Superiority trials in osteoarthritis using glucosamine hydrochloride as comparator: an overview of reviews and indirect comparison with Rosa canina

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Abstract
Introduction
In the absence of randomised trials making head-to-head comparisons, we wanted to evaluate the pain-reducing effect of glucosamine hydrochloride (GH) and the use of the Rosa canina (RP) therapy in patients with osteoarthritis by using an indirect comparison meta-analysis.

Materials and methods
Randomised controlled trials included in published meta-analyses were eligible for inclusion. The standardised mean difference (SMD) was used as an effective measure, and the difference between GH and RP was calculated using the Bucher approach.

Results
There was no heterogeneity for any nutraceuticals. GH studies were consistently around an effect size of zero [SMD = −0.01 (−0.14; −0.12)], whereas RP studies consistently pointed towards an effect size of 0.4 [SMD = −0.37 (−0.60; −0.13)]. Testing whether there was any significant difference between GH and RP (both in contrast to placebo), we applied the Bucher approach, which resulted in an effect size of 0.36 in favour of RP [SMD = 0.36 (0.09; 0.62), Z = 2.65; P = 0.0082].

Conclusion
GH should not be used in clinical practice. However, we see no harm in having patients continuing with GH therapy as long as they perceive a benefit and cover the costs of the treatment themselves. It may be used as an ethically ineffective active comparator in osteoarthritis trials.

Introduction
Osteoarthritis (OA) is a common joint disorder and may occur in any synovial joint in the body, although the condition is most common in hands, knees, hips and spine. The clinical problems, along with the pathological and radiographic changes, include joint pain, stiffness, movement with a restricted range and cracking of joints (crepitus) and decreased function with loss of muscle strength. Drug therapy in OA mainly consists of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). Pharmacological therapy for pain relief is widely perceived to be the backbone of effective management. Unfortunately, many of the most effective pain relievers, especially NSAIDs, have well-known side effects that limit their use. In OA, specific food substances such as nutraceuticals are expected to affect the course of the disease in the degenerating joints. Nutraceuticals are functional ingredients commercially available as powders, pills and other medicinal forms and are generally not associated with food.

Glucosamine, which is classified as a ‘dietary supplement’ in the United States and as a pharmaceutical in some European countries, is available over the counter, appears to be safe and is widely marketed for pain relief in OA. However, its efficacy is uncertain; heterogeneity among trials of glucosamine is larger than that expected by chance. Among trials with involvement of pharmaceutical industries, effect sizes are consistently higher. Potential explanations include different glucosamine preparations, inadequate allocation concealment and industry bias.

On the basis of three randomized controlled trials (RCTs), Vlad et al. concluded that glucosamine hydrochloride (GH) has consistently no effect on pain, and the absence of heterogeneity (i.e. homogeneity) among these trials suggests that this summary effect is robust and valid; i.e., future studies of this preparation are unlikely to yield useful results. In contrast, the hip powder Rosa canina [or rosehip powder (RP)] has shown promising results as a pain-killing nutraceutical—based on three RCTs with homogeneous efficacy results—without any contradictory results.

As guidelines such as those from the Osteoarthritis Research Society International are intended to provide concise, patient-focused, up-to-date, evidence-based, expert consensus recommendations for the management of hip and knee OA, an empirical comparison of the observed efficacy from the assumed well-known GH and any new nutraceutical compound seems relevant.

Scientifically, efficacy is most convincingly established by demonstrating superiority to placebo in a placebo-controlled trial, by showing superiority to an active control treatment or by demonstrating a dose-response relationship. This type of trial is referred to as a superiority trial: a trial with the primary objective of showing that the

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response to the investigational product is superior to a comparative agent (active or placebo control)\textsuperscript{12}. In some cases, an investigational product is compared with a reference treatment without the objective of showing superiority. This type of trial is referred to as a non-inferiority trial: a trial with the primary objective of showing that the response to the investigational product is not clinically inferior to a comparative agent (active or placebo control)\textsuperscript{12}.

Active comparators should be chosen with care. We sepculate that as GH is widely used and broadly displays lack of efficacy, we are confident that this result will be consistent across all trials.

Using overview of reviews methodology, our objectives were firstly, to evaluate the analgesic effect of GH products opposed to that of RP compounds used in OA treatment via an indirect comparison meta-analysis, and secondly, to include these estimates in a concise epidemiological study\textsuperscript{13} applicable for researchers designing a superiority trial with the objective of using GH as an ineffective ‘active comparator’ in a head-to-head comparison with a new nutraceutical in OA treatment.

Materials and methods

This work conforms to the values laid down in the Declaration of Helsinki (1964).

The protocol of this study has been approved by the relevant ethical committee related to our institution in which it was performed. All subjects gave full informed consent to participate in this study.

This overview of reviews was designed to compile and compare the evidence from published systematic reviews on GH and RP for pain reduction in OA\textsuperscript{16}.

