function, with no change on the Roland Morris Disability Questionnaire (RMDQ) score in all studies. Conflicting evidence was demonstrated with pain scores with 2 studies showing no difference and one study with a high risk-of-bias showing both a statistically and clinically significant improvement from taking glucosamine.

Conclusion: Based on current research, there is insufficient evidence to recommend the use of oral glucosamine for patients with chronic LBP and radiographic changes of spinal OA,

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however any effect glucosamine may exert cannot be completely excluded due to the low quality of existing research.

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Introduction

Rationale

Low back pain (LBP) affects around one-third of UK adults each year.[1 2] Around 20% will consult their general practitioner (GP), making it one of the commonest presentations seen in primary care.[3] Additionally, there are considerable financial consequences associated with back pain with previous estimates of direct healthcare costs in the UK amounting to over £1.6 billion and indirect costs from informal care and loss of productivity to the economy, of £10.7 billion.[4]

Osteoarthritis (OA) is a highly prevalent degenerative joint condition that the World Health Organisation (WHO) Scientific Group on Rheumatic Diseases estimates is the cause of significant clinical problems in at least 10% of patients who are 60 years or older.[5]

OA can affect several parts of the body including the spine. Within the spine, OA affects the vertebral facet joints[6] and may occur with or without the presence of LBP.[7]

Borenstein suggested that OA may cause LBP [8] however; this relationship is complex and controversial. Some of the evidence supporting a link between spinal OA and LBP comes from early studies which showed improved back pain following intra-articular or peri-artciular joint injections. [9 10 11] However it is apparent that not all patients with LBP will have symptoms that correlate with severity of radiographic OA changes on imaging.[7]

A further degenerative process can be found in the spine in the form of intervertebral degenerative disc disease (DDD). A recent twin study demonstrated the presence of lumbar degenerative discs on MRI to be a major determinate feature of patients with LBP.[12] Although the prevalence of DDD and facet joint OA correlate[13], it is unclear with they are

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independent of one another or whether they are different ends of the spectrum of the same pathological process.

Pharmacological therapies are the most frequently used intervention for LBP,[14] however serious side effects associated with long term use of some medications such as non-steroidal anti-inflammatory drugs (NSAIDS), has led patients to seek alternative medicines such as glucosamine.

Glucosamine is available to purchase as a food supplement and is gaining popularity amongst patients in the UK for the relief of knee and hip pain associated with osteoarthritis, however more than 25% of patients have tried glucosamine for LBP. [15]

Glucosamine is a naturally occurring amino monosaccharide and is a precursor for glycosaminoglycans, a major component of joint cartilage and synovial fluid[16] and this forms the basis of the rationale for its use in OA. Glucosamine is available in over fifty different preparations most commonly in the form of glucosamine sulphate and hydrochloride.[17]

Glucosamine Hydrochorlide (Alateris®) is the only preparation licensed for medical use in the UK and the license is restricted to the symptomatic relief of mild to moderate knee OA. Despite its license there is less evidence for its use compared with glucosamine sulphate and neither are currently recommended by the National Institute for Health and Clinical Excellence (NICE).[18]

Several trials and systematic reviews have looked into the use of glucosamine in knee and hip arthritis. A Cochrane review identified 16 double-blind randomised controlled trials (RCTs) and concluded that there was good evidence that glucosamine is both effective and safe in treating OA, but this did not assess spinal OA[19] This review was updated and failed to show a uniformly positive conclusion, if only high quality studies were included[20]. Analysis

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restricted to studies with adequate allocation concealment failed to show any benefit of glucosamine for pain, function and stiffness based on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) used to assess pain, stiffness and function in patients with hip and knee OA. However the review also assessed pain and function on the Lequesne index which did reveal an improvement after glucosamine when compared to placebo. The disparity between these findings remains unexplained by the authors, however a study that compared and tested the validity of WOMAC and Lequense index found that although both measures show internal validity when assessing function in hip and knee OA, only the WOMAC is consistently reliable when assessing symptoms such as pain.[21]

Given the lack of conclusive evidence regarding an improvement in LBP from glucosamine and at present no recommendations from NICE, the indications for using glucosamine remain controversial for clinicians and patients.

Reviews so far have focused on trials looking at the use of glucosamine in hip and knee OA.[22] The current study has been undertaken to provide an up to date systematic review of the evidence for the use of glucosamine in LBP.

Objective

To systematically search and assess the quality of the evidence of the efficacy of glucosamine on low back pain symptoms in patients diagnosed with spinal facet joint OA or degenerative disc disease.

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Methods

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were considered for this review as randomisation ensures that patients in the treatment and control groups are comparable from the start. In the hierarchy of study designs, RCTs and systematic reviews are considered the highest level of evidence.[23] At least one day of follow-up was required to ascertain any effect of an intervention. RCTs were included if they: 1) evaluated the efficacy and toxicity of glucosamine in OA, 2) were placebo-based or comparative studies, 3) were open-label, single-blinded or double-blinded, 4) evaluated glucosamine-only or combination preparations**,** 5) utilised oral administration of glucosamine as this is the route which will be used by the majority of patients.

Types of participants

Participant inclusion criteria for this review included: adult subjects (≥18 years), with chronic back pain (≥12 weeks) and signs of spinal OA. As there are no consensus guidelines about constitutes a diagnosis of OA in the spine any radiographic changes consistent with OA were included. A variety of radiographic grading systems have been proposed but there is no single global staging system suitable for the assessment of OA at all sites. [24]

The exclusion criteria were: trials that included subjects with specific LBP caused by other pathologies such as vertebral canal stenosis, ankylosing spondylitis, scoliosis and coccycydinia and trials that looked at OA at multiple sites but did not separate the data from the different sites making conclusions regarding changes in spinal symptoms difficult.

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Types of Interventions

Both placebo-controlled trials and comparative studies were eligible. Types of comparison considered appropriate were conventional therapies used for OA such as physical therapy, analgesics and anti-inflammatories.

Types of Outcome Measures

For inclusion, at least one of the following outcome measures, recommended by the Cochrane Back Review Group (CBRG), had to be observed: 1) pain intensity, for example visual analogue scale, 2) reliable and valid measure of functional status or disability for example, the Roland-Morris Disability Questionnaire (RMDQ)[25 26] 3) perceived recovery, 4) return-to-work status 5) structural benefits measured by radiography 6) adverse effects. The primary outcomes for this review were pain and functional status. The timing of measured outcomes had to be explicitly described.

Search methods for identification of studies

All three authors are practicing clinicians in the United Kingdom and have either completed or are undertaking higher research degrees.

The search strategy was formualated jointly by the first two named authors. Retrieval of searches, reference screening and subsequent data synthesis was subsequently performed independently. Differences were resolved after discussion with the thirdauthor . The search was conducted up to March 2011 and included grey literature, searched via opensigle. Papers not published in English were excluded. By searching MEDLINE (medical, nursing and biomedical journals), it was anticipated that approximately half of available RCTs would be identified, therefore a subsequent search of EMBASE (biochemical and pharmaceutical

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journals) would ensure a comprehensive search as there is little overlap between these databases and in the field of LBP, EMBASE has been shown to retrieve more clinical trials.[27] Searching AMED and CINHAL would cover complementary medicine and allied health journals, whilst including Cochrane enabled high quality evidence from RCTs and systematic reviews to be included. References of relevant studies were screened to identify additional studies.

The electronic search strategy outlined in Appendix 1 was developed in MEDLINE and adapted for the other databases. The search was developed by reviewing relevant articles in the area of back pain and OA and combining search terms used in these studies.

Risk-of-bias assessment and quality

The risk of bias was assessed using the criteria advised by the CBRG.[27] Each criterion was scored as yes, unclear or no, where yes indicated the criterion had been met. Studies are rated as having a low 'risk of bias' when at least 6 of the 12 CBRG criteria have been met with no serious flaws.

Data Extraction

Data was recorded onto a standardised form and described the main trial characteristics, patient demographics, interventions, comparisons, outcomes, analysis, results and assessment of trial quality (tables 1 and 2).

Quality of the Evidence

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Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria were used to evaluate the overall quality of the evidence. This is recommended by the Cochrane Handbook to rate the quality of evidence for each important patient-centred outcome as it goes beyond the reporting of quantitative analysis. The quality of evidence was based on 5 domains: limitations of the study design, inconsistency, indirectness (inability to generalise), imprecision (insufficient or imprecise data) of results and publication bias across all studies that measure that particular outcome.[28] The overall quality was considered to be high when at least 75% of the RCTs with no limitations of study design had consistent findings, direct and precise data and no known or suspected publication biases.[27] The grades of quality of evidence are outlined in Appendix 2. [29]

Results

Description of studies

Study selection

Studies were identified through the following databases: Medline (11), Embase (53), Cochrane library (84) (Cochrane reviews (10), other reviews (7), clinical trials (67)). Three studies were included (Table 1). Reasons for exclusion are outlined in Figure 1. Due to differences in the study design of included trials, metanalysis was not attempted.

Risk of bias in included studies

The risk-of-bias assessment is shown in table 2. Although all studies were described as randomised, only two described adequate randomisation.[30 31] One trial was open-label and did not report compliance.[31] One trial had a 20% drop-out rate.[32] All trials had similar groups at baseline, timings of outcome assessments and co-interventions in both groups.

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From this assessment two studies have been rated as having a low risk of bias. The one study rated as a high risk of bias scored six, but its open-label design was considered to be a significant methodological flaw.

Effects of intervention

Tables 3, 4 and 5 summarise the findings with respect to the main outcomes measured. For pain, the two studies with a low risk of bias failed to show any significant improvement with glucosamine compared with placebo, whilst the one study with a high risk-of-bias did show a significant difference with glucosamine compared to no glucosamine.

Back function/disability was measured by Owestry Disability Index (ODI) and RMDQ, both validated tools[26 33]; there was no significant difference in the RMDQ scores with glucosamine as an intervention. The study with a high risk of bias demonstrated a statistically significant difference in the ODI score reduction for the glucosamine group, although this difference was small.[31]

With respect to adverse effects, one trial revealed ~ 30% of participants experienced adverse effects irrespective of whether they were in the placebo or glucosamine group.[30]

Other outcomes that were considered but not across all trials included an assessment of quality of life measured by the Euro-Qol-5 Dimensions (EQ-5D) index and overall health status measured by EQ-VAS.[30] There was no significant difference found between glucosamine and placebo with these outcomes.

One study used several assessments which were totalled to provide an overall summary score.[32] In addition to measuring pain and function, physical examination scores and running times were assessed. There were no statistically significant changes in the LBP group when considering the overall summary score or individual outcome measures.

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None of the studies looked at radiographic changes in association with glucosamine use.

Discussion

In this review three RCTs were included that evaluated the effectiveness of glucosamine as an intervention for chronic low back pain associated with spinal OA. [30 31 32]

Overall, the review found the limited number of studies had methodological deficiencies. The studies did not demonstrate a clear beneficial effect of using glucosamine for LBP due to OA[30 32]. One study however showed a statistically significant difference in the ODI score reduction for the glucosamine group [31], although this difference was small and does not appear to reach the minimally clinical important difference (MCID) alluded to in previous research.[34]

There was conflicting evidence regarding the effect of glucosamine on pain scores. Two studies showed no statistically significant difference on pain scores between the intervention and placebo group. [30 32] One study did show a statistical and clinically significant reduction in pain scores for those taking glucosamine.[31] Whilst this study had significant methodological shortcomings which are discussed in the next section, this alone may not completely explain differences when compared to the two other studies. A possible reason was that the study recruited older patients with a mean age of 64 compared with a much younger demographic in the remaining two studies. Facet joint OA is known to become more prevalent with age[13] and therefore the proportion of patients with pain related to facet joints as opposed to discogenic pain may have been higher. This combined with a theoretical possibility that glucosamine may predominantly affect articular cartilage as opposed to intervertebral discs,

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may lead to an under representation of the affect of glucosamine in studies with a younger cohort.

Methodological considerations

There were several factors that contributed to the very low or low quality assessment for the main outcomes measured in the trials. The results of one study [31] in particular which found positive effects of glucosamine on both pain and function appears to contradict the findings of the other two, however, this may be partly explained by its limitations. A key limitation was its open-label design. Since participants and clinicians were aware of group allocation, bias was introduced.

Another study had unclear details about its randomisation.[32] Blinding and randomisation decrease the likelihood of selection and performance bias which would affect the internal validity of the study.[35] This same RCT employed a cross-over design, which may intrinsically have introduced bias if the 5 week wash-out period employed was too short.

To minimize attrition bias, the drop-out rate should be described and acceptable with all the randomised patients analysed in the group to which they were allocated, by an intention to treat analysis (ITT) [35]. One trial did not employ an ITT analysis and compliance was unclear.[31]

There are difficulties in how the trials can be directly applied to the general population and this adversely affects their relevance to practice and external validity. One trial used patients from US Navy diving and special warfare community who have a history of high activity levels and unique occupational exposures. They were also all male; hence the results may not be generalisable.[32] This study used a mixed population of both knee and back pain patients,

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with some participants having both knee and back pain. The proportion of patients in each group was described and the data was separated.

Despite the fact that the risk of bias was low in two studies, the studies collectively showed flaws regarding concealment of treatment allocation, adequate randomisation, compliance and drop-out rates. The review findings were significantly influenced by these shortcomings despite the fact that the study by Wilkens et al was of a high quality and well designed. The quality of future RCTs needs to be improved to reduce bias in future reviews.

Review Strengths and Limitations

The selection procedure and literature search utilised in this review may have introduced bias. The selection criteria did not place limits on the ages of participants and as the pathology of low back pain may change with age, direct comparisons between studies of patients with different patient demographics needs to taken with caution.

Relevant, unpublished trials may have been omitted and as these are likely to be small studies without positive results this may lead to publication bias. Studies not published in English were excluded and may also have introduced bias. Utilising references of the included trials to identify other studies may have also led to an over-representation of positive studies.

The search strategy was however vigorous with several databases utilised, in addition to reference screening of included studies which ensured that the omission of relevant studies was minimised.

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Implications for Health Practice

LBP is extremely prevalent with considerable financial consequences.[4] OA accounts for a significant proportion of LBP seen by GPs and secondary care clinicians. Current treatment options such as NSAIDs and surgery have some potentially serious adverse effects .Therefore alternative treatments such as glucosamine which may provide a possible solution to this problem seem attractive.

Global sales of glucosamine reached almost £1.3billion in 2008.[36] Currently in the UK, glucosamine is available as a food supplement and can be prescribed for knee OA. The evidence for its use in back pain is conflicting, it is therefore imperative that a consensus based on sound clinical evidence is reached to justify this immense cost to the public.

This review helps clarify the existing evidence for the use of glucosamine in back pain which will be of particular relevance to patients and clinicians considering using glucosamine.

The current review has demonstrated that if only the studies with a low risk of bias are considered, there is no evidence of a significant difference between glucosamine and placebo for pain or pain-related disability associated with OA in the lower back.

The mechanism by which glucosamine may exert its effect is poorly understood. Wilkens et al, previously proposed that glucosamine may reduce LBP by inhibiting interleukin (IL)-1β which is present in lumbar discs and facet joints. This mechanism is purely theoretical with no conclusive evidence demonstrating a direct pharmacological effect on the spine. The lack of a sound scientific rationale for the use of glucosamine in LBP makes it difficult to successfully design a study to prove any clinical benefit it may have. In addition, there is much debate as to the relationship between LBP and spinal OA findings. Not all patients with LBP have spinal OA and vice versa, however most studies assume they are correlated.

