

Are chondroitin and glucosamine in combination effective in the treatment of osteoarthritic pain?

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Non-steroidal anti-inflammatory drugs today are contraindicated for osteoarthritic pain in elderly patients with cardiovascular disease due to adverse effects. An internet review of the evidence regarding the use in osteoarthritis of oral chondroitin and glucosamine in combination produced three relevant randomised controlled trials with valid results. After critical appraisal for reliability and applicability, chondroitin-glucosamine was found to significantly reduce pain in moderate knee osteoarthritis, while significantly improving disability in mild to moderate cases. If the results are generalisable to osteoarthritis of all joints, combined chondroitin-glucosamine in purified therapeutic doses should help care for osteoarthritis patients safely and at moderate expense.

Introduction

Osteoarthritis (OA), the commonest form of arthritis, is the medical condition associated with the highest risk of disabling

immobility over the age of 65 years when the knee joint is involved.¹ Beyond disability, OA also affects quality of life, with consequences on emotional well-

being and body image, relationships, social activities and socio-economic status.²

Of non-surgical treatments for OA, non-steroidal anti-inflammatory drugs (NSAIDs) are effective in reducing pain (as is paracetamol) and inflammation³. However, besides their well-documented adverse effects on the gastrointestinal tract,⁴ some NSAIDs have been said to worsen OA through accelerating cartilage degeneration or analgesia-associated joint overuse.⁵ Recently NSAIDs have also been associated with increased risk of myocardial infarction.³ In fact, the latest NSAIDs of the selective COX-2 inhibitor group are now contraindicated in vascular disease,⁴ which of course is predominant in the elderly.

Therefore, as NSAIDs can no longer be used for OA in elderly patients with cardiovascular disease, and if paracetamol is found to be ineffective, in such cases there certainly would be a place for another form of oral treatment. Chondroitin and glucosamine are such alternative therapies for osteoarthritis made popular with the general public as a result of media publicity.^{1,6,7}

Glucosamine stimulates the production of glycosaminoglycan, a constituent of joint cartilage, while the degradation of glycosaminoglycan is inhibited by chondroitin, thus leading to the hypothesis of a synergistic effect when these are used in combination.^{7,8} Glucosamine and chondroitin thus may be effective in slowing the degenerative process of OA as disease-modifying osteoarthritis drugs, and could have an important effect in postponing the need for joint replacement in severe OA.⁷

A review of the evidence was thus performed regarding the use of oral forms of chondroitin and glucosamine in combination as an alternative treatment for osteoarthritis, which would effectively tackle the pain without causing the adverse effects associated with traditional analgesics.

Methodology

The review was carried out through an internet search of secondary and primary sources, followed by a critical evaluation of the results. Primary sources consist of original research studies, of which Randomised Controlled Trials (RCTs) are

Table 1: Details of the four evaluated randomised double-blind controlled trials

<i>Author/s ± Name</i>	<i>Subjects</i>	<i>Inclusion criteria</i>	<i>Method</i>
Leffler <i>et al.</i> ⁵	34 US Navy males in their 40s	Chronic pain for at least 3 months due to radiographic mild to moderate degenerative joint disease of the knee and/or lower back	One group treated with capsules of glucosamine 1500mg/day, chondroitin 1200mg/day and manganese 228mg/day, with the other given placebo capsules, for 8 weeks. Patients then crossed over to the alternative regimen for an additional 8 weeks, with the study thus lasting 16 weeks in all*
Das & Hammad ⁷	93 patients (aged 45 to 75 years, of both sexes), from a single orthopaedic practice in the USA	Radiographic evidence of mild to severe osteoarthritis (OA) of the knee and symptoms for more than 6 months	Intervention group was prescribed capsules of glucosamine 2000mg/day, chondroitin 1600mg/day and manganese 304mg/day, with the other group receiving placebo capsules, for 6 months
Rai <i>et al.</i> ¹⁶	100 out-patients (ages 50 years plus) from an orthopaedic department in north India	Clinical and radiological OA of the knee	Chondroitin and glucosamine (at unspecified doses) to intervention group and placebo capsules to control group, for 1 year
Clegg <i>et al.</i> 'Glucosamine/ chondroitin Arthritis Intervention Trail' (GAIT) ⁶	1583 patients (from both sexes, 40-70 years old) in 16 US centres	Over 6 months' symptoms of radiographic OA knee	5 groups received one of the following treatments for 24 weeks: glucosamine 1500mg/day, chondroitin 1200mg/day, glucosamine 1500mg/day plus chondroitin 1200mg/day, celecoxib 200mg/day, or placebo

*The trial attempted to minimise post-treatment crossover effects through washout periods before data collection (5 weeks for dairy data and 7 weeks for examination data)

regarded as the gold standard. Secondary sources comprise reviews or meta-analyses of primary studies (normally RCTs).