Searches and selection of meta-analyses

The Cochrane Library, Medline, EMBASE and CINAHL were searched using a combination of keywords and text words related to OA, which were combined with validated filters for controlled clinical trials and meta-analyses. Details of the search strategy are described in previous papers\textsuperscript{10,11,14}. A specific search methodology for locating published systematic reviews with meta-analyses on these OA topics is described elsewhere\textsuperscript{15}.

Meta-analyses of randomized or quasi-randomized trials in patients with OA of the knee or hip were eligible if they evaluated patient-reported pain\textsuperscript{16} in patients allocated to GH\textsuperscript{9} or RP\textsuperscript{16} compared with patients allocated to placebo.

Data collection and quality assessment

A standardised form was used to extract data from the original reports of individual trials on authors of the study, year of publication, trial design, study length, number of patients randomised (i.e. the ITT population, \(N_{\text{total}}\)), number of patients for whom detailed outcome data were available for meta-analysis in each group [E(exposed) and C(control)] included in the individual-study statistical tests (\(N_{\text{e}}\) and \(N_{\text{c}}\) respectively), average patient age, sex and site of OA. When necessary, we approximated means and measures of dispersion from figures and \(P\)-values. For crossover trials, we extracted data from the first period only\textsuperscript{17}. Disagreements were resolved by discussion with a third reviewer and subsequent consensus.

The risk of bias assessment according to the quality of included studies is described in detail elsewhere\textsuperscript{6,10}, including assessment of appropriateness of randomisation, masking and handling of withdrawals.

Data synthesis

We expressed treatment effects as SMDs by dividing the difference in mean (MD) values by pooled standard deviation (SD)\textsuperscript{12}. Negative SMD values indicated a beneficial (pain-reducing) effect of the experimental intervention. The corresponding variance (SE\textsuperscript{2}) was calculated based on the individuals SMD and number of patients included\textsuperscript{10,11}. As the unadjusted (Cohen’s) SMD in principle does not treat the variance (SE\textsuperscript{2}) as an estimate, we applied (i.e. via multiplication) the Hedges’ bias-correction by default, adjusting for small sample bias\textsuperscript{19}.

We used a standard inverse-variance random effects meta-analysis technique to combine effect sizes across trials and calculated the variance estimate \(\tau^2\) as a measure of heterogeneity\textsuperscript{20}, for GH and RP, respectively. The \(I^2\) index for evaluation of the amount of heterogeneity was also calculated\textsuperscript{21}, which describes the inconsistency via the percentage of total variation across trials that is attributable to heterogeneity rather than chance\textsuperscript{22}.

In the absence of randomised trials making head-to-head comparisons, an indirect comparison is possible using a common comparator\textsuperscript{23,24}. The indirect method may produce less biased results than direct comparisons when evaluating new pharmaceutical interventions\textsuperscript{25}. As described above, we performed two separate meta-analyses, one combining trials of GH versus placebo to obtain estimated SMD(GH) and the second comparing RP versus placebo yielding an estimated SMD(RP).

The estimated difference in effect of GH and RP, SMD(GH-RP) was calculated using the Bucher approach\textsuperscript{23}, comparing the two estimated SMDs as follows:

\[
\text{SMD(GH-RP)} = \text{SMD(GH)} - \text{SMD(RP)}
\]

\[
\text{Var(SMD(GH-RP))} = (\text{SE(GH)})^2 + (\text{SE(RP)})^2
\]

\[
\text{SE(SMD(GH-RP))} = \sqrt{\text{Var(SMD(GH-RP))}}
\]

where ‘Var’ (as in variance) indicates the square of the standard error. From these values we calculated a 95% confidence interval for SMD(GH-RP). This analysis can be seen as the simplest form of meta-regression with a single binary trial factor or, equivalently, as an examination of the interaction between treatment effect and type of nutraceutical\textsuperscript{26}.

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Modelling the empirical data distribution
To explore potential model distributional differences between the observed efficacy data for GH and RP, we used Monte Carlo simulation to generate and model the assumed normally distributed data for the SMD values, and subsequently non-parametric descriptive statistics to describe the empirical 95% confidence intervals (using the 2.5 and 97.5 percentiles in the overall distribution of mean values) for each of the products, GH and RP, respectively.

Results
Description of included reviews
As described by Vlad et al.,5 there were three RCTs eligible for inclusion, all applying GH27–29. The extension data from the GAIT study30 were considered ineligible for our meta-epidemiological study, as the data available on pain were considered secondary to those in the Clegg et al. paper29. This is in agreement with the Cochrane review recently updated by Towheed et al.8 One minor discrepancy between Vlad et al. and Towheed et al. is that Towheed (first author on the Cochrane review) considers the McAlindon trial28 to be a glucosamine sulphate trial, in contrast to Vlad et al. who describes it as a hydrochloride trial. As TE McAlindon is co-authoring the paper published by Vlad et al., the judgement by Vlad and co-authors on the labelling of the product used is preferred3,28. However, the actual data (means and SDs) used in this meta-epidemiological study for GH were adapted from the published tables of Towheed et al. In terms of comparing RP with placebo—or any other active compound—no new RCTs were available since the meta-analysis by Christensen et al.10; thus, three studies were eligible for inclusion31–33. A recent RCT34 assessed the symptomatic efficacy in rheumatoid arthritis patients; thus, it was not considered to be eligible for inclusion in the present meta-epidemiological study.