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All of the studies included in the review had limitations. All were single centre trials and two had small sample sizes. There were methodological differences in randomisation, blinding, allocation concealment and varying outcome measures. Inclusion criteria varied between trials some looked at both facet joint OA and degenerative disc disease. These two conditions do not necessarily represent the same pathological process. In addition the method for diagnosing the OA differed as there is no existing consensus or criteria for diagnosis. Back pain is complex and whilst spinal OA may cause low back pain, several other structures may be responsible and pathologies may co-exist.

It is possible that glucosamine may work better in more severe disease as has been suggested with knee OA.[37] The studies reviewed all had varying severities of OA symptoms required for inclusion. This limits the conclusions that can be made as the studies did not separate out the data for different levels of severity in the analysis.

OA is a chronic disease and patients taking supplements such as glucosamine may do so for several years. Follow-up periods for the trials varied from eight weeks to one year. Glucosamine may take longer than this to have an apparent affect. A case report revealed an improvement in the structural quality of disc cartilage on MRI in a patient taking glucosamine over a two year period.[38] The patient's symptoms only began to improve at six months and continued until the end of the study period. None of the studies in this review looked at objective radiographic changes as an outcome and whilst there are obvious limitations to drawing any broad conclusions form a single case report, this provides an argument for a longer follow-up RCT and more objective outcome measures.

A strength of this review is that it contained several placebo-controlled RCTs. One especially well-designed study clearly showed that patients treated with glucosamine for one year who

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had a combination of chronic LBP and either or both facet joint OA and degenerative disc disease, had no difference in pain or disability when compared to placebo.

An important factor to consider when assessing the relevance of trial data to everyday practice is the generalisability or external validity of the studies. The current review included one study which used a relatively young cohort of male patients who were from a US Navy diving and special warfare community who had a history of high activity levels and unique occupational exposures. This is not the profile of a typical OA patient a doctor would see in general practice.

An important distinction is between statistical significance and clinical relevance of findings. One study showed a statistically significant difference in pain related disability on the ODI, however the difference was very small and may not have represented a clinically relevant change.[31] Currently there is consensus regarding minimal clinically important changes for pain and function (measured by RMDQ not ODI) in back pain.[27] For LBP, 30% on VAS/NRS for pain is considered as clinically significant and 2 to 3 points (8 -12%) on the RMDQ for function is considered as clinically significant.[39]

Glucosamine may be viewed as a relatively safe medication however the current review nonetheless highlights a high incidence of adverse effects and although these were mild, it is an important consideration when recommending it.

Based on the current evidence explored in this review, there is insufficient evidence to either demonstrate or exclude a clinical benefit of glucosamine for spinal OA. Using more objective measures such as radiography to look at any change in OA progression, refining study inclusion criteria, providing longer follow-up periods and trying to establish a clear biochemical model for glucosamine may enable more definitive conclusions to be drawn so that clinicians can confidently advise their patients based on the best available evidence.

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APPENDICES

Appendix 1. Electronic search strategy

1. exp osteoarthritis, spine
2. degenerative arthritis. mp. or exp osteoarthritis
3. osteoarthr*
4. degenerative joint disease. Mp.
5. degenerative disc disease
6. exp low back pain
7. exp back pain
8. exp spine
9. exp lumbar vertebrae
10. chronic back pain. mp.
11. exp glucosamine/ or glucosamine. mp.
12. glucosamine sulphate. mp.
13.exp acetylglucosamine/ or acetylglucosamine. mp.
14. glucosamine hydrochloride. mp.
15. n-acetyl-d-glucosamine.tw.
16. or/1-5
17. or/6-10
18. or/11-15
19. 16 and 17 and 18

Appendix 2: Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria

High quality (at least 75% of the RCTs with no limitations of study design have consistent findings, direct and precise data and no known or suspected publication biases)	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality 1 of the domains are not met	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality 2 of the domains are not met	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to

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change the estimate

Very low quality Any estimate of effect is very uncertain

3 of the domains are not met

5 Domains:

Limitations of the study design, inconsistency, indirectness (inability to generalise), imprecision (insufficient or imprecise data) and publication bias.**References:**

1. Macfarlane GJ, Beasley M, Jones EA, Prescott GJ, Docking R, Keeley P, McBeth J, Jones GT. The prevalence and management of low back pain across adulthood: Results from a population-based cross-sectional study (the MUSICIAN study). *Pain* 2012; 153(1):27-32.
2. Papageorgiou AC, Croft PR, Thomas E, Ferry S, Jayson MI, Silman AJ. Influence of previous pain experience on the episode incidence of low back pain: results from the South Manchester Back Pain Study. *Pain* 1996; 66(2-3):181-5.
3. Papageorgiou AC, Rigby AS. Review of UK data on the rheumatic diseases--7. Low back pain. *Br J Rheumatol*. 1991; 30(3):208-10.
4. Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain* 2000; 84 (1):95-103.
5. Murray CJL, Lopez AD. The global burden of disease. A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge (MA): Harvard School of Public Health on behalf of the *World Health Organization* and *The World Bank*; 1996.
6. Kalichman L, Hunter DJ. Lumbar facet joint osteoarthritis: a review. *Semin Arthritis Rheum*. 2007; 37(2):69-80.
7. Kalichman L, Li L, Kim D, Guermazi A, Berkin V, O'Donnell C, Hoffmann U, Cole R, Hunter D. Facet joint osteoarthritis and low back pain in the community-based population. *Spine* 2008;33(23): 2560–2565.
8. Borenstein D. Does osteoarthritis of the lumbar spine cause chronic low back pain? *Curr Pain Headache Rep*. 2004;8(6):512-517.
9. Goldthwait J. The lumbosacral articulation. An explanation of many cases of lumbago, sciatica, and paraplegia. *Boston Med and Surg J*. 1911;164:365–372.
10. Schwarzer AC, Aprill C, Derby R. Clinical features of patients with pain stemming from the lumbar zygapophyseal joints. Is the lumbar facet syndrome a clinical entity? *Spine* 1994;10:1132–1137.
11. Dreyer SJ, Dreyfuss PH. Low back pain and the zygapophysial (facet) joints. *Arch Phys Med Rehabil*. 1996;77:290–300.
12. Livshits G, Popham M, Malkin I, Sambrook PN, Macgregor AJ, Spector T, Williams FM. Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study. *Ann Rheum Dis.* 2011;70(10):1740-5.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

13. Li J, Muehleman C, Abe Y, Masuda K. Prevalence of facet joint degeneration in association with intervertebral joint degeneration in a sample of organ donors. *J Orthop Res*. 2011;29(8):1267-74.
14. Kuijpers T, Van Middelkoop M, Rbinstein S, Ostelo R, Verhagen A, Koes B, Van Turner M. A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. *Eur Spine J*. 2011; 20:40-50.
15. Avins A. Glucosamine and the ongoing enigma of chronic low back pain *JAMA* 2010;304:1.
16. Arendt-Nielsen L, Weidner M, Bartholin D, Rosetzsky. A double- blind randomized placebo controlled parallel group study evaluation the effects of Ibuprofen and glucosamine sulphate on exercise induced muscle soreness. *Journal of Musculoskeletal Pain*. 2007; 15(1):21-28
17. C+D Data, 2008. *The Product File* [online]. Available: http://www.cddata.co.uk [Product search for "glucosamine": 20 October 2008].
18. NICE Guideline CG59 Osteoarthritis the care and management of osteoarthritis in adults http://www.nice.org.uk/guidance/index Feb 2008.
19. Towheed TE, Anastassiades TP, Shea B, Houpt J, Welch V, Hochberg MC. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2001;(1):CD002946.
20. Towheed T, Maxwell L, Anastassiades T, Shea B, Houpt J, Welch V, Hochberg M, Wells G. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2009, Issue 4. Oxford: Update Software.
21. Stucki G, Sangha O, Stucki S, Michel BA, Tyndall A, Dick W, Theiler R. Comparison of the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index and a self-report format of the self-administered Lequesne-Algofunctional index in patients with knee and hip osteoarthritis. *Osteoarthritis Cartilage*. 1998;6(2):79-86.
22. Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ*. 2010; 16:341.
23. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines for the Scottish Intercollegiate Guidelines Network Grading Review Group. (SIGN) *BMJ* 2001;323:334-336.
24. Roland W. Moskowitz M., Roy D. Altman, M, . Hochberg M. Osteoarthrits: Diagnosis and medical /surgical management *Lippincott,Willliams and Wilkens* 4th Ed 2006.
25. Roland M, Morris R A study of the natural history of backpain: Development of a reliable and sensitive measure of disability in low-back pain. *Spine* 1983;8:141–144
26. Stratford PW, Binkley JM, Riddle DL, Guyatt GH Sensitivity to change the Roland–Morris back pain Questionnaire:Part 1. *Phys Ther* 1998;78:1186–1196.
27. Furlan A, Pennick V, Bombardier C, van Tulder M Updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine* 2009;34(18):1929-1941

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

28. Atkins D, Best D, Briss P. GRADE Working group. Grading quality of evidence and strength of recommendations. *BMJ* 2006; 328:1490
29. Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, for the GRADE Working Group**.** Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations**.** *BMJ* 2008;336:924-926
30. Wilkens P, Scheel I, Grundes O, Hellum C, Storheim K. Effect of Glucosamine on Pain-Related Disability in Patients with Chronic Low Back Pain and Degenerative Lumbar Osteoarthritis. *JAMA*. 2010;304(1):45-52
31. Tant L, Gillard B, Appelboom T. (2005) Open-label, randomized, controlled pilot study of the effects of a glucosamine complex on low back pain. *Current Therapeutic Res.* 2005;66(6):511-521
32. Leffler C, Philippi A, Leffler S, Mosure J, Kim P. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo controlled pilot study. *Mil Med*. 1999;164(2):85-91.
33. Fairbank J, Couper J, Davies J, O'Brien J The Owestry low back pain disability questionnaire. *Physiotherapy* 1980;66: 271-273.
34. Lauridsen HH, Manniche C, Korsholm L, Grunnet-Nilsson N, Hartvigsen J. What is an acceptable outcome of treatment before it begins? Methodological considerations and implications for patients with chronic low back pain. *Eur Spine J*. 2009 Dec;18(12):1858-66.
35. Hart A. Making sense of statistics in health care *Radcliffe Medical Press* 2001.
36. Heller L. US glucosamine grows slow, lags global sales. 2009. www.nutraingredients-usa.com/Consumer-Trends/US-glucosamine-grows-slow-lags-global-sales.
37. Clegg D, Reda D, Harris C. Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis. *New England Journal of Medicine*, 2006; 354:795-808.
38. Van Blitterswijk W, van de Nes J, Wuisman P. Glucosamine and chondroitin sulphate supplementation to treat symptomatic disc degeneration: Biochemical rationale and case report. *BMC Complementary and Alternative Medicine* 2003;3:2 ;1-8
39. Ostelo R, Deyo R. Stratford P Interpreting change scores for pain and function status in low back pain: towards international consensus regarding minimal important change. *Spine* 2008;33: 90-94

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The use of glucosamine for chronic low back pain: A systematic review of randomised control trials

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Abstract

Background: The use of glucosamine as a treatment for ~~symptomatic~~ osteoarthritis (OA) remains controversial. The aim of this review is to ascertain whether the use of oral glucosamine influences symptoms or functional outcomes in patients with chronic low back pain (LBP) thought to be related to spinal OA.

Data Sources: Searches were performed ~~by two reviewers independently~~ up to March 2011 on Medline, AMED, CINHAL, Cochrane and EMBASE with subsequent reference screening of retrieved studies. In addition grey literature was searched via opensigle.

Methods: Included studies were required to incorporate at least one of the Cochrane Back Pain Review Group's (CBRG) outcome measures as part of their design. Trials with participants over 18 years with a minimum of 12 weeks ~~3 months~~ of back pain, in combination with radiographic changes of OA in the spine were included. Studies were rated for risk-of-bias and graded for quality.

Results:148 studies were identified, after screening and meeting eligibility requirements 3 RCTs (n=309) were included in the quantitative synthesis. The review found there was low quality but generally no evidence of an effect from glucosamine on function, with no change on the Roland Morris Disability Questionnaire (RMDQ) score in all studies. Conflicting evidence was demonstrated with pain scores with 2 studies showing no difference and one study with a high risk-of-bias showing both a statistically and clinically significant improvement from taking glucosamine.

Conclusion: Based on current research, there is insufficient evidence to recommend the use of oral glucosamine for patients with chronic LBP and radiographic changes of spinal OA,

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however any effect glucosamine may exert cannot be completely excluded due to the low quality of existing research.

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Introduction

Rationale

Low back pain (LBP) affects around one-third of UK adults each year.[1 2] Around 20% will consult their general practitioner (GP), making it one of the commonest presentations seen in primary care.[3] Additionally, there are considerable financial consequences associated with back pain with previous estimates of direct healthcare costs in the UK amounting to over £1.6 billion and indirect costs from informal care and loss of productivity to the economy, of £10.7 billion.[4]

Osteoarthritis (OA) is a highly prevalent degenerative joint condition that the World Health Organisation (WHO) Scientific Group on Rheumatic Diseases estimates is the cause of significant clinical problems in at least 10% of patients who are 60 years or older.[5]

OA can affect several parts of the body including the spine. Within the spine, OA affects the vertebral facet joints[6] and may occur with or without the presence of LBP.[7]

Borenstein suggested that OA may cause LBP [8] however; this relationship is complex and controversial. Some of the evidence supporting a link between spinal OA and LBP comes from early studies which showed improved back pain following intra-articular or peri-artciular joint injections. [9 10 11] However it is apparent that not all patients with LBP will have symptoms that correlate with severity of radiographic OA changes on imaging.[7]

A further degenerative process can be found in the spine in the form of intervertebral degenerative disc disease (DDD). A recent twin study demonstrated the presence of lumbar degenerative discs on MRI to be a major determinate feature of patients with LBP.[12] Although the prevalence of DDD and facet joint OA correlate[13], it is unclear with they are

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independent of one another or whether they are different ends of the spectrum of the same pathological process.

Pharmacological therapies are the most frequently used intervention for LBP,[14] however serious side effects associated with long term use of some medications such as non-steroidal anti-inflammatory drugs (NSAIDS), has led patients to seek alternative medicines such as glucosamine.

Glucosamine is available to purchase as a food supplement and is gaining popularity amongst patients in the UK for the relief of knee and hip pain associated with osteoarthritis, however more than 25% of patients have tried glucosamine for LBP. [15]

Glucosamine is a naturally occurring amino monosaccharide and is a precursor for glycosaminoglycans, a major component of joint cartilage and synovial fluid[16] and this forms the basis of the rationale for its use in OA. Glucosamine is available in over fifty different preparations most commonly in the form of glucosamine sulphate and hydrochloride.[17]

Glucosamine Hydrochorlide (Alateris®) is the only preparation licensed for medical use in the UK and the license is restricted to the symptomatic relief of mild to moderate knee OA. Despite its license there is less evidence for its use compared with glucosamine sulphate and neither are currently recommended by the National Institute for Health and Clinical Excellence (NICE).[18]

Several trials and systematic reviews have looked into the use of glucosamine in knee and hip arthritis. A Cochrane review identified 16 double-blind randomised controlled trials (RCTs) and concluded that there was good evidence that glucosamine is both effective and safe in treating OA, but this did not assess spinal OA[19] This review was updated and failed to show a uniformly positive conclusion, if only high quality studies were included[20]. Analysis

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restricted to studies with adequate allocation concealment failed to show any benefit of glucosamine for pain, function and stiffness based on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) used to assess pain, stiffness and function in patients with hip and knee OA. However the review also assessed pain and function on the Lequesne index which did reveal an improvement after glucosamine when compared to placebo. The disparity between these findings remains unexplained by the authors, however a study that compared and tested the validity of WOMAC and Lequense index found that although both measures show internal validity when assessing function in hip and knee OA, only the WOMAC is consistently reliable when assessing symptoms such as pain.[21]

Given the lack of conclusive evidence regarding an improvement in LBP from glucosamine and at present no recommendations from NICE, the indications for using glucosamine remain controversial for clinicians and patients.