Secondary source search and evaluation

The Cochrane Database of Systematic Reviews (<http://www.cochrane.org/>) was searched for the combined terms "osteoarthritis", "chondroitin" and "glucosamine" in all fields. Only two reviews (by Singh *et al.*⁹ and Towheed *et al.*¹⁰) looked at the use of chondroitin and glucosamine for the treatment of osteoarthritis. However, as the therapies were assessed on an individual basis (chondroitin and glucosamine respectively) and not in combination, they were unsuitable for consideration by this study.

Subsequently the Database of Abstracts of Reviews of Effects (DARE) (<http://nhscrd.york.ac.uk/>) was searched for these same combined terms in all fields, and produced two hits, namely McAlindon *et al.*¹¹ and Richy *et al.*¹² As these two meta-analyses appraised studies of separate (not combined) use of chondroitin and glucosamine, they too could not be

considered for this review. The next section will thus focus on the primary search for relevant evidence.

Primary source search and evaluation

A search was performed of Medline through PubMed (<http://www.pubmed.gov/>) for the Medical Subject Headings (MeSH) terms "Osteoarthritis/therapy"[MeSH] AND "Chondroitin/therapeutic use"[MeSH] AND "Glucosamine/therapeutic use"[MeSH] using the following limits: '10 Years, only items with abstracts, English, Randomized Controlled Trial, Humans'. This search resulted in six randomised controlled trials.^{5-8,13,14} Two other pertinent RCTs^{15,16} were identified through a search of the Cochrane Central Register of Controlled Trials (CENTRAL) 2006 Issue 1 (<http://www.cochrane.org/>) using the combined terms "osteoarthritis", "chondroitin" and "glucosamine" in an 'all field' search.

Of these eight relevant RCTs, four were eliminated immediately as three did not consider the effect of combined glucosamine and chondroitin as oral therapy^{13,15} for radiologically confirmed

osteoarthritis,⁸ while the fourth just looked for a possible side effect on glycosylated haemoglobin levels.¹⁴ The remaining four trials which were suitable for evaluation are described in Table 1. These four RCTs were then critically appraised for the validity, reliability and applicability of their results.

Critical appraisal of validity of results

The validity of the results of the RCTs was critically appraised using questions developed by Rosenberg & Donald¹⁷ shown in Table 2. Of the four trials, that by Rai *et al.*¹⁶ did not account properly for all patients who entered the trial and attribute them at its conclusion. Moreover, it was the only one of the four studies which did not specify the doses of chondroitin and glucosamine administered. As such, this study was eliminated from further consideration.

Critical appraisal of reliability and applicability of results

This critical appraisal of the reliability and applicability of the three remaining trials is based on the check-list of questions

Table 2: Critical appraisal of result validity of the relevant RCTs based on questions developed by Rosenberg & Donald¹⁷

Are the results valid?	Leffler <i>et al.</i> ⁵	Das & Hammad ⁷	Rai <i>et al.</i> ¹⁶	Clegg <i>et al.</i> ⁶
1. Was the assignment of patients to treatments randomised?	Yes	Yes	Yes	Yes
2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?	Yes	Yes	No	Yes
3. Was follow-up complete?	Yes	Yes	Yes	Yes
4. Were patients analysed in the groups to which they were randomised?	Yes	Yes	Yes	Yes
5. Were patients, health workers and study personnel blinded to treatment?	Yes	Yes	Yes	Yes
6. Were the groups similar at the start of the trial?	Yes	Yes	Yes	Yes
7. Aside from the experimental intervention, were the groups treated equally?"	Yes	Yes	Yes	Yes

(Rosenberg & Donald)¹⁷ shown in Table 3. All three RCTs were performed for a minimum of 8 weeks and a maximum of 6 months, giving enough time for the medication to have an effect, and included at least two recommended outcome measures¹⁸ (see Table 4 for details).

