Wu D, Huang Y, Gu Y, and et al. Efficacies of different preparations of glucosamine for the treatment of osteoarthritis: a meta-analysis of randomized, double-blind, placebo-controlled trials. *Int J Clin Pract* 2013; 67:(6) 585–594.

Design: Systematic review and meta-analysis of randomized clinical trials
Date: 1-23-15 LM

Study Question: To determine the efficacies of 2 different preparations of glucosamine (glucosamine sulphate (GS) and glucosamine hydrochloride (GH)) for the treatment of knee or hip osteoarthritis (OA) on pain and physical function, and investigate the possible reasons for heterogeneity among trials.

PICOs:

- Patients: Participants were adults with knee or hip osteoarthritis as defined by the original authors
- Interventions: 1) glucosamine sulphate (GS); and 2) glucosamine hydrochloride (GH).
- Comparison interventions: A placebo control group
- Outcomes: The primary outcome was global pain reduction assessed by the visual analogue scale (VAS pain) or the Western Ontario McMaster University Osteoarthritis Index (WOMAC pain). The secondary outcome was physical function measured by the Lequesne Index (LI). Outcomes were assessed at the endpoint of trials ranging from 4 to 156 weeks.
- Study types: Randomized controlled trials comparing glucosamine alone to a group receiving only placebo.

Study selection:

- Databases included Medline, Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews for articles published up to March 2012. There were no language restrictions. A manual search of scientific conferences held during the last 3 years was conducted to detect trials reported more recently at yearly scientific conferences.
- Two authors independently reviewed the articles to extract all relevant details. Disagreements were resolved by consensus.
- Two authors independently assessed articles on trial quality. Risk of bias was assessed applying the criteria from Jadad which considers the following domains; random sequence generation, allocation concealment, blinding of participants, providers, and outcome assessors, description and % of withdrawals, dropouts, and intention to treat analysis.
- Trials were considered to be ‘adequate’ if the article described an approach to protect the randomization process, so that the treatment allocated remained unknown before the subjects were entered into the study, such as sequentially numbered, opaque sealed envelopes. If the approach did not meet these criteria or was not described, it was labelled as ‘inadequate’.

- Trials were included if they were designed as randomized, double-blind and placebo –controlled.
- Studies that investigated glucosamine together with another agent were included if the study also included a group of subjects treated with glucosamine alone compared with a group receiving only placebo.
- The effect of the intervention was calculated as the standardized mean difference (SMD) allowing pooling of individualized trials. Effect sizes of
    - 0.2-0.5 = small
    - 0.5-0.8 = moderate effect (clinically important)
    - > 0.8 = large effect
- Negative values (ES < 0) of the effect sizes indicated a benefit of glucosamine treatment, whereas positive values (ES > 0) indicated a benefit of placebo.
- Between-study heterogeneity was assessed using the I^2 statistic. I^2 values of 25%, 50% and 75% indicate low, moderate and high heterogeneity, respectively.
- A meta-analysis was conducted to obtain the average effect for the two different glucosamine preparations.
- Subgroup analyses were performed by stratifying the available data according to joint affected, allocation concealment, ITT analysis, and trial duration. A random-effect model was used to pool the data for the meta-analysis. Possible publication bias was also investigated.

Results:

- 215 citations were retrieved and screened for inclusion. Overall, 19 trials with 3159 participants reported between 1980 and 2010 met criteria and were included. 15 trials (1941 participants) evaluated GS, and 4 trials (1218 participants) evaluated GH, all compared to placebo controls. The trials ranged in size from 20 to 630 subjects.
- Seventeen articles evaluated knee OA alone, one study evaluated hip OA alone, and one assessed knee or hip OA.
- Of the 19 trials, 14 had adequate allocation concealment and 14 also performed ITT analysis.
- For the primary outcome of pain reduction, 17 studies (2752 participants) evaluating either GS or GH contributed to the overall meta-analysis, and no treatment effect was found (-0.16, 95% CI -0.34 to 0.01). An I^2 of 78.3% indicated high heterogeneity.
    - Thirteen GS studies (1534 participants) showed no pooled treatment effect for pain reduction compared with placebo (-0.22, 95% CI -0.48 to 0.04). However, pooling of the results was not recommended because of their high degree of heterogeneity (I^2 = 82.3%).
    - A pooled effect size of -0.03, (95% CI -0.14 to 0.08) in 4 GH studies (1218 participants) showed no significant effect vs. placebo on pain reduction, with a heterogeneity of zero.
- Stratified analyses showed that duration of treatment period, allocation concealment, and ITT analysis had a significant influence on the effect sizes for pain or function.
    - Stratified analyses for the pain outcome was performed in the 13 GS studies (1534 participants), since heterogeneity was absent in the GH studies.
        - Stratified analysis on trial duration showed a pooled effect size of

-0.38 (95% CI -0.99 to 0.23) in 7 trials (470 participants) lasting less than 24 weeks, but the I^2 remained high (I^2 = 88.5%). No significant treatment effect 0.09 (95% CI -0.21 to 0.03) was found in 6 trials (1063 participants) lasting longer than 24 weeks compared with placebo, with a heterogeneity of zero. It appears that the shorter trials inflated the effect size and increased the heterogeneity.