Reviews so far have focused on trials looking at the use of glucosamine in hip and knee OA.[22] The current study has been undertaken to provide an up to date systematic review of the evidence for the use of glucosamine in LBP.

Objective

To systematically search and assess the quality of the evidence of the efficacy of glucosamine on low back pain symptoms in patients diagnosed with spinal facet joint OA or degenerative disc disease.

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Methods

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were considered for this review as randomisation ensures that patients in the treatment and control groups are comparable from the start. In the hierarchy of study designs, RCTs and systematic reviews are considered the highest level of evidence.[23] At least one day of follow-up was required to ascertain any effect of an intervention. RCTs were included if they: 1) evaluated the efficacy and toxicity of glucosamine in OA, 2) were placebo-based or comparative studies, 3) were open-label, single-blinded or double-blinded, 4) evaluated glucosamine-only or combination preparations**,** 5) utilised oral administration of glucosamine as this is the route which will be used by the majority of patients.

Types of participants

Participant inclusion criteria for this review included: adult subjects (≥18 years), with chronic back pain (≥12 weeks) and signs of ~~with a diagnosis of~~ spinal OA. As there are no consensus guidelines about constitutes a diagnosis of OA in the spine any radiographic changes consistent with OA were included. A variety of radiographic grading systems have been proposed but there is no single global staging system suitable for the assessment of OA at all sites. [24]

The exclusion criteria were: trials that included subjects with specific LBP caused by other pathologies such as vertebral canal stenosis, ankylosing spondylitis, scoliosis and

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coccycydinia and trials that looked at OA at multiple sites but did not separate the data from the different sites making conclusions regarding changes in spinal symptoms difficult.

Types of Interventions

Both placebo-controlled trials and comparative studies were eligible. Types of comparison considered appropriate were conventional therapies used for OA such as physical therapy, analgesics and anti-inflammatories.

Types of Outcome Measures

For inclusion, at least one of the following outcome measures, recommended by the Cochrane Back Review Group (CBRG), had to be observed: 1) pain intensity, for example visual analogue scale, 2) reliable and valid measure of functional status or disability for example, the Roland-Morris Disability Questionnaire (RMDQ)[25 26] 3) perceived recovery, 4) return-to-work status 5) structural benefits measured by radiography 6) adverse effects. The primary outcomes for this review were pain and functional status. The timing of measured outcomes had to be explicitly described.

Search methods for identification of studies

All three authors are practicing clinicians in the United Kingdom and have either completed or are undertaking higher research degrees.

The search strategy was formualated jointly by the first two named authors. Retrieval of searches, reference screening ~~Searches~~ and subsequent data synthesis was subsequently ~~ere~~ performed ~~by two reviewers~~ independently. Differences were resolved after discussion with the ~~a~~ third-author ~~reviewer~~. The search was conducted up to March 2011 and included grey

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literature, searched via opensigle. ~~No language restriction was applied~~ Papers not published in English were excluded. By searching MEDLINE (medical, nursing and biomedical journals), it was anticipated that approximately half of available RCTs would be identified, therefore a subsequent search of EMBASE (biochemical and pharmaceutical journals) would ensure a comprehensive search as there is little overlap between these databases and in the field of LBP, EMBASE has been shown to retrieve more clinical trials.[27] Searching AMED and CINHAL would cover complementary medicine and allied health journals, whilst including Cochrane enabled high quality evidence from RCTs and systematic reviews to be included. References of relevant studies were screened to identify additional studies.

The electronic search strategy outlined in Appendix 1 was developed in MEDLINE and adapted for the other databases. The search was developed by reviewing relevant articles in the area of back pain and OA and combining search terms used in these studies.

Risk-of-bias assessment and quality

The risk of bias was assessed using the criteria advised by the CBRG.[27] Each criterion was scored as yes, unclear or no, where yes indicated the criterion had been met. Studies are rated as having a low 'risk of bias' when at least 6 of the 12 CBRG criteria have been met with no serious flaws.

Data Extraction

Data was recorded onto a standardised form and described the main trial characteristics, patient demographics, interventions, comparisons, outcomes, analysis, results and assessment of trial quality (tables 1 and 2).

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Quality of the Evidence

Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria were used to evaluate the overall quality of the evidence. This is recommended by the Cochrane Handbook to rate the quality of evidence for each important patient-centred outcome as it goes beyond the reporting of quantitative analysis. The quality of evidence was based on 5 domains: limitations of the study design, inconsistency, indirectness (inability to generalise), imprecision (insufficient or imprecise data) of results and publication bias across all studies that measure that particular outcome.[28] The overall quality was considered to be high when at least 75% of the RCTs with no limitations of study design had consistent findings, direct and precise data and no known or suspected publication biases.[27] The grades of quality of evidence are outlined in Appendix 2. [29]

Results

Description of studies

Study selection

Studies were identified through the following databases: Medline (11), Embase (53), Cochrane library (84) (Cochrane reviews (10), other reviews (7), clinical trials (67)). Three studies were included (Table 1). Reasons for exclusion are outlined in Figure 1. Due to differences in the study design of included trials, metanalysis was not attempted.

Risk of bias in included studies

The risk-of-bias assessment is shown in table 2. Although all studies were described as randomised, only two described adequate randomisation.[30 31] One trial was open-label and did not report compliance.[31] One trial had a 20% drop-out rate.[32] All trials had similar groups at baseline, timings of outcome assessments and co-interventions in both groups.

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From this assessment two studies have been rated as having a low risk of bias. The one study rated as a high risk of bias scored six, but its open-label design was considered to be a significant methodological flaw.

Effects of intervention

Tables 3, 4 and 5 summarise the findings with respect to the main outcomes measured. For pain, the two studies with a low risk of bias failed to show any significant improvement with glucosamine compared with placebo, whilst the one study with a high risk-of-bias did show a significant difference with glucosamine compared to no glucosamine.

Back function/disability was measured by Owestry Disability Index (ODI) and RMDQ, both validated tools[26 33]; there was no significant difference in the RMDQ scores with glucosamine as an intervention. The study with a high risk of bias demonstrated a statistically significant difference in the ODI score reduction for the glucosamine group, although this difference was small.[31]

With respect to adverse effects, one trial revealed ~ 30% of participants experienced adverse effects irrespective of whether they were in the placebo or glucosamine group.[30]

Other outcomes that were considered but not across all trials included an assessment of quality of life measured by the Euro-Qol-5 Dimensions (EQ-5D) index and overall health status measured by EQ-VAS.[30] There was no significant difference found between glucosamine and placebo with these outcomes.

One study used several assessments which were totalled to provide an overall summary score.[32] In addition to measuring pain and function, physical examination scores and running times were assessed. There were no statistically significant changes in the LBP group when considering the overall summary score or individual outcome measures.

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None of the studies looked at radiographic changes in association with glucosamine use.

Discussion

In this review three RCTs were included that evaluated the effectiveness of glucosamine as an intervention for chronic low back pain associated with spinal OA. [30 31 32]

Overall, the review found the limited number of studies had methodological deficiencies. The studies did not demonstrate a clear beneficial effect of using glucosamine for LBP due to OA[30 32]. One study however showed a statistically significant difference in the ODI score reduction for the glucosamine group [31], although this difference was small and does not appear to reach the minimally clinical important difference (MCID) alluded to in previous research.[34]

There was conflicting evidence regarding the effect of glucosamine on pain scores. Two studies showed no statistically significant difference on pain scores between the intervention and placebo group. [30 32] One study did show a statistical and clinically significant reduction in pain scores for those taking glucosamine.[31] ~~Quality and methodological differences may account for the discrepancies between these studies and this is discussed below.~~ Whilst this study had significant methodological shortcomings which are discussed in the next section, this alone may not completely explain differences when compared to the two other studies. A possible reason was that the study recruited older patients with a mean age of 64 compared with a much younger demographic in the remaining two studies. Facet joint OA is known to become more prevalent with age[13] and therefore the proportion of patients with pain related to facet joints as opposed to discogenic pain may have been higher. This combined with a

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theoretical possibility that glucosamine may predominantly affect articular cartilage as opposed to intervertebral discs, may lead to an under representation of the affect of glucosamine in studies with a younger cohort.

Methodological considerations

There were several factors that contributed to the very low or low quality assessment for the main outcomes measured in the trials. The results of one study [31] in particular which found positive effects of glucosamine on both pain and function appears to contradict the findings of the other two, however, this may be partly explained by its limitations. A key limitation was its open-label design. Since participants and clinicians were aware of group allocation, bias was introduced.

Another study had unclear details about its randomisation.[32] Blinding and randomisation decrease the likelihood of selection and performance bias which would affect the internal validity of the study.[35] This same RCT employed a cross-over design, which may intrinsically have introduced bias if the 5 week wash-out period employed was too short.

To minimize attrition bias, the drop-out rate should be described and acceptable with all the randomised patients analysed in the group to which they were allocated, by an intention to treat analysis (ITT) [35]. One trial did not employ an ITT analysis and compliance was unclear.[31]

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There are difficulties in how the trials can be directly applied to the general population and this adversely affects their relevance to practice and external validity. One trial used patients from US Navy diving and special warfare community who have a history of high activity levels and unique occupational exposures. They were also all male; hence the results may not be generalisable.[32] This study used a mixed population of both knee and back pain patients, with some participants having both knee and back pain. The proportion of patients in each group was described and the data was separated.

Despite the fact that the risk of bias was low in two studies, the studies collectively showed flaws regarding concealment of treatment allocation, adequate randomisation, compliance and drop-out rates. The review findings were significantly influenced by these shortcomings despite the fact that the study by Wilkens et al was of a high quality and well designed. The quality of future RCTs needs to be improved to reduce bias in future reviews.

Review Strengths and Limitations

The selection procedure and literature search utilised in this review may have introduced bias. The selection criteria did not place limits on the ages of participants and as the pathology of low back pain may change with age, direct comparisons between studies of patients with different patient demographics needs to taken with caution.

Relevant, unpublished trials may have been omitted and as these are likely to be small studies without positive results this may lead to publication bias. Studies not published in English were excluded and may also have introduced bias. ~~Utilsing~~Utilising references of the

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included trials to identify other studies may have also led to an over-representation of positive studies.

The search strategy was however vigorous with several databases utilised, in addition to reference screening of included studies which ensured that the omission of relevant studies was minimised.

Implications for Health Practice

LBP is extremely prevalent with considerable financial consequences.[4] OA accounts for a significant proportion of LBP seen by GPs and secondary care clinicians. Current treatment options such as NSAIDs and surgery have some potentially serious adverse effects .Therefore alternative treatments such as glucosamine which may provide a possible solution to this problem seem attractive.

Global sales of glucosamine reached almost £1.3billion in 2008.[36] Currently in the UK, glucosamine is available as a food supplement and can be prescribed for knee OA. The evidence for its use in back pain is conflicting, it is therefore imperative that a consensus based on sound clinical evidence is reached to justify this immense cost to the public.

This review helps clarify the existing evidence for the use of glucosamine in back pain which will be of particular relevance to patients and clinicians considering using glucosamine.

The current review has demonstrated that if only the studies with a low risk of bias are considered, there is no evidence of a significant difference between glucosamine and placebo for pain or pain-related disability associated with OA in the lower back.

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The mechanism by which glucosamine may exert its effect is poorly understood. Wilkens et al, previously proposed that glucosamine may reduce LBP by inhibiting interleukin (IL)-1β which is present in lumbar discs and facet joints. This mechanism is purely theoretical with no conclusive evidence demonstrating a direct pharmacological effect on the spine. The lack of a sound scientific rationale for the use of glucosamine in LBP makes it difficult to successfully design a study to prove any clinical benefit it may have. In addition, there is much debate as to the relationship between LBP and spinal OA findings. Not all patients with LBP have spinal OA and vice versa, however most studies assume they are correlated.

All of the studies included in the review had limitations. All were single centre trials and two had small sample sizes. There were methodological differences in randomisation, blinding, allocation concealment and varying outcome measures. Inclusion criteria varied between trials some looked at both facet joint OA and degenerative disc disease. These two conditions do not necessarily represent the same pathological process. In addition the method for diagnosing the OA differed as there is no existing consensus or criteria for diagnosis. Back pain is complex and whilst spinal OA may cause low back pain, several other structures may be responsible and pathologies may co-exist.

It is possible that glucosamine may work better in more severe disease as has been suggested with knee OA.[37] The studies reviewed all had varying severities of OA symptoms required for inclusion. This limits the conclusions that can be made as the studies did not separate out the data for different levels of severity in the analysis.

OA is a chronic disease and patients taking supplements such as glucosamine may do so for several years. Follow-up periods for the trials varied from eight weeks to one year. Glucosamine may take longer than this to have an apparent affect. A case report revealed an improvement in the structural quality of disc cartilage on MRI in a patient taking

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glucosamine over a two year period.[38] The patient's symptoms only began to improve at six months and continued until the end of the study period. None of the studies in this review looked at objective radiographic changes as an outcome and whilst there are obvious limitations to drawing any broad conclusions form a single case report, this provides an argument for a longer follow-up RCT and more objective outcome measures.

A strength of this review is that it contained several placebo-controlled RCTs. One especially well-designed study clearly showed that patients treated with glucosamine for one year who had a combination of chronic LBP and either or both facet joint OA and degenerative disc disease, had no difference in pain or disability when compared to placebo.

An important factor to consider when assessing the relevance of trial data to everyday practice is the generalisability or external validity of the studies. The current review included one study which used a relatively young cohort of male patients who were from a US Navy diving and special warfare community who had a history of high activity levels and unique occupational exposures. This is not the profile of a typical OA patient a doctor would see in general practice.

An important distinction is between statistical significance and clinical relevance of findings. One study showed a statistically significant difference in pain related disability on the ODI, however the difference was very small and may not have represented a clinically relevant change.[31] Currently there is consensus regarding minimal clinically important changes for pain and function (measured by RMDQ not ODI) in back pain.[27] For LBP, 30% on VAS/NRS for pain is considered as clinically significant and 2 to 3 points (8 -12%) on the RMDQ for function is considered as clinically significant.[39]

~~Although some of the trials showed no difference between glucosamine and placebo, there was an overall reduction in pain and disability scores across both groups. This may provide a~~

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~~justification for advising patients that they may experience some benefit from taking glucosamine albeit only due to the 'placebo effect'. However~~ Glucosamine may be viewed as a relatively safe medication however the current review nonetheless highlights ~~showed~~ a high incidence of adverse effects and although these were mild, it is an important consideration when recommending it.

Based on the current evidence explored in this review, there is ~~not~~ insufficient evidence to either demonstrate or exclude a clinical benefit of glucosamine for spinal OA. Using more objective measures such as radiography to look at any change in OA progression, refining study inclusion criteria, providing longer follow-up periods and trying to establish a clear biochemical model for glucosamine may enable more definitive conclusions to be drawn so that clinicians can confidently advise their patients based on the best available evidence.

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APPENDICES

Appendix 1. Electronic search strategy

1. exp osteoarthritis, spine
2. degenerative arthritis. mp. or exp osteoarthritis
3. osteoarthr*
4. degenerative joint disease. Mp.
5. degenerative disc disease
6. exp low back pain
7. exp back pain
8. exp spine
9. exp lumbar vertebrae
10. chronic back pain. mp.
11. exp glucosamine/ or glucosamine. mp.
12. glucosamine sulphate. mp.
13.exp acetylglucosamine/ or acetylglucosamine. mp.
14. glucosamine hydrochloride. mp.
15. n-acetyl-d-glucosamine.tw.
16. or/1-5
17. or/6-10
18. or/11-15
19. 16 and 17 and 18

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Appendix 2: Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria

High quality (at least 75% of the RCTs with no limitations of study design have consistent findings, direct and precise data and no known or suspected publication biases)	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality 1 of the domains are not met	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality 2 of the domains are not met	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality 3 of the domains are not met	Any estimate of effect is very uncertain

5 Domains:

Limitations of the study design, inconsistency, indirectness (inability to generalise), imprecision (insufficient or imprecise data) and publication bias.