The Leffler *et al.*⁵ study of mild to moderate OA showed a statistically significant improvement in visual analogue scale for pain ($p=0.02$) for knee and back data in subjects in the intervention group. This was attributed mainly to the knee data which, when examined individually, showed a mean reduction in the visual analogue score for pain of -26.6% during clinic visits (95% CI -53.0% to -0.20%; $p=0.048$) and -28.6% in a diary kept by subjects (95% CI -52.7% to -4.50%; $p=0.02$).

In the Das & Hammad trial⁷, there was a statistically significant drop in the Lequesne disability index in subjects with mild to moderate OA (N=72) treated with chondroitin/glucosamine compared to the placebo group, from 10.2 (± 0.4) at baseline, to 7.2 (± 0.6 ; $p=0.003$) at 4 months, and 7.4 (± 0.6 ; $p=0.04$) at 6 months.

In the GAIT large multi-centre study, Clegg *et al.*⁶ found that, in subjects with moderate to severe OA (N=352), chondroitin and glucosamine in combination were significantly more effective than placebo (24.9 % points higher in the WOMAC pain score, $p=0.002$). For mild to severe OA, combined chondroitin-glucosamine also showed a higher rate of response compared to placebo than either of its individual components, but this improvement did not reach significance (when taken as $p<0.05$).

Table 3: Critical appraisal of the reliability and applicability of the relevant RCTs (Rosenberg & Donald)¹⁷

Are the results reliable?

- How precise was the treatment effect?
- How large was the treatment effect?

Are the results applicable?

- Can the results be applied to my patient care?
- Will the results help me care for my patients?
- Were all clinically important outcomes considered?
- Are the likely benefits worth the potential harms and costs?

Table 4: Outcome measures recommended for osteoarthritis trials by the Osteoarthritis Research Society¹⁸ and their use by the three appraised trials

Outcome measure	Used by
Global pain score for index joint (visual analogue or Likert scale)	Clegg <i>et al.</i> ⁶ Das & Hammad ⁷ Leffler <i>et al.</i> ⁵
Pain on walking for index joint (visual analogue or Likert scale)	None
Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index Pain Subscale (visual analogue or Likert scale)	Clegg <i>et al.</i> ⁶ Das & Hammad ⁷
Lequesne index (questionnaire-based disability score)	Das & Hammad ⁷ Leffler <i>et al.</i> ⁵
Pain in index joint during activities other than walking (visual analogue or Likert scale)	None

Discussion

When the results of the three RCTs are taken together, chondroitin and glucosamine in combination were found to:

- significantly reduce pain in mild to moderate OA measured by the global pain

visual analogue scale⁵, and in moderate to severe OA measured by the WOMAC Scale;⁶

- significantly improve disability in mild to moderate OA as measured by the Lequesne Index.⁷

As patients in the community have similar characteristics to the subjects within the three trials (males and females aged over forty, with painful mild, moderate or severe osteoarthritis of the knee), the results can be applied to such patient care. However the quality and standardisation of commercially-available food supplements such as chondroitin and glucosamine are questionable, and thus effects in practice may not be equivalent to RCTs' results based upon purified and assayed preparations.^{6,7,19,20}

Nevertheless, if the results are taken to be generalisable to OA of all joints, and if the chondroitin-glucosamine combination used in practice is pure and potent, the results should help care for patients in practice as long as the optimal therapeutic

doses are used. This would involve doses ranging from glucosamine 1500mg/day and chondroitin 1200mg/day^{5,6} to glucosamine 2000mg/day and chondroitin 1600mg/day.⁷

As signs and symptoms of side effects were rare and mild, and were similar between the intervention and placebo groups, the benefit-risk ratio seems favourable. However, one needs to consider the adverse effects of long term use, such as on diabetes control¹⁴, and also any effects resulting from drug interactions. Regarding financial aspects, chondroitin and glucosamine each cost up to \$25 each month.¹⁹ Studies need to be carried out to establish if this expense may be considered as an investment in view of a possible reduction of any expensive management options necessitated by complications of osteoarthritis.

Conclusion

There are good indications that combined oral preparations of chondroitin and glucosamine may be effective and quite useful in the treatment of osteoarthritis due to their safety and moderate expense, as long as their purity and potency are ensured. In order to facilitate any possible recommendations for their use in clinical practice, long-term and larger studies are needed to elaborate more definite results and investigate their preventive use as disease-modifying osteoarthritis drugs.

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