Effects of interventions
Figure 1 illustrates a typical meta-analysis plot—a so-called forest plot35—where the individual study effect sizes are illustrated by squares, and the statistical uncertainty is presented with 95% confidence intervals; i.e. if the 95% confidence intervals are not overlapping the null-line, the statistical test (for the null hypothesis) would correspond to a P-value of <0.05. The area of the square is proportional to the precision assigned to that study in a fixed-effect meta-analysis (1/SE2). These forest plots include the result of the overall effect from the GH and RP meta-analyses at the bottom of the graph; a diamond is used to distinguish it from the individual studies. As anticipated, there is no need to worry about heterogeneity for any nutraceuticals. As indicated by the I² value (0%), there was no inconsistency: GH studies are consistently located around an effect size of zero [SMD= −0.01 (−0.14 ; 0.12)], whereas RP studies consistently point towards an effect size of 0.4 [SMD = −0.37 (−0.60 ; −0.13)]. As illustrated by the dotted line indicating all studies combined, there seems to be a clear difference between the empirical data derived from these nutraceuticals.

Comparing the two separate meta-analyses
As presented in Figure 1, two clear distinctions between GH and RP are obvious: one being that the number of included patients in the RP trials (287 patients) is far less than that included in the GH trials (933 patients)—with the majority of clinical observations (76%) being from

Figure 1: Two meta-analyses (of 3 trials) testing a nutraceutical against placebo for pain reduction in OA patients [SMD (95% CI)]. The area of the block is proportional to the weight assigned to that study in the meta-analysis. The dotted line indicates the overall random-effects analysis if one (falsely) were to combine both GH and RP in the same meta-analysis (Q = 7.662, I² = 35%), ignoring the clinical difference between nutraceuticals.

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GH trials. The other major difference is the clear distinction between where the observed effect sizes are situated; eye-balling the data clearly indicates a systematic difference between GH and RP. To formally test whether there is any difference between GH and RP (both in contrast to placebo), we applied the Bucher approach, resulting in an effect size of 0.36 in favour of RP [SMD = 0.36 (0.09; 0.62), Z = 2.65; P = 0.0082].

**Empirical data distribution**

When combining the six individual data sets, we were able to analyse the data set in a more classically statistical way. Figure 2 illustrates the empirical data distributions revealing (again) that trials testing GH compared with those testing placebo cannot be expected to add value to the patients (empirical mean = −0.03, SE = 0.16, Z = 0.18, P = 0.86); whereas, RP still seems a promising therapeutic strategy to be explored in more detail with an expected effect size of −0.37 (empirical mean = −0.37, SE = 0.21). In contrast to the basic statistical meta-analysis model, this simulated empirical model indicates that there is some evidence that RP could be more efficacious than placebo; however, till date, no truly convincing data have been reported (Z = 1.77, P = 0.076).

**Figure 2:** Empirical data distributions comparing GH with placebo (empirical mean = −0.03, SE = 0.16, Z = 0.18, P = 0.86); RP seems to be a promising therapeutic strategy to explore in more detail (empirical mean = −0.37, SE = 0.21).

**Discussion**

This paper clearly illustrates the ineffectiveness of GH in the treatment of OA. As this type of glucosamine is still widely used, it is obvious that it could be easily applied as an ineffective active comparator in a (pseudo-) superiority trial, where a novel nutraceutical may want to benchmark against a widely used nutraceutical.

We provide such an example based on a previous meta-analysis on RP for OA—apparently a promising nutraceutical—although it still remains to show efficacy in a promising phase-3-like trial. As evident from these data, manufacturers of a new nutraceutical with an anticipated pain-reducing capacity over GH (ES ≥ 0.36) would need to include 163 patients in each group—for a two-group comparison—to be able to show that RP is superior to GH (i.e. given a power of 90% and P < 0.05). In comparison, if the authors want to lower power a priori to around 80%, then they would require 122 patients in each group36.

The quality of the evidence of inefficiency of GH is very consistent and robust and should exclude potential biases in the process. The data from three studies of RP are equally consistent, while studies from independent sources are lacking.

**Conclusion**

GH should not be used in clinical practice. However, we echo the conclusion from Wandel et al., according to which we see no harm in having patients continuing with GH therapy as long as they perceive a benefit and cover the costs of the treatment themselves. GH may be used as an inactive comparator in trials. Further evidence of the effect of nutraceuticals should be gathered in studies independent of the industry manufacturing products.

**Abbreviations list**

GH, glucosamine hydrochloride; OA, osteoarthritis; NSAIDs, non-steroidal anti-inflammatory drugs; RCTs, randomized controlled trials; RP, rosehip powder; SMD, standardized mean difference.

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**References**

Systematic Review


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