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References:

1. Macfarlane GJ, Beasley M, Jones EA, Prescott GJ, Docking R, Keeley P, McBeth J, Jones GT. The prevalence and management of low back pain across adulthood: Results from a population-based cross-sectional study (the MUSICIAN study). *Pain* 2012; 153(1):27-32.
2. Papageorgiou AC, Croft PR, Thomas E, Ferry S, Jayson MI, Silman AJ. Influence of previous pain experience on the episode incidence of low back pain: results from the South Manchester Back Pain Study. *Pain* 1996; 66(2-3):181-5.
3. Papageorgiou AC, Rigby AS. Review of UK data on the rheumatic diseases--7. Low back pain. *Br J Rheumatol*. 1991; 30(3):208-10.
4. Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain* 2000; 84 (1):95-103.
5. Murray CJL, Lopez AD. The global burden of disease. A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge (MA): Harvard School of Public Health on behalf of the *World Health Organization* and *The World Bank*; 1996.
6. Kalichman L, Hunter DJ. Lumbar facet joint osteoarthritis: a review. *Semin Arthritis Rheum*. 2007; 37(2):69-80.
7. Kalichman L, Li L, Kim D, Guermazi A, Berkin V, O'Donnell C, Hoffmann U, Cole R, Hunter D. Facet joint osteoarthritis and low back pain in the community-based population. *Spine* 2008;33(23): 2560–2565.
8. Borenstein D. Does osteoarthritis of the lumbar spine cause chronic low back pain? *Curr Pain Headache Rep*. 2004;8(6):512-517.
9. Goldthwait J. The lumbosacral articulation. An explanation of many cases of lumbago, sciatica, and paraplegia. *Boston Med and Surg J*. 1911;164:365–372.
10. Schwarzer AC, Aprill C, Derby R. Clinical features of patients with pain stemming from the lumbar zygapophyseal joints. Is the lumbar facet syndrome a clinical entity? *Spine* 1994;10:1132–1137.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

11. Dreyer SJ, Dreyfuss PH. Low back pain and the zygapophysial (facet) joints. *Arch Phys Med Rehabil*. 1996;77:290–300.
12. Livshits G, Popham M, Malkin I, Sambrook PN, Macgregor AJ, Spector T, Williams FM. Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study. *Ann Rheum Dis.* 2011;70(10):1740-5.
13. Li J, Muehleman C, Abe Y, Masuda K. Prevalence of facet joint degeneration in association with intervertebral joint degeneration in a sample of organ donors. *J Orthop Res*. 2011;29(8):1267-74.
14. Kuijpers T, Van Middelkoop M, Rbinstein S, Ostelo R, Verhagen A, Koes B, Van Turner M. A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. *Eur Spine J*. 2011; 20:40-50.
15. Avins A. Glucosamine and the ongoing enigma of chronic low back pain *JAMA* 2010;304:1.
16. Arendt-Nielsen L, Weidner M, Bartholin D, Rosetzsky. A double- blind randomized placebo controlled parallel group study evaluation the effects of Ibuprofen and glucosamine sulphate on exercise induced muscle soreness. *Journal of Musculoskeletal Pain*. 2007; 15(1):21-28
17. C+D Data, 2008. *The Product File* [online]. Available: http://www.cddata.co.uk [Product search for "glucosamine": 20 October 2008].
18. NICE Guideline CG59 Osteoarthritis the care and management of osteoarthritis in adults http://www.nice.org.uk/guidance/index Feb 2008.
19. Towheed TE, Anastassiades TP, Shea B, Houpt J, Welch V, Hochberg MC. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2001;(1):CD002946.
20. Towheed T, Maxwell L, Anastassiades T, Shea B, Houpt J, Welch V, Hochberg M, Wells G. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2009, Issue 4. Oxford: Update Software.
21. Stucki G, Sangha O, Stucki S, Michel BA, Tyndall A, Dick W, Theiler R. Comparison of the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index and a self-report format of the self-administered Lequesne-Algofunctional index in patients with knee and hip osteoarthritis. *Osteoarthritis Cartilage*. 1998;6(2):79-86.
22. Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ*. 2010; 16:341.
23. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines for the Scottish Intercollegiate Guidelines Network Grading Review Group. (SIGN) *BMJ* 2001;323:334-336.
24. Roland W. Moskowitz M., Roy D. Altman, M, . Hochberg M. Osteoarthrits: Diagnosis and medical /surgical management *Lippincott,Willliams and Wilkens* 4th Ed 2006.
25. Roland M, Morris R A study of the natural history of backpain: Development of a reliable and sensitive measure of disability in low-back pain. *Spine* 1983;8:141–144

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26. Stratford PW, Binkley JM, Riddle DL, Guyatt GH Sensitivity to change the Roland–Morris back pain Questionnaire:Part 1. *Phys Ther* 1998;78:1186–1196.
27. Furlan A, Pennick V, Bombardier C, van Tulder M Updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine* 2009;34(18):1929-1941
28. Atkins D, Best D, Briss P. GRADE Working group. Grading quality of evidence and strength of recommendations. *BMJ* 2006; 328:1490
29. Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, for the GRADE Working Group**.** Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations**.** *BMJ* 2008;336:924-926
30. Wilkens P, Scheel I, Grundes O, Hellum C, Storheim K. Effect of Glucosamine on Pain-Related Disability in Patients with Chronic Low Back Pain and Degenerative Lumbar Osteoarthritis. *JAMA.* 2010;304(1):45-52
31. Tant L, Gillard B, Appelboom T. (2005) Open-label, randomized, controlled pilot study of the effects of a glucosamine complex on low back pain. *Current Therapeutic Res.* 2005;66(6):511-521
32. Leffler C, Philippi A, Leffler S, Mosure J, Kim P. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo controlled pilot study. *Mil Med*. 1999;164(2):85-91.
33. Fairbank J, Couper J, Davies J, O'Brien J The Owestry low back pain disability questionnaire. *Physiotherapy* 1980;66: 271-273.
34. Lauridsen HH, Manniche C, Korsholm L, Grunnet-Nilsson N, Hartvigsen J. What is an acceptable outcome of treatment before it begins? Methodological considerations and implications for patients with chronic low back pain. *Eur Spine J*. 2009 Dec;18(12):1858-66.
35. Hart A. Making sense of statistics in health care *Radcliffe Medical Press* 2001.
36. Heller L. US glucosamine grows slow, lags global sales. 2009. www.nutraingredients-usa.com/Consumer-Trends/US-glucosamine-grows-slow-lags-global-sales.
37. Clegg D, Reda D, Harris C. Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis. *New England Journal of Medicine*, 2006; 354:795-808.
38. Van Blitterswijk W, van de Nes J, Wuisman P. Glucosamine and chondroitin sulphate supplementation to treat symptomatic disc degeneration: Biochemical rationale and case report. *BMC Complementary and Alternative Medicine* 2003;3:2 ;1-8
39. Ostelo R, Deyo R. Stratford P Interpreting change scores for pain and function status in low back pain: towards international consensus regarding minimal important change. *Spine* 2008;33: 90-94

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Table 1: Characteristics of studies included

	Methods	Participants	Interventions	Outcome measures	Notes
Wilkens 2010	RCT Double-blind Single centre	Outpatients (N=250) Country – Norway Mean age 48.5, 48.4% female Inclusion criteria: Chronic LBP > 6 months, MRI findings indicating degenerative lumbar OA, age >25	1500mg glucosamine sulphate versus placebo for 6 months	Primary outcome: disability – RMDQ Secondary outcomes: pain at rest and during activity (11-point scale), quality of life (QOL): EQ-5D and EQ-VAS, global perception of effect (7 point scale) Adverse effects	Sponsored by Pharma Nord.
Tant 2005	RCT Open-label Single centre	Outpatients (N=36) Country – Belgium Mean age 64, 43.8% female Inclusion criteria: LBP > 12 weeks with associated signs of lumbar arthrosis on radiography, pain score on VAS >3mm	Conventional treatment (CT) (anti-inflammatory and physical therapy) plus glucosamine complex (containing equivalent :1500mg glucosamine, 200mg of Ribes nigrum, 2000mg methylsulfonylmethane and 100mg colloidal silicon) for 12 weeks versus CT alone	Primary outcome: pain at rest on VAS Secondary outcomes: lumbar stiffness on VAS, 2 QOL questionnaires – ODI and RMDQ, global assessment of treatment (satisfied or not) Adverse effects	Sponsored by Pierre Fabre Sante
Leffler 1997	RCT (cross-over) Double-blind Single centre	Outpatients (N=34, 23 back patients) Country – USA Mean age 43.5 100%male Inclusion Criteria: chronic knee or low back pain on most days for at least 3 months and radiographic evidence of degenerative joint disease	16 weeks (8 weeks each arm). 1500mg glucosamine hydrochloride, 1200mg chondroitin sulphate, 228g manganese ascorbate versus placebo	Pain (VAS scores), Function: Lequesne Index (knee), RMDQ (back), patient assessment of handicap, physician assessment of severity and physical exam scores	Patients from US Navy diving and special warfare community Mixed population of knee and back pain (21 – knee OA, 23 - spinal degenerative joint disease. Data separated by site for analysis. Sponsored by Nutramax

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Table 2: Methodological quality assessment and risk of bias

	Randomisation adequate?	Allocation concealed?	Groups similar at baseline?	Patient blinded?	Care provider blinded?	Outcome assessor blinded?	Drop-out rate described and acceptable?	Intention to treat analysis?	Co-interventions avoided or similar?	Compliance acceptable?	Timing outcome assessment similar?	Report free of selective outcome reporting	Total
Wilkens 2010	yes	yes	yes	Yes	yes	yes	Yes	yes	Yes	yes	yes	yes	12
Tant 2005	yes	no	yes	No	no	no	Yes	no	Yes	unclear	yes	yes	6
Leffler 1999	unclear	yes	yes	Yes	yes	yes	No	yes	Yes	yes	yes	yes	10

Risk of bias assessed using criteria from the CBRG (Furlan et al, 2009). Studies rated as having a 'low risk of bias' when at least 6 of the 12 CBRG criteria have been met and it has no serious flaws.

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Table 3: Key findings: Effect of glucosamine on back pain outcomes

Study	Risk of bias	Method of assessment	Key findings	Notes
Wilkens, 2010	Low	Low back and leg pain intensities during activity and rest measured by 11-point numeric pain rating scale (NRS) Patients assessed at baseline, 6 weeks, 3 months, 6 months, 1 year.	Baseline NRS LBP at rest for the glucosamine group was 3.7 (95% CI 3.3-4.1) and 3.9 (95% CI 3.5-4.3) for placebo. The 6-month NRS score was 2.5 (95% CI 2.1-2.9) for glucosamine and 2.4 (95% CI 2.0-2.8) for placebo. No statistical difference in change between the two groups found at 6 months (P =0.91) for LBP at rest and (P= 0.97) for LBP during activity.	No significant difference between glucosamine and placebo
Tant 2005	High	VAS for pain at rest and on movement (0-10cm) measured every 4 weeks	At week 4, mean change from baseline VAS scores for pain at rest was significantly greater in the glucosamine group compared with control group (-2.18 vs +0.13, P<0.001). Difference also significant at 8 and 12 weeks (both P<0.01). The between-group difference in mean VAS scores for pain on movement was only significant at week 12 (2.08) in glucosamine group versus (4.00) in control group; (P=0.029)	Significant difference between CT+glucosamine and CT
Leffler 1997	Low	VAS for pain recorded at clinic visits (0-10cm) VAS for pain recorded in a daily diary by patients (VAS 0-7cm). Assessed after weeks 7&8 Knee and back data were separated in later analysis.	Back: The VAS for pain showed a mean change of -28.0% when medication was compared to placebo during the clinic visit (p>0.06) and -21.0% in the diary data (p>0.06). No CI.	No significant effect on back pain between glucosamine and placebo.

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Table 4 Key findings: Effect of Glucosamine on function outcomes

Study	Risk of bias	Method of function assessment	Key findings	Notes
Wilkens, 2010	Low	RMDQ	At baseline, mean RMDQ scores were 9.2 (95% CI 8.4-10.0) for glucosamine and 9.7 (95% CI 8.9-10.5) for the placebo group. At 6 months, the mean RMDQ score was the same for the glucosamine and placebo groups (5.0; 95% CI 4.2-5.8). No statistically significant difference in change between the groups found when assessed at 6 months and 1 year (P=0.72).	No significant difference between placebo and glucosamine
Tant 2005	High	RMDQ and ODI	Mean score on the ODI significantly improved from baseline at weeks 4, 8 and 12 in the glucosamine group (all P<0.001). In the control group no significant improvement in score until week 12 (p<0.001). At 12 weeks: significant difference in ODI score between the 2 groups (P=0.028) At baseline, mean RMDQ scores were 9.76 for glucosamine and 7.86 for placebo group. Mean RMDQ scores significantly improved from baseline at weeks 4, 8 and 12 in both groups (all P<0.001) but no significant between-group differences found.	No significant difference between CT+glucosamine and CT for RMDQ but significant difference for ODI.
Leffler 1997	Low	RMDQ	Back: Mean baseline RMDQ score was 6.9 with a mean change of -13.7% when medication was compared to placebo (p>0.06) No CI.	No significance difference between placebo and glucosamine.

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Table 5 Key findings: Adverse Effects

Study	Risk of bias	Monitoring	Adverse effects	Notes
Wilkens, 2010	Low	Adverse events, blood pressure (bp) monitored every visit. Fasting blood glucose, cholesterol levels before and following intervention.	Adverse events (n=86), 40 in glucosamine group, 46 in placebo group. ~ 30% of patients had adverse events. 10 patients withdrew due to adverse events. Adverse events: mild gastrointestinal and dermatological symptoms. All self-limiting. Fasting blood glucose, cholesterol and bp did not alter.	1 patient died in glucosamine group 1 participant in each group developed a disc herniation requiring surgery, events not considered study related.
Tant 2005	High	Patients interviewed at clinic visit regarding undesirable effects	Abdominal discomfort reported at 8 weeks by 1 patient in the glucosamine group and 1in the control group. None of the patients discontinued treatment due to an adverse event.	Adverse effect may have been due to analgesic/anti-inflammatory treatment instead of glucosamine as abdominal discomfort also occurred in 1 patient not receiving glucosamine.
Leffler 1997	Low	Patient survey of toxicity symptoms and faecal occult blood testing at end of each phase. Bp and pulse measured 21 patients had blood count and coagulation studies done.	No patients reported symptoms requiring termination of the study. Symptom frequency on medication was similar to that at baseline. Vital signs, occult blood testing and haematological parameters did not change significantly from placebo to medication.	

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Table 6: GRADE evidence profile

Quality Assessment							
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Quality**
Pain measured on VAS, follow up (4weeks – 1year)							
3	Randomised trials	Serious[1]	Serious[2]	Serious[3]	No serious imprecision	None	Very low
Function/disability measured on RMDQ, Follow up (4weeks – 1year)							
3	Randomised trials	Serious[1]	No serious inconsistency	Serious[3]	No serious imprecision	None	Low
Adverse effects							
3	Randomised trials	Serious[1]	No serious inconsistency	Serious[3]	No serious imprecision	None	Low

[1]One study was open-label (Tant, 2005). There were limitations regarding unclear randomisation in another trial (Leffler, 1999). One trial did not clearly employ an intention to treat analysis and compliance was also unclear (Tant 2005).

[2]Two trials with a low risk of bias failed to show any significant decrease in pain levels (Wilkens, 2005 and Leffler, 1999), whereas one trial with a high risk of bias (Tant 2005) showed a significant effect of glucosamine on back pain.

[3]One trial used male patients from US Navy special warfare community with a history of high activity levels and unique occupational exposures; hence the results may not be generalisable (Leffler, 1999). One study used a mixed population of both knee and back pain patients and some patients had both, although data was separated by site (Leffler, 1999).

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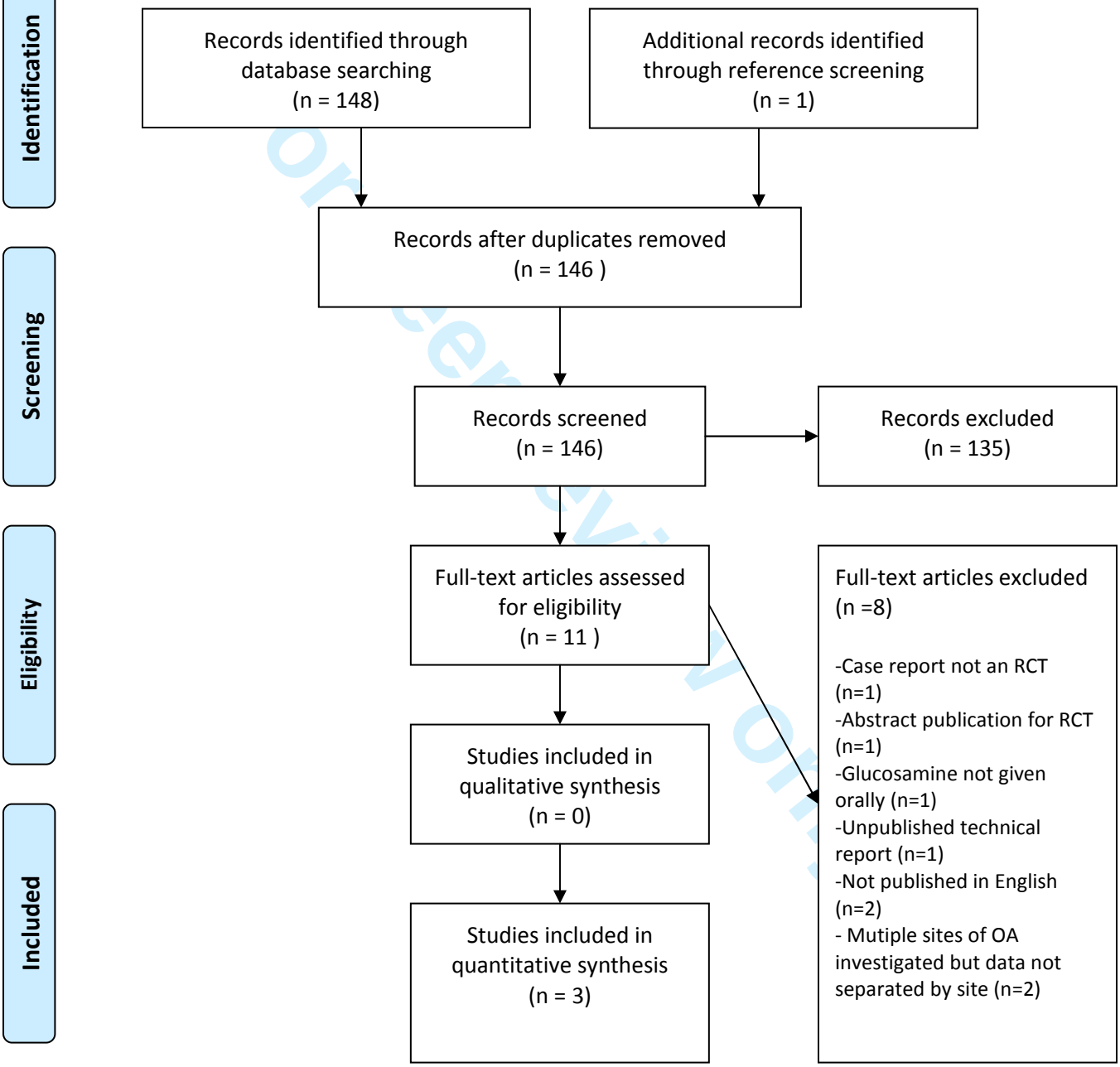
Figure 1: Flow diagram of inclusion and exclusion of articles for glucosamine use in spinal OA (PRISMA 2009 Flow Diagram) (Moher et al)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Appendix 3 – Prisma 2009 Checklist (Moher et al)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	-
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6,7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	-
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7,8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	-

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Appendix 3 – Prisma 2009 Checklist (Moher et al)

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	-

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2&6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 3,4,5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10,11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10,11,12,part B
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

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Appendix 3 – Prisma 2009 Checklist (Moher et al)

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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The use of glucosamine for chronic low back pain: A systematic review of randomised control trials

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The use of glucosamine for chronic low back pain: A systematic review of randomised control trials

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Abstract

Background: The use of glucosamine as a treatment for osteoarthritis (OA) remains controversial. The aim of this review is to ascertain whether the use of oral glucosamine influences symptoms or functional outcomes in patients with chronic low back pain (LBP) thought to be related to spinal OA.

Data Sources: Searches were performed up to March 2011 on Medline, AMED, CINHAL, Cochrane and EMBASE with subsequent reference screening of retrieved studies. In addition grey literature was searched via opensigle.

Methods: Included studies were required to incorporate at least one of the Cochrane Back Pain Review Group's (CBRG) outcome measures as part of their design. Trials with participants over 18 years with a minimum of 12 weeks of back pain, in combination with radiographic changes of OA in the spine were included. Studies were rated for risk-of-bias and graded for quality.

Results:148 studies were identified, after screening and meeting eligibility requirements 3 RCTs (n=309) were included in the quantitative synthesis. The review found there was low quality but generally no evidence of an effect from glucosamine on function, with no change on the Roland Morris Disability Questionnaire (RMDQ) score in all studies. Conflicting evidence was demonstrated with pain scores with 2 studies showing no difference and one study with a high risk-of-bias showing both a statistically and clinically significant improvement from taking glucosamine.

Conclusion: Based on current research, any clinical benefit of oral glucosamine for patients with chronic low back pain and radiographic changes of spinal OA cannot be demonstrated nor excluded based on insufficient data and low quality existing studies.

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Introduction

Rationale

Low back pain (LBP) affects around one-third of UK adults each year.[1 2] Around 20% will consult their general practitioner (GP), making it one of the commonest presentations seen in primary care.[3] Additionally, there are considerable financial consequences associated with back pain with previous estimates of direct healthcare costs in the UK amounting to over £1.6 billion and indirect costs from informal care and loss of productivity to the economy, of £10.7 billion.[4]

Osteoarthritis (OA) is a highly prevalent degenerative joint condition that the World Health Organisation (WHO) Scientific Group on Rheumatic Diseases estimates is the cause of significant clinical problems in at least 10% of patients who are 60 years or older.[5]

OA can affect several parts of the body including the spine. Within the spine, OA affects the vertebral facet joints[6] and may occur with or without the presence of LBP.[7]

Borenstein suggested that OA may cause LBP [8] however; this relationship is complex and controversial. Some of the evidence supporting a link between spinal OA and LBP comes from early studies which showed improved back pain following intra-articular or peri-artciular joint injections. [9 10 11] However it is apparent that not all patients with LBP will have symptoms that correlate with severity of radiographic OA changes on imaging.[7]

A further degenerative process can be found in the spine in the form of intervertebral degenerative disc disease (DDD). A recent twin study demonstrated the presence of lumbar degenerative discs on MRI to be a major determinate feature of patients with LBP.[12] Although the prevalence of DDD and facet joint OA correlate[13], it is unclear with they are

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independent of one another or whether they are different ends of the spectrum of the same pathological process.

Pharmacological therapies are the most frequently used intervention for LBP,[14] however serious side effects associated with long term use of some medications such as non-steroidal anti-inflammatory drugs (NSAIDS), has led patients to seek alternative medicines such as glucosamine.

Glucosamine is available to purchase as a food supplement and is gaining popularity amongst patients in the UK for the relief of knee and hip pain associated with osteoarthritis, however more than 25% of patients have tried glucosamine for LBP. [15]

Glucosamine is a naturally occurring amino monosaccharide and is a precursor for glycosaminoglycans, a major component of joint cartilage and synovial fluid[16] and this forms the basis of the rationale for its use in OA. Glucosamine is available in over fifty different preparations most commonly in the form of glucosamine sulphate and hydrochloride.[17]

Glucosamine Hydrochorlide (Alateris®) is the only preparation licensed for medical use in the UK and the license is restricted to the symptomatic relief of mild to moderate knee OA. Despite its license there is less evidence for its use compared with glucosamine sulphate and neither are currently recommended by the National Institute for Health and Clinical Excellence (NICE).[18]

Several trials and systematic reviews have looked into the use of glucosamine in knee and hip arthritis. A Cochrane review identified 16 double-blind randomised controlled trials (RCTs) and concluded that there was good evidence that glucosamine is both effective and safe in treating OA, but this did not assess spinal OA[19] This review was updated and failed to show a uniformly positive conclusion, if only high quality studies were included[20]. Analysis restricted to studies with adequate allocation concealment failed to show any benefit of

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glucosamine for pain, function and stiffness based on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) used to assess pain, stiffness and function in patients with hip and knee OA. However the review also assessed pain and function on the Lequesne index which did reveal an improvement after glucosamine when compared to placebo. The disparity between these findings remains unexplained by the authors, however a study that compared and tested the validity of WOMAC and Lequense index found that although both measures show internal validity when assessing function in hip and knee OA, only the WOMAC is consistently reliable when assessing symptoms such as pain.[21]

Given the lack of conclusive evidence regarding an improvement in LBP from glucosamine and at present no recommendations from NICE, the indications for using glucosamine remain controversial for clinicians and patients.

Reviews so far have focused on trials looking at the use of glucosamine in hip and knee OA.[22] The current study has been undertaken to provide an up to date systematic review of the evidence for the use of glucosamine in LBP.

Objective

To systematically search and assess the quality of the evidence of the efficacy of glucosamine on low back pain symptoms in patients diagnosed with spinal facet joint OA or degenerative disc disease.

Methods

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Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were considered for this review as randomisation ensures that patients in the treatment and control groups are comparable from the start. In the hierarchy of study designs, RCTs and systematic reviews are considered the highest level of evidence.[23] At least one day of follow-up was required to ascertain any effect of an intervention. RCTs were included if they: 1) evaluated the efficacy and toxicity of glucosamine in OA, 2) were placebo-based or comparative studies, 3) were open-label, single-blinded or double-blinded, 4) evaluated glucosamine-only or combination preparations**,** 5) utilised oral administration of glucosamine as this is the route which will be used by the majority of patients.

Types of participants

Participant inclusion criteria for this review included: adult subjects (≥18 years), with chronic back pain (≥12 weeks) and signs of spinal OA. As there are no consensus guidelines about constitutes a diagnosis of OA in the spine any radiographic changes consistent with OA were included. A variety of radiographic grading systems have been proposed but there is no single global staging system suitable for the assessment of OA at all sites. [24]

The exclusion criteria were: trials that included subjects with specific LBP caused by other pathologies such as vertebral canal stenosis, ankylosing spondylitis, scoliosis and coccycydinia and trials that looked at OA at multiple sites but did not separate the data from the different sites making conclusions regarding changes in spinal symptoms difficult.

Types of Interventions

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Both placebo-controlled trials and comparative studies were eligible. Types of comparison considered appropriate were conventional therapies used for OA such as physical therapy, analgesics and anti-inflammatories.

Types of Outcome Measures

For inclusion, at least one of the following outcome measures, recommended by the Cochrane Back Review Group (CBRG), had to be observed: 1) pain intensity, for example visual analogue scale, 2) reliable and valid measure of functional status or disability for example, the Roland-Morris Disability Questionnaire (RMDQ)[25 26] 3) perceived recovery, 4) return-to-work status 5) structural benefits measured by radiography 6) adverse effects. The primary outcomes for this review were pain and functional status. The timing of measured outcomes had to be explicitly described.

Search methods for identification of studies

All three authors are practicing clinicians in the United Kingdom and have either completed or are undertaking higher research degrees.

The search strategy was formualated jointly by the first two named authors. Retrieval of searches, reference screening and subsequent data synthesis was subsequently performed independently. Differences were resolved after discussion with the thirdauthor . The search was conducted up to March 2011 and included grey literature, searched via opensigle. Papers not published in English were excluded. By searching MEDLINE (medical, nursing and biomedical journals), it was anticipated that approximately half of available RCTs would be identified, therefore a subsequent search of EMBASE (biochemical and pharmaceutical journals) would ensure a comprehensive search as there is little overlap between these

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databases and in the field of LBP, EMBASE has been shown to retrieve more clinical trials.[27] Searching AMED and CINHAL would cover complementary medicine and allied health journals, whilst including Cochrane enabled high quality evidence from RCTs and systematic reviews to be included. References of relevant studies were screened to identify additional studies.

The electronic search strategy outlined in Appendix 1 was developed in MEDLINE and adapted for the other databases. The search was developed by reviewing relevant articles in the area of back pain and OA and combining search terms used in these studies.

Risk-of-bias assessment and quality

The risk of bias was assessed using the criteria advised by the CBRG.[27] Each criterion was scored as yes, unclear or no, where yes indicated the criterion had been met. Studies are rated as having a low 'risk of bias' when at least 6 of the 12 CBRG criteria have been met with no serious flaws.

Data Extraction

Data was recorded onto a standardised form and described the main trial characteristics, patient demographics, interventions, comparisons, outcomes, analysis, results and assessment of trial quality (tables 1 and 2).

Quality of the Evidence

Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria were used to evaluate the overall quality of the evidence. This is recommended by the

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Cochrane Handbook to rate the quality of evidence for each important patient-centred outcome as it goes beyond the reporting of quantitative analysis. The quality of evidence was based on 5 domains: limitations of the study design, inconsistency, indirectness (inability to generalise), imprecision (insufficient or imprecise data) of results and publication bias across all studies that measure that particular outcome.[28] The overall quality was considered to be high when at least 75% of the RCTs with no limitations of study design had consistent findings, direct and precise data and no known or suspected publication biases.[27] The grades of quality of evidence are outlined in Appendix 2. [29]

Results

Description of studies

Study selection

Studies were identified through the following databases: Medline (11), Embase (53), Cochrane library (84) (Cochrane reviews (10), other reviews (7), clinical trials (67)). Three studies were included (Table 1). Reasons for exclusion are outlined in Figure 1. Due to differences in the study design of included trials, metanalysis was not attempted.

Risk of bias in included studies

The risk-of-bias assessment is shown in table 2. Although all studies were described as randomised, only two described adequate randomisation.[30 31] One trial was open-label and did not report compliance.[31] One trial had a 20% drop-out rate.[32] All trials had similar groups at baseline, timings of outcome assessments and co-interventions in both groups.

From this assessment two studies have been rated as having a low risk of bias. The one study rated as a high risk of bias scored six, but its open-label design was considered to be a significant methodological flaw.

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Effects of intervention

Tables 3, 4 and 5 summarise the findings with respect to the main outcomes measured. For pain, the two studies with a low risk of bias failed to show any significant improvement with glucosamine compared with placebo, whilst the one study with a high risk-of-bias did show a significant difference with glucosamine compared to no glucosamine.

Back function/disability was measured by Owestry Disability Index (ODI) and RMDQ, both validated tools[26 33]; there was no significant difference in the RMDQ scores with glucosamine as an intervention. The study with a high risk of bias demonstrated a statistically significant difference in the ODI score reduction for the glucosamine group, although this difference was small.[31]

With respect to adverse effects, one trial revealed ~ 30% of participants experienced adverse effects irrespective of whether they were in the placebo or glucosamine group.[30]

Other outcomes that were considered but not across all trials included an assessment of quality of life measured by the Euro-Qol-5 Dimensions (EQ-5D) index and overall health status measured by EQ-VAS.[30] There was no significant difference found between glucosamine and placebo with these outcomes.

One study used several assessments which were totalled to provide an overall summary score.[32] In addition to measuring pain and function, physical examination scores and running times were assessed. There were no statistically significant changes in the LBP group when considering the overall summary score or individual outcome measures.

None of the studies looked at radiographic changes in association with glucosamine use.

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Discussion

In this review three RCTs were included that evaluated the effectiveness of glucosamine as an intervention for chronic low back pain associated with spinal OA. [30 31 32]

Overall, the review found the limited number of studies had methodological deficiencies. The studies did not demonstrate a clear beneficial effect of using glucosamine for LBP due to OA[30 32]. One study however showed a statistically significant difference in the ODI score reduction for the glucosamine group [31], although this difference was small and does not appear to reach the minimally clinical important difference (MCID) alluded to in previous research.[34]

There was conflicting evidence regarding the effect of glucosamine on pain scores. Two studies showed no statistically significant difference on pain scores between the intervention and placebo group. [30 32] One study did show a statistical and clinically significant reduction in pain scores for those taking glucosamine.[31] Whilst this study had significant methodological shortcomings which are discussed in the next section, this alone may not completely explain differences when compared to the two other studies. A possible reason was that the study recruited older patients with a mean age of 64 compared with a much younger demographic in the remaining two studies. Facet joint OA is known to become more prevalent with age[13] and therefore the proportion of patients with pain related to facet joints as opposed to discogenic pain may have been higher. This combined with a theoretical possibility that glucosamine may predominantly affect articular cartilage as opposed to intervertebral discs, may lead to an under representation of the affect of glucosamine in studies with a younger cohort.

Methodological considerations

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There were several factors that contributed to the very low or low quality assessment for the main outcomes measured in the trials. The results of one study [31] in particular which found positive effects of glucosamine on both pain and function appears to contradict the findings of the other two, however, this may be partly explained by its limitations. A key limitation was its open-label design. Since participants and clinicians were aware of group allocation, bias was introduced.

Another study had unclear details about its randomisation.[32] Blinding and randomisation decrease the likelihood of selection and performance bias which would affect the internal validity of the study.[35] This same RCT employed a cross-over design, which may intrinsically have introduced bias if the 5 week wash-out period employed was too short.

To minimize attrition bias, the drop-out rate should be described and acceptable with all the randomised patients analysed in the group to which they were allocated, by an intention to treat analysis (ITT) [35]. One trial did not employ an ITT analysis and compliance was unclear.[31]

There are difficulties in how the trials can be directly applied to the general population and this adversely affects their relevance to practice and external validity. One trial used patients from US Navy diving and special warfare community who have a history of high activity levels and unique occupational exposures. They were also all male; hence the results may not be generalisable.[32] This study used a mixed population of both knee and back pain patients, with some participants having both knee and back pain. The proportion of patients in each group was described and the data was separated.

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Despite the fact that the risk of bias was low in two studies, the studies collectively showed flaws regarding concealment of treatment allocation, adequate randomisation, compliance and drop-out rates. The review findings were significantly influenced by these shortcomings despite the fact that the study by Wilkens et al was of a high quality and well designed. The quality of future RCTs needs to be improved to reduce bias in future reviews.

Review Strengths and Limitations

The selection procedure and literature search utilised in this review may have introduced bias. The selection criteria did not place limits on the ages of participants and as the pathology of low back pain may change with age, direct comparisons between studies of patients with different patient demographics needs to taken with caution.

Relevant, unpublished trials may have been omitted and as these are likely to be small studies without positive results this may lead to publication bias. Studies not published in English were excluded and may also have introduced bias. Utilising references of the included trials to identify other studies may have also led to an over-representation of positive studies.

The search strategy was however vigorous with several databases utilised, in addition to reference screening of included studies which ensured that the omission of relevant studies was minimised.

Implications for Health Practice

LBP is extremely prevalent with considerable financial consequences.[4] OA accounts for a significant proportion of LBP seen by GPs and secondary care clinicians. Current treatment

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options such as NSAIDs and surgery have some potentially serious adverse effects .Therefore alternative treatments such as glucosamine which may provide a possible solution to this problem seem attractive.

Global sales of glucosamine reached almost £1.3billion in 2008.[36] Currently in the UK, glucosamine is available as a food supplement and can be prescribed for knee OA. The evidence for its use in back pain is conflicting, it is therefore imperative that a consensus based on sound clinical evidence is reached to justify this immense cost to the public.

This review helps clarify the existing evidence for the use of glucosamine in back pain which will be of particular relevance to patients and clinicians considering using glucosamine.

The current review has demonstrated that if only the studies with a low risk of bias are considered, there is no evidence of a significant difference between glucosamine and placebo for pain or pain-related disability associated with OA in the lower back.

The mechanism by which glucosamine may exert its effect is poorly understood. Wilkens et al, previously proposed that glucosamine may reduce LBP by inhibiting interleukin (IL)-1β which is present in lumbar discs and facet joints. This mechanism is purely theoretical with no conclusive evidence demonstrating a direct pharmacological effect on the spine. The lack of a sound scientific rationale for the use of glucosamine in LBP makes it difficult to successfully design a study to prove any clinical benefit it may have. In addition, there is much debate as to the relationship between LBP and spinal OA findings. Not all patients with LBP have spinal OA and vice versa, however most studies assume they are correlated.

All of the studies included in the review had limitations. All were single centre trials and two had small sample sizes. There were methodological differences in randomisation, blinding, allocation concealment and varying outcome measures. Inclusion criteria varied between trials some looked at both facet joint OA and degenerative disc disease. These two conditions

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do not necessarily represent the same pathological process. In addition the method for diagnosing the OA differed as there is no existing consensus or criteria for diagnosis. Back pain is complex and whilst spinal OA may cause low back pain, several other structures may be responsible and pathologies may co-exist.

It is possible that glucosamine may work better in more severe disease as has been suggested with knee OA.[37] The studies reviewed all had varying severities of OA symptoms required for inclusion. This limits the conclusions that can be made as the studies did not separate out the data for different levels of severity in the analysis.

OA is a chronic disease and patients taking supplements such as glucosamine may do so for several years. Follow-up periods for the trials varied from eight weeks to one year. Glucosamine may take longer than this to have an apparent affect. A case report revealed an improvement in the structural quality of disc cartilage on MRI in a patient taking glucosamine over a two year period.[38] The patient's symptoms only began to improve at six months and continued until the end of the study period. None of the studies in this review looked at objective radiographic changes as an outcome and whilst there are obvious limitations to drawing any broad conclusions form a single case report, this provides an argument for a longer follow-up RCT and more objective outcome measures.

A strength of this review is that it contained several placebo-controlled RCTs. One especially well-designed study clearly showed that patients treated with glucosamine for one year who had a combination of chronic LBP and either or both facet joint OA and degenerative disc disease, had no difference in pain or disability when compared to placebo.

An important factor to consider when assessing the relevance of trial data to everyday practice is the generalisability or external validity of the studies. The current review included one study which used a relatively young cohort of male patients who were from a US Navy

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diving and special warfare community who had a history of high activity levels and unique occupational exposures. This is not the profile of a typical OA patient a doctor would see in general practice.

An important distinction is between statistical significance and clinical relevance of findings. One study showed a statistically significant difference in pain related disability on the ODI, however the difference was very small and may not have represented a clinically relevant change.[31] Currently there is consensus regarding minimal clinically important changes for pain and function (measured by RMDQ not ODI) in back pain.[27] For LBP, 30% on VAS/NRS for pain is considered as clinically significant and 2 to 3 points (8 -12%) on the RMDQ for function is considered as clinically significant.[39]

Glucosamine may be viewed as a relatively safe medication however the current review nonetheless highlights a high incidence of adverse effects and although these were mild, it is an important consideration when recommending it.

Based on the current evidence explored in this review, there is insufficient evidence to either demonstrate or exclude a clinical benefit of glucosamine for spinal OA. Using more objective measures such as radiography to look at any change in OA progression, refining study inclusion criteria, providing longer follow-up periods and trying to establish a clear biochemical model for glucosamine may enable more definitive conclusions to be drawn so that clinicians can confidently advise their patients based on the best available evidence.

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APPENDICES

Appendix 1. Electronic search strategy

1. exp osteoarthritis, spine
2. degenerative arthritis. mp. or exp osteoarthritis
3. osteoarthr*
4. degenerative joint disease. Mp.
5. degenerative disc disease
6. exp low back pain
7. exp back pain
8. exp spine
9. exp lumbar vertebrae
10. chronic back pain. mp.
11. exp glucosamine/ or glucosamine. mp.
12. glucosamine sulphate. mp.
13.exp acetylglucosamine/ or acetylglucosamine. mp.
14. glucosamine hydrochloride. mp.
15. n-acetyl-d-glucosamine.tw.
16. or/1-5
17. or/6-10
18. or/11-15
19. 16 and 17 and 18

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Appendix 2: Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria

High quality (at least 75% of the RCTs with no limitations of study design have consistent findings, direct and precise data and no known or suspected publication biases)	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality 1 of the domains are not met	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality 2 of the domains are not met	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality 3 of the domains are not met	Any estimate of effect is very uncertain

5 Domains:

Limitations of the study design, inconsistency, indirectness (inability to generalise), imprecision (insufficient or imprecise data) and publication bias.

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References:

1. Macfarlane GJ, Beasley M, Jones EA, Prescott GJ, Docking R, Keeley P, McBeth J, Jones GT. The prevalence and management of low back pain across adulthood: Results from a population-based cross-sectional study (the MUSICIAN study). *Pain* 2012; 153(1):27-32.
2. Papageorgiou AC, Croft PR, Thomas E, Ferry S, Jayson MI, Silman AJ. Influence of previous pain experience on the episode incidence of low back pain: results from the South Manchester Back Pain Study. *Pain* 1996; 66(2-3):181-5.
3. Papageorgiou AC, Rigby AS. Review of UK data on the rheumatic diseases--7. Low back pain. *Br J Rheumatol*. 1991; 30(3):208-10.
4. Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain* 2000; 84 (1):95-103.
5. Murray CJL, Lopez AD. The global burden of disease. A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge (MA): Harvard School of Public Health on behalf of the *World Health Organization* and *The World Bank*; 1996.
6. Kalichman L, Hunter DJ. Lumbar facet joint osteoarthritis: a review. *Semin Arthritis Rheum*. 2007; 37(2):69-80.
7. Kalichman L, Li L, Kim D, Guermazi A, Berkin V, O'Donnell C, Hoffmann U, Cole R, Hunter D. Facet joint osteoarthritis and low back pain in the community-based population. *Spine* 2008;33(23): 2560–2565.
8. Borenstein D. Does osteoarthritis of the lumbar spine cause chronic low back pain? *Curr Pain Headache Rep*. 2004;8(6):512-517.
9. Goldthwait J. The lumbosacral articulation. An explanation of many cases of lumbago, sciatica, and paraplegia. *Boston Med and Surg J*. 1911;164:365–372.
10. Schwarzer AC, Aprill C, Derby R. Clinical features of patients with pain stemming from the lumbar zygapophyseal joints. Is the lumbar facet syndrome a clinical entity? *Spine* 1994;10:1132–1137.
11. Dreyer SJ, Dreyfuss PH. Low back pain and the zygapophysial (facet) joints. *Arch Phys Med Rehabil*. 1996;77:290–300.
12. Livshits G, Popham M, Malkin I, Sambrook PN, Macgregor AJ, Spector T, Williams FM. Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study. *Ann Rheum Dis*. 2011;70(10):1740-5.
13. Li J, Muehleman C, Abe Y, Masuda K. Prevalence of facet joint degeneration in association with intervertebral joint degeneration in a sample of organ donors. *J Orthop Res*. 2011;29(8):1267-74.
14. Kuijpers T, Van Middelkoop M, Rbinstein S, Ostelo R, Verhagen A, Koes B, Van Turner M. A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. *Eur Spine J*. 2011; 20:40-50.
15. Avins A. Glucosamine and the ongoing enigma of chronic low back pain *JAMA* 2010;304:1.
16. Arendt-Nielsen L, Weidner M, Bartholin D, Rosetzsky. A double- blind randomized placebo controlled parallel group study evaluation the effects of Ibuprofen and glucosamine sulphate on exercise induced muscle soreness. *Journal of Musculoskeletal Pain*. 2007; 15(1):21-28

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

17. C+D Data, 2008. *The Product File* [online]. Available: http://www.cddata.co.uk [Product search for "glucosamine": 20 October 2008].
18. NICE Guideline CG59 Osteoarthritis the care and management of osteoarthritis in adults http://www.nice.org.uk/guidance/index Feb 2008.
19. Towheed TE, Anastassiades TP, Shea B, Houpt J, Welch V, Hochberg MC. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2001;(1):CD002946.
20. Towheed T, Maxwell L, Anastassiades T, Shea B, Houpt J, Welch V, Hochberg M, Wells G. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2009, Issue 4. Oxford: Update Software.
21. Stucki G, Sangha O, Stucki S, Michel BA, Tyndall A, Dick W, Theiler R. Comparison of the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index and a self-report format of the self-administered Lequesne-Algofunctional index in patients with knee and hip osteoarthritis. *Osteoarthritis Cartilage*. 1998;6(2):79-86.
22. Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ*. 2010; 16:341.
23. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines for the Scottish Intercollegiate Guidelines Network Grading Review Group. (SIGN) *BMJ* 2001;323:334-336.
24. Roland W. Moskowitz M., Roy D. Altman, M, . Hochberg M. Osteoarthrits: Diagnosis and medical /surgical management *Lippincott,Willliams and Wilkens* 4th Ed 2006.
25. Roland M, Morris R A study of the natural history of backpain: Development of a reliable and sensitive measure of disability in low-back pain. *Spine* 1983;8:141–144
26. Stratford PW, Binkley JM, Riddle DL, Guyatt GH Sensitivity to change the Roland–Morris back pain Questionnaire:Part 1. *Phys Ther* 1998;78:1186–1196.
27. Furlan A, Pennick V, Bombardier C, van Tulder M Updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine* 2009;34(18):1929-1941
28. Atkins D, Best D, Briss P. GRADE Working group. Grading quality of evidence and strength of recommendations. *BMJ* 2006; 328:1490
29. Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, for the GRADE Working Group**.** Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations**.** *BMJ* 2008;336:924-926
30. Wilkens P, Scheel I, Grundes O, Hellum C, Storheim K. Effect of Glucosamine on Pain-Related Disability in Patients with Chronic Low Back Pain and Degenerative Lumbar Osteoarthritis. *JAMA*. 2010;304(1):45-52
31. Tant L, Gillard B, Appelboom T. (2005) Open-label, randomized, controlled pilot study of the effects of a glucosamine complex on low back pain. *Current Therapeutic Res*. 2005;66(6):511-521

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

32. Leffler C, Philippi A, Leffler S, Mosure J, Kim P. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo controlled pilot study. *Mil Med*. 1999;164(2):85-91.
33. Fairbank J, Couper J, Davies J, O'Brien J The Owestry low back pain disability questionnaire. *Physiotherapy* 1980;66: 271-273.
34. Lauridsen HH, Manniche C, Korsholm L, Grunnet-Nilsson N, Hartvigsen J. What is an acceptable outcome of treatment before it begins? Methodological considerations and implications for patients with chronic low back pain. *Eur Spine J*. 2009 Dec;18(12):1858-66.
35. Hart A. Making sense of statistics in health care *Radcliffe Medical Press* 2001.
36. Heller L. US glucosamine grows slow, lags global sales. 2009. www.nutraingredients-usa.com/Consumer-Trends/US-glucosamine-grows-slow-lags-global-sales.
37. Clegg D, Reda D, Harris C. Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis. *New England Journal of Medicine*, 2006; 354:795-808.
38. Van Blitterswijk W, van de Nes J, Wuisman P. Glucosamine and chondroitin sulphate supplementation to treat symptomatic disc degeneration: Biochemical rationale and case report. *BMC Complementary and Alternative Medicine* 2003;3:2 ;1-8
39. Ostelo R, Deyo R. Stratford P Interpreting change scores for pain and function status in low back pain: towards international consensus regarding minimal important change. *Spine* 2008;33: 90-94

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The use of glucosamine for chronic low back pain: A systematic review of randomised control trials

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Abstract

Background: The use of glucosamine as a treatment for osteoarthritis (OA) remains controversial. The aim of this review is to ascertain whether the use of oral glucosamine influences symptoms or functional outcomes in patients with chronic low back pain (LBP) thought to be related to spinal OA.

Data Sources: Searches were performed up to March 2011 on Medline, AMED, CINHAL, Cochrane and EMBASE with subsequent reference screening of retrieved studies. In addition grey literature was searched via opensigle.

Methods: Included studies were required to incorporate at least one of the Cochrane Back Pain Review Group's (CBRG) outcome measures as part of their design. Trials with participants over 18 years with a minimum of 12 weeks of back pain, in combination with radiographic changes of OA in the spine were included. Studies were rated for risk-of-bias and graded for quality.

Results:148 studies were identified, after screening and meeting eligibility requirements 3 RCTs (n=309) were included in the quantitative synthesis. The review found there was low quality but generally no evidence of an effect from glucosamine on function, with no change on the Roland Morris Disability Questionnaire (RMDQ) score in all studies. Conflicting evidence was demonstrated with pain scores with 2 studies showing no difference and one study with a high risk-of-bias showing both a statistically and clinically significant improvement from taking glucosamine.

Conclusion: Based on current research, ~~there is insufficient evidence to recommend the use of oral glucosamine for patients with chronic LBP and radiographic changes of OA, however anyeffect glucosamine may exert cannot be completely excluded due to the low quality of existing research.~~any clinical benefit of oral glucosamine for patients with chronic low back

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pain and radiographic changes of spinal OA cannot be demonstrated nor excluded based on insufficient data and low quality existing studies.

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Introduction

Rationale

Low back pain (LBP) affects around one-third of UK adults each year.[1 2] Around 20% will consult their general practitioner (GP), making it one of the commonest presentations seen in primary care.[3] Additionally, there are considerable financial consequences associated with back pain with previous estimates of direct healthcare costs in the UK amounting to over £1.6 billion and indirect costs from informal care and loss of productivity to the economy, of £10.7 billion.[4]

Osteoarthritis (OA) is a highly prevalent degenerative joint condition that the World Health Organisation (WHO) Scientific Group on Rheumatic Diseases estimates is the cause of significant clinical problems in at least 10% of patients who are 60 years or older.[5]

OA can affect several parts of the body including the spine. Within the spine, OA affects the vertebral facet joints[6] and may occur with or without the presence of LBP.[7]

Borenstein suggested that OA may cause LBP [8] however; this relationship is complex and controversial. Some of the evidence supporting a link between spinal OA and LBP comes from early studies which showed improved back pain following intra-articular or peri-artciular joint injections. [9 10 11] However it is apparent that not all patients with LBP will have symptoms that correlate with severity of radiographic OA changes on imaging.[7]

A further degenerative process can be found in the spine in the form of intervertebral degenerative disc disease (DDD). A recent twin study demonstrated the presence of lumbar degenerative discs on MRI to be a major determinate feature of patients with LBP.[12] Although the prevalence of DDD and facet joint OA correlate[13], it is unclear with they are

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independent of one another or whether they are different ends of the spectrum of the same pathological process.

Pharmacological therapies are the most frequently used intervention for LBP,[14] however serious side effects associated with long term use of some medications such as non-steroidal anti-inflammatory drugs (NSAIDS), has led patients to seek alternative medicines such as glucosamine.

Glucosamine is available to purchase as a food supplement and is gaining popularity amongst patients in the UK for the relief of knee and hip pain associated with osteoarthritis, however more than 25% of patients have tried glucosamine for LBP. [15]

Glucosamine is a naturally occurring amino monosaccharide and is a precursor for glycosaminoglycans, a major component of joint cartilage and synovial fluid[16] and this forms the basis of the rationale for its use in OA. Glucosamine is available in over fifty different preparations most commonly in the form of glucosamine sulphate and hydrochloride.[17]

Glucosamine Hydrochorlide (Alateris®) is the only preparation licensed for medical use in the UK and the license is restricted to the symptomatic relief of mild to moderate knee OA. Despite its license there is less evidence for its use compared with glucosamine sulphate and neither are currently recommended by the National Institute for Health and Clinical Excellence (NICE).[18]

Several trials and systematic reviews have looked into the use of glucosamine in knee and hip arthritis. A Cochrane review identified 16 double-blind randomised controlled trials (RCTs) and concluded that there was good evidence that glucosamine is both effective and safe in treating OA, but this did not assess spinal OA[19] This review was updated and failed to show a uniformly positive conclusion, if only high quality studies were included[20]. Analysis restricted to studies with adequate allocation concealment failed to show any benefit of

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glucosamine for pain, function and stiffness based on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) used to assess pain, stiffness and function in patients with hip and knee OA. However the review also assessed pain and function on the Lequesne index which did reveal an improvement after glucosamine when compared to placebo. The disparity between these findings remains unexplained by the authors, however a study that compared and tested the validity of WOMAC and Lequense index found that although both measures show internal validity when assessing function in hip and knee OA, only the WOMAC is consistently reliable when assessing symptoms such as pain.[21]

Given the lack of conclusive evidence regarding an improvement in LBP from glucosamine and at present no recommendations from NICE, the indications for using glucosamine remain controversial for clinicians and patients.

Reviews so far have focused on trials looking at the use of glucosamine in hip and knee OA.[22] The current study has been undertaken to provide an up to date systematic review of the evidence for the use of glucosamine in LBP.

Objective

To systematically search and assess the quality of the evidence of the efficacy of glucosamine on low back pain symptoms in patients diagnosed with spinal facet joint OA or degenerative disc disease.

Methods

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Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were considered for this review as randomisation ensures that patients in the treatment and control groups are comparable from the start. In the hierarchy of study designs, RCTs and systematic reviews are considered the highest level of evidence.[23] At least one day of follow-up was required to ascertain any effect of an intervention. RCTs were included if they: 1) evaluated the efficacy and toxicity of glucosamine in OA, 2) were placebo-based or comparative studies, 3) were open-label, single-blinded or double-blinded, 4) evaluated glucosamine-only or combination preparations**,** 5) utilised oral administration of glucosamine as this is the route which will be used by the majority of patients.

Types of participants

Participant inclusion criteria for this review included: adult subjects (≥18 years), with chronic back pain (≥12 weeks) and signs of spinal OA. As there are no consensus guidelines about constitutes a diagnosis of OA in the spine any radiographic changes consistent with OA were included. A variety of radiographic grading systems have been proposed but there is no single global staging system suitable for the assessment of OA at all sites. [24]

The exclusion criteria were: trials that included subjects with specific LBP caused by other pathologies such as vertebral canal stenosis, ankylosing spondylitis, scoliosis and coccycydinia and trials that looked at OA at multiple sites but did not separate the data from the different sites making conclusions regarding changes in spinal symptoms difficult.

Types of Interventions

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Both placebo-controlled trials and comparative studies were eligible. Types of comparison considered appropriate were conventional therapies used for OA such as physical therapy, analgesics and anti-inflammatories.

Types of Outcome Measures

For inclusion, at least one of the following outcome measures, recommended by the Cochrane Back Review Group (CBRG), had to be observed: 1) pain intensity, for example visual analogue scale, 2) reliable and valid measure of functional status or disability for example, the Roland-Morris Disability Questionnaire (RMDQ)[25 26] 3) perceived recovery, 4) return-to-work status 5) structural benefits measured by radiography 6) adverse effects. The primary outcomes for this review were pain and functional status. The timing of measured outcomes had to be explicitly described.

Search methods for identification of studies

All three authors are practicing clinicians in the United Kingdom and have either completed or are undertaking higher research degrees.

The search strategy was formualated jointly by the first two named authors. Retrieval of searches, reference screening and subsequent data synthesis was subsequently performed independently. Differences were resolved after discussion with the thirdauthor . The search was conducted up to March 2011 and included grey literature, searched via opensigle. Papers not published in English were excluded. By searching MEDLINE (medical, nursing and biomedical journals), it was anticipated that approximately half of available RCTs would be identified, therefore a subsequent search of EMBASE (biochemical and pharmaceutical journals) would ensure a comprehensive search as there is little overlap between these

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databases and in the field of LBP, EMBASE has been shown to retrieve more clinical trials.[27] Searching AMED and CINHAL would cover complementary medicine and allied health journals, whilst including Cochrane enabled high quality evidence from RCTs and systematic reviews to be included. References of relevant studies were screened to identify additional studies.

The electronic search strategy outlined in Appendix 1 was developed in MEDLINE and adapted for the other databases. The search was developed by reviewing relevant articles in the area of back pain and OA and combining search terms used in these studies.

Risk-of-bias assessment and quality

The risk of bias was assessed using the criteria advised by the CBRG.[27] Each criterion was scored as yes, unclear or no, where yes indicated the criterion had been met. Studies are rated as having a low 'risk of bias' when at least 6 of the 12 CBRG criteria have been met with no serious flaws.

Data Extraction

Data was recorded onto a standardised form and described the main trial characteristics, patient demographics, interventions, comparisons, outcomes, analysis, results and assessment of trial quality (tables 1 and 2).

Quality of the Evidence

Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria were used to evaluate the overall quality of the evidence. This is recommended by the

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Cochrane Handbook to rate the quality of evidence for each important patient-centred outcome as it goes beyond the reporting of quantitative analysis. The quality of evidence was based on 5 domains: limitations of the study design, inconsistency, indirectness (inability to generalise), imprecision (insufficient or imprecise data) of results and publication bias across all studies that measure that particular outcome.[28] The overall quality was considered to be high when at least 75% of the RCTs with no limitations of study design had consistent findings, direct and precise data and no known or suspected publication biases.[27] The grades of quality of evidence are outlined in Appendix 2. [29]

Results

Description of studies

Study selection

Studies were identified through the following databases: Medline (11), Embase (53), Cochrane library (84) (Cochrane reviews (10), other reviews (7), clinical trials (67)). Three studies were included (Table 1). Reasons for exclusion are outlined in Figure 1. Due to differences in the study design of included trials, metanalysis was not attempted.

Risk of bias in included studies

The risk-of-bias assessment is shown in table 2. Although all studies were described as randomised, only two described adequate randomisation.[30 31] One trial was open-label and did not report compliance.[31] One trial had a 20% drop-out rate.[32] All trials had similar groups at baseline, timings of outcome assessments and co-interventions in both groups.

From this assessment two studies have been rated as having a low risk of bias. The one study rated as a high risk of bias scored six, but its open-label design was considered to be a significant methodological flaw.

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Effects of intervention

Tables 3, 4 and 5 summarise the findings with respect to the main outcomes measured. For pain, the two studies with a low risk of bias failed to show any significant improvement with glucosamine compared with placebo, whilst the one study with a high risk-of-bias did show a significant difference with glucosamine compared to no glucosamine.

Back function/disability was measured by Owestry Disability Index (ODI) and RMDQ, both validated tools[26 33]; there was no significant difference in the RMDQ scores with glucosamine as an intervention. The study with a high risk of bias demonstrated a statistically significant difference in the ODI score reduction for the glucosamine group, although this difference was small.[31]

With respect to adverse effects, one trial revealed ~ 30% of participants experienced adverse effects irrespective of whether they were in the placebo or glucosamine group.[30]

Other outcomes that were considered but not across all trials included an assessment of quality of life measured by the Euro-Qol-5 Dimensions (EQ-5D) index and overall health status measured by EQ-VAS.[30] There was no significant difference found between glucosamine and placebo with these outcomes.

One study used several assessments which were totalled to provide an overall summary score.[32] In addition to measuring pain and function, physical examination scores and running times were assessed. There were no statistically significant changes in the LBP group when considering the overall summary score or individual outcome measures.

None of the studies looked at radiographic changes in association with glucosamine use.

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Discussion

In this review three RCTs were included that evaluated the effectiveness of glucosamine as an intervention for chronic low back pain associated with spinal OA. [30 31 32]

Overall, the review found the limited number of studies had methodological deficiencies. The studies did not demonstrate a clear beneficial effect of using glucosamine for LBP due to OA[30 32]. One study however showed a statistically significant difference in the ODI score reduction for the glucosamine group [31], although this difference was small and does not appear to reach the minimally clinical important difference (MCID) alluded to in previous research.[34]

There was conflicting evidence regarding the effect of glucosamine on pain scores. Two studies showed no statistically significant difference on pain scores between the intervention and placebo group. [30 32] One study did show a statistical and clinically significant reduction in pain scores for those taking glucosamine.[31] Whilst this study had significant methodological shortcomings which are discussed in the next section, this alone may not completely explain differences when compared to the two other studies. A possible reason was that the study recruited older patients with a mean age of 64 compared with a much younger demographic in the remaining two studies. Facet joint OA is known to become more prevalent with age[13] and therefore the proportion of patients with pain related to facet joints as opposed to discogenic pain may have been higher. This combined with a theoretical possibility that glucosamine may predominantly affect articular cartilage as opposed to intervertebral discs, may lead to an under representation of the affect of glucosamine in studies with a younger cohort.

Methodological considerations

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There were several factors that contributed to the very low or low quality assessment for the main outcomes measured in the trials. The results of one study [31] in particular which found positive effects of glucosamine on both pain and function appears to contradict the findings of the other two, however, this may be partly explained by its limitations. A key limitation was its open-label design. Since participants and clinicians were aware of group allocation, bias was introduced.

Another study had unclear details about its randomisation.[32] Blinding and randomisation decrease the likelihood of selection and performance bias which would affect the internal validity of the study.[35] This same RCT employed a cross-over design, which may intrinsically have introduced bias if the 5 week wash-out period employed was too short.

To minimize attrition bias, the drop-out rate should be described and acceptable with all the randomised patients analysed in the group to which they were allocated, by an intention to treat analysis (ITT) [35]. One trial did not employ an ITT analysis and compliance was unclear.[31]

There are difficulties in how the trials can be directly applied to the general population and this adversely affects their relevance to practice and external validity. One trial used patients from US Navy diving and special warfare community who have a history of high activity levels and unique occupational exposures. They were also all male; hence the results may not be generalisable.[32] This study used a mixed population of both knee and back pain patients, with some participants having both knee and back pain. The proportion of patients in each group was described and the data was separated.

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Despite the fact that the risk of bias was low in two studies, the studies collectively showed flaws regarding concealment of treatment allocation, adequate randomisation, compliance and drop-out rates. The review findings were significantly influenced by these shortcomings despite the fact that the study by Wilkens et al was of a high quality and well designed. The quality of future RCTs needs to be improved to reduce bias in future reviews.

Review Strengths and Limitations

The selection procedure and literature search utilised in this review may have introduced bias. The selection criteria did not place limits on the ages of participants and as the pathology of low back pain may change with age, direct comparisons between studies of patients with different patient demographics needs to taken with caution.

Relevant, unpublished trials may have been omitted and as these are likely to be small studies without positive results this may lead to publication bias. Studies not published in English were excluded and may also have introduced bias. Utilising references of the included trials to identify other studies may have also led to an over-representation of positive studies.

The search strategy was however vigorous with several databases utilised, in addition to reference screening of included studies which ensured that the omission of relevant studies was minimised.

Implications for Health Practice

LBP is extremely prevalent with considerable financial consequences.[4] OA accounts for a significant proportion of LBP seen by GPs and secondary care clinicians. Current treatment

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options such as NSAIDs and surgery have some potentially serious adverse effects .Therefore alternative treatments such as glucosamine which may provide a possible solution to this problem seem attractive.

Global sales of glucosamine reached almost £1.3billion in 2008.[36] Currently in the UK, glucosamine is available as a food supplement and can be prescribed for knee OA. The evidence for its use in back pain is conflicting, it is therefore imperative that a consensus based on sound clinical evidence is reached to justify this immense cost to the public.

This review helps clarify the existing evidence for the use of glucosamine in back pain which will be of particular relevance to patients and clinicians considering using glucosamine.

The current review has demonstrated that if only the studies with a low risk of bias are considered, there is no evidence of a significant difference between glucosamine and placebo for pain or pain-related disability associated with OA in the lower back.

The mechanism by which glucosamine may exert its effect is poorly understood. Wilkens et al, previously proposed that glucosamine may reduce LBP by inhibiting interleukin (IL)-1β which is present in lumbar discs and facet joints. This mechanism is purely theoretical with no conclusive evidence demonstrating a direct pharmacological effect on the spine. The lack of a sound scientific rationale for the use of glucosamine in LBP makes it difficult to successfully design a study to prove any clinical benefit it may have. In addition, there is much debate as to the relationship between LBP and spinal OA findings. Not all patients with LBP have spinal OA and vice versa, however most studies assume they are correlated.

All of the studies included in the review had limitations. All were single centre trials and two had small sample sizes. There were methodological differences in randomisation, blinding, allocation concealment and varying outcome measures. Inclusion criteria varied between trials some looked at both facet joint OA and degenerative disc disease. These two conditions

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do not necessarily represent the same pathological process. In addition the method for diagnosing the OA differed as there is no existing consensus or criteria for diagnosis. Back pain is complex and whilst spinal OA may cause low back pain, several other structures may be responsible and pathologies may co-exist.

It is possible that glucosamine may work better in more severe disease as has been suggested with knee OA.[37] The studies reviewed all had varying severities of OA symptoms required for inclusion. This limits the conclusions that can be made as the studies did not separate out the data for different levels of severity in the analysis.

OA is a chronic disease and patients taking supplements such as glucosamine may do so for several years. Follow-up periods for the trials varied from eight weeks to one year. Glucosamine may take longer than this to have an apparent affect. A case report revealed an improvement in the structural quality of disc cartilage on MRI in a patient taking glucosamine over a two year period.[38] The patient's symptoms only began to improve at six months and continued until the end of the study period. None of the studies in this review looked at objective radiographic changes as an outcome and whilst there are obvious limitations to drawing any broad conclusions form a single case report, this provides an argument for a longer follow-up RCT and more objective outcome measures.

A strength of this review is that it contained several placebo-controlled RCTs. One especially well-designed study clearly showed that patients treated with glucosamine for one year who had a combination of chronic LBP and either or both facet joint OA and degenerative disc disease, had no difference in pain or disability when compared to placebo.

An important factor to consider when assessing the relevance of trial data to everyday practice is the generalisability or external validity of the studies. The current review included one study which used a relatively young cohort of male patients who were from a US Navy

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diving and special warfare community who had a history of high activity levels and unique occupational exposures. This is not the profile of a typical OA patient a doctor would see in general practice.

An important distinction is between statistical significance and clinical relevance of findings. One study showed a statistically significant difference in pain related disability on the ODI, however the difference was very small and may not have represented a clinically relevant change.[31] Currently there is consensus regarding minimal clinically important changes for pain and function (measured by RMDQ not ODI) in back pain.[27] For LBP, 30% on VAS/NRS for pain is considered as clinically significant and 2 to 3 points (8 -12%) on the RMDQ for function is considered as clinically significant.[39]

Glucosamine may be viewed as a relatively safe medication however the current review nonetheless highlights a high incidence of adverse effects and although these were mild, it is an important consideration when recommending it.

Based on the current evidence explored in this review, there is insufficient evidence to either demonstrate or exclude a clinical benefit of glucosamine for spinal OA. Using more objective measures such as radiography to look at any change in OA progression, refining study inclusion criteria, providing longer follow-up periods and trying to establish a clear biochemical model for glucosamine may enable more definitive conclusions to be drawn so that clinicians can confidently advise their patients based on the best available evidence.

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APPENDICES

Appendix 1. Electronic search strategy

1. exp osteoarthritis, spine
2. degenerative arthritis. mp. or exp osteoarthritis
3. osteoarthr*
4. degenerative joint disease. Mp.
5. degenerative disc disease
6. exp low back pain
7. exp back pain
8. exp spine
9. exp lumbar vertebrae
10. chronic back pain. mp.
11. exp glucosamine/ or glucosamine. mp.
12. glucosamine sulphate. mp.
13.exp acetylglucosamine/ or acetylglucosamine. mp.
14. glucosamine hydrochloride. mp.
15. n-acetyl-d-glucosamine.tw.
16. or/1-5
17. or/6-10
18. or/11-15
19. 16 and 17 and 18

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Appendix 2: Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria

High quality (at least 75% of the RCTs with no limitations of study design have consistent findings, direct and precise data and no known or suspected publication biases)	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality 1 of the domains are not met	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality 2 of the domains are not met	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality 3 of the domains are not met	Any estimate of effect is very uncertain

5 Domains:

Limitations of the study design, inconsistency, indirectness (inability to generalise), imprecision (insufficient or imprecise data) and publication bias.

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References:

1. Macfarlane GJ, Beasley M, Jones EA, Prescott GJ, Docking R, Keeley P, McBeth J, Jones GT. The prevalence and management of low back pain across adulthood: Results from a population-based cross-sectional study (the MUSICIAN study). *Pain* 2012; 153(1):27-32.
2. Papageorgiou AC, Croft PR, Thomas E, Ferry S, Jayson MI, Silman AJ. Influence of previous pain experience on the episode incidence of low back pain: results from the South Manchester Back Pain Study. *Pain* 1996; 66(2-3):181-5.
3. Papageorgiou AC, Rigby AS. Review of UK data on the rheumatic diseases--7. Low back pain. *Br J Rheumatol*. 1991; 30(3):208-10.
4. Maniadakis N, Gray A. The economic burden of back pain in the UK. *Pain* 2000; 84 (1):95-103.
5. Murray CJL, Lopez AD. The global burden of disease. A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge (MA): Harvard School of Public Health on behalf of the *World Health Organization* and *The World Bank*; 1996.
6. Kalichman L, Hunter DJ. Lumbar facet joint osteoarthritis: a review. *Semin Arthritis Rheum*. 2007; 37(2):69-80.
7. Kalichman L, Li L, Kim D, Guermazi A, Berkin V, O'Donnell C, Hoffmann U, Cole R, Hunter D. Facet joint osteoarthritis and low back pain in the community-based population. *Spine* 2008;33(23): 2560–2565.
8. Borenstein D. Does osteoarthritis of the lumbar spine cause chronic low back pain? *Curr Pain Headache Rep*. 2004;8(6):512-517.
9. Goldthwait J. The lumbosacral articulation. An explanation of many cases of lumbago, sciatica, and paraplegia. *Boston Med and Surg J*. 1911;164:365–372.
10. Schwarzer AC, Aprill C, Derby R. Clinical features of patients with pain stemming from the lumbar zygapophyseal joints. Is the lumbar facet syndrome a clinical entity? *Spine* 1994;10:1132–1137.
11. Dreyer SJ, Dreyfuss PH. Low back pain and the zygapophysial (facet) joints. *Arch Phys Med Rehabil*. 1996;77:290–300.
12. Livshits G, Popham M, Malkin I, Sambrook PN, Macgregor AJ, Spector T, Williams FM. Lumbar disc degeneration and genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study. *Ann Rheum Dis*. 2011;70(10):1740-5.
13. Li J, Muehleman C, Abe Y, Masuda K. Prevalence of facet joint degeneration in association with intervertebral joint degeneration in a sample of organ donors. *J Orthop Res*. 2011;29(8):1267-74.
14. Kuijpers T, Van Middelkoop M, Rbinstein S, Ostelo R, Verhagen A, Koes B, Van Turner M. A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. *Eur Spine J*. 2011; 20:40-50.
15. Avins A. Glucosamine and the ongoing enigma of chronic low back pain *JAMA* 2010;304:1.
16. Arendt-Nielsen L, Weidner M, Bartholin D, Rosetzsky. A double- blind randomized placebo controlled parallel group study evaluation the effects of Ibuprofen and glucosamine sulphate on exercise induced muscle soreness. *Journal of Musculoskeletal Pain*. 2007; 15(1):21-28

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17. C+D Data, 2008. *The Product File* [online]. Available: http://www.cddata.co.uk [Product search for "glucosamine": 20 October 2008].
18. NICE Guideline CG59 Osteoarthritis the care and management of osteoarthritis in adults http://www.nice.org.uk/guidance/index Feb 2008.
19. Towheed TE, Anastassiades TP, Shea B, Houpt J, Welch V, Hochberg MC. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2001;(1):CD002946.
20. Towheed T, Maxwell L, Anastassiades T, Shea B, Houpt J, Welch V, Hochberg M, Wells G. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*. 2009, Issue 4. Oxford: Update Software.
21. Stucki G, Sangha O, Stucki S, Michel BA, Tyndall A, Dick W, Theiler R. Comparison of the WOMAC (Western Ontario and McMaster Universities) osteoarthritis index and a self-report format of the self-administered Lequesne-Algofunctional index in patients with knee and hip osteoarthritis. *Osteoarthritis Cartilage*. 1998;6(2):79-86.
22. Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ*. 2010; 16:341.
23. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines for the Scottish Intercollegiate Guidelines Network Grading Review Group. (SIGN) *BMJ* 2001;323:334-336.
24. Roland W. Moskowitz M., Roy D. Altman, M, . Hochberg M. Osteoarthrits: Diagnosis and medical /surgical management *Lippincott,Willliams and Wilkens* 4th Ed 2006.
25. Roland M, Morris R A study of the natural history of backpain: Development of a reliable and sensitive measure of disability in low-back pain. *Spine* 1983;8:141–144
26. Stratford PW, Binkley JM, Riddle DL, Guyatt GH Sensitivity to change the Roland–Morris back pain Questionnaire:Part 1. *Phys Ther* 1998;78:1186–1196.
27. Furlan A, Pennick V, Bombardier C, van Tulder M Updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine* 2009;34(18):1929-1941
28. Atkins D, Best D, Briss P. GRADE Working group. Grading quality of evidence and strength of recommendations. *BMJ* 2006; 328:1490
29. Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, for the GRADE Working Group**.** Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations**.** *BMJ* 2008;336:924-926
30. Wilkens P, Scheel I, Grundes O, Hellum C, Storheim K. Effect of Glucosamine on Pain-Related Disability in Patients with Chronic Low Back Pain and Degenerative Lumbar Osteoarthritis. *JAMA*. 2010;304(1):45-52
31. Tant L, Gillard B, Appelboom T. (2005) Open-label, randomized, controlled pilot study of the effects of a glucosamine complex on low back pain. *Current Therapeutic Res*. 2005;66(6):511-521

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32. Leffler C, Philippi A, Leffler S, Mosure J, Kim P. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo controlled pilot study. *Mil Med*. 1999;164(2):85-91.
33. Fairbank J, Couper J, Davies J, O'Brien J The Owestry low back pain disability questionnaire. *Physiotherapy* 1980;66: 271-273.
34. Lauridsen HH, Manniche C, Korsholm L, Grunnet-Nilsson N, Hartvigsen J. What is an acceptable outcome of treatment before it begins? Methodological considerations and implications for patients with chronic low back pain. *Eur Spine J*. 2009 Dec;18(12):1858-66.
35. Hart A. Making sense of statistics in health care *Radcliffe Medical Press* 2001.
36. Heller L. US glucosamine grows slow, lags global sales. 2009. www.nutraingredients-usa.com/Consumer-Trends/US-glucosamine-grows-slow-lags-global-sales.
37. Clegg D, Reda D, Harris C. Glucosamine, Chondroitin Sulfate, and the Two in Combination for Painful Knee Osteoarthritis. *New England Journal of Medicine*, 2006; 354:795-808.
38. Van Blitterswijk W, van de Nes J, Wuisman P. Glucosamine and chondroitin sulphate supplementation to treat symptomatic disc degeneration: Biochemical rationale and case report. *BMC Complementary and Alternative Medicine* 2003;3:2 ;1-8
39. Ostelo R, Deyo R. Stratford P Interpreting change scores for pain and function status in low back pain: towards international consensus regarding minimal important change. *Spine* 2008;33: 90-94

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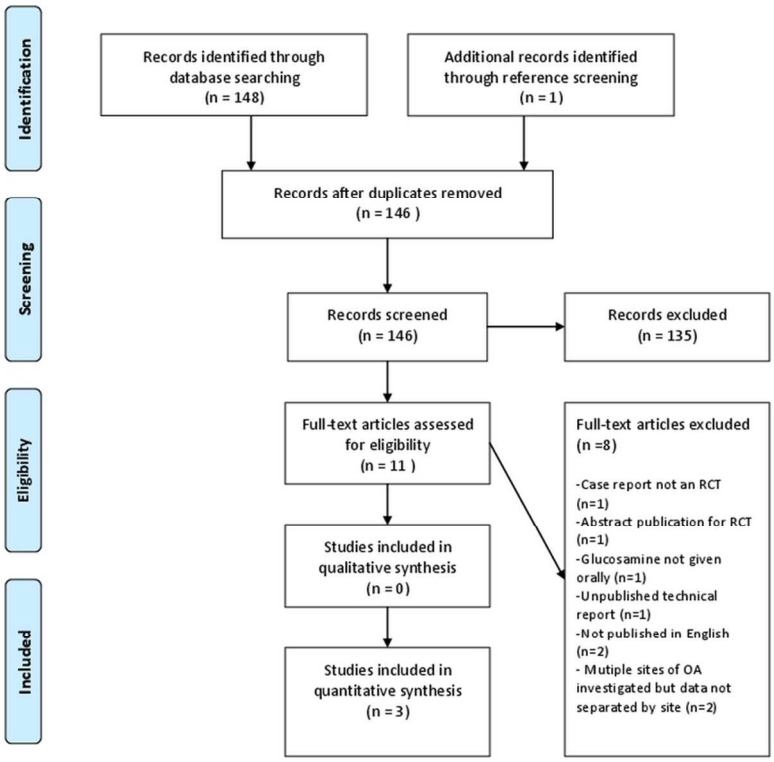
Figure 1: Flow diagram of inclusion and exclusion of articles for glucosamine use in spinal OA (PRISMA 2009 Flow Diagram) (Moher et al)



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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90x116mm (300 x 300 DPI)

Appendix 3 – Prisma 2009 Checklist (Moher et al)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	-
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6,7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	-
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7,8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	-

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Appendix 3 – Prisma 2009 Checklist (Moher et al)

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	-

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2&6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 3,4,5
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10,11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10,11,12,part B
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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