  - Stratified analysis by joint affected divided the trials into knee OA alone, and knee or hip OA groups. Eleven knee alone trials (1284 participants) showed a pooled effect of -0.26 (95% CI -0.56 to 0.04), compared with a pooled effect of 0.03 (95% CI -0.22 to 0.28) for two knee or hip trials (250 participants). Heterogeneity remained high in knee alone trials (I^2 = 84.3%), but was absent in knee or hip trials.
  - Stratified analysis by allocation concealment compared trials with adequate allocation concealment vs. those with inadequate allocation concealment. Nine adequate trials (1282 participants) showed a pooled effect of -0.12 (95% CI -0.42 to 0.19), compared with a pooled effect of -0.52 (95% CI -1.10, 0.06) for 4 inadequate trials (252 participants). Heterogeneity remained high in both (85.2% and 76.5%), but inadequate trials inflated the effect size.
  - Stratified analysis by ITT analysis compared trials that conducted ITT analysis vs. those that did not conduct ITT analysis. Ten trials with ITT analysis (1372 participants) showed a pooled effect of -0.17 (95% CI -0.46 to 0.11), compared with a pooled effect of -0.54 (95% CI -1.51, 0.43) for 3 trials without ITT analysis (162 participants). Heterogeneity remained high in both (84.4% and 80.6%), but trials without ITT analysis inflated the effect size.

- The secondary outcome of functional improvement could not be assessed on the 4 GH studies, because these studies did not report LI function reduction.
- Five studies (975 participants) analyzed the efficacy of GS in terms of LI reduction as a functional improvement outcome, all of which were treating knee OA. Pooling the data for these 5 trials produced an effect size of -0.47 (95% CI -0.82 to -0.12) with a high degree of heterogeneity (86.2%).
  - Stratified analysis by trial duration for the functional improvement outcome compared GS trials that lasted less than 24 weeks vs. GS trials that lasted more than 24 weeks. Three trials that lasted less than 24 weeks (563 participants) showed a pooled effect size of -0.55 (95% CI -1.22 to 0.11) with a high degree of heterogeneity (I^2= 92.9%), compared with a significant small to moderate pooled effect size of -0.36 (95% CI -0.56, -0.17) for 2 trials that were longer than 24 weeks (412 participants) with no heterogeneity. This pooled SMD for functional improvement was the only statistically significant result in this meta-analysis. Trials of less than 24 weeks not only inflated the effect size, but increased the heterogeneity.
- The funnel plot shows points distributed slightly asymmetrically on the right side of the graph, suggesting that more small-sample studies were associated with larger effect sizes than with smaller effects, indicting the existence of possible publication bias. No publication bias was detected using the Egger test (p = 0.429).

- No studies were found that directly compared the two glucosamine preparations to each other.
- Out of the 17 individual studies reporting the pain outcome, 11 favored glucosamine for pain reduction and 6 trials favored placebo. Only 5 studies produced small to large effect sizes that were statistically significant in reducing pain with 4 studies favoring glucosamine and 1 study favoring placebo.

Authors' conclusions:

- The main findings of this meta-analysis support the fact that GS treatment for more than 6 months improves joint function, but not joint pain, in patients with knee OA. GH is ineffective for relieving pain in OA patients. Additional trials of GS for the treatment of knee or hip OA are needed to confirm this apparent lack of benefit of GS.
- To date, the results of RCTs studying the efficacy of glucosamine are conflicting. At least 6 systematic reviews have investigated the efficacy of glucosamine for treating knee or hip OA, but between-trial heterogeneity has been a major problem leading to uncertainties regarding the effects of glucosamine treatment in OA patients. Also, no meta-analysis independently assessing the effects of different formulations of glucosamine on pain and function in the treatment of knee or hip OA is currently available.
- Pooling the results of 6 trials that lasted for more than 24 weeks showed no significant pain reduction effect of GS compared with placebo. The heterogeneity among these trials was zero, suggesting that this summary effect was valid. Trials with a duration of less than 24 weeks also demonstrated no effect of GS compared with control, but pooling was inappropriate because of the high degree of heterogeneity.
- For the effects of GS on function, a significant moderate benefit favoring GS was found in trials with a duration of more than 24 weeks, which together with the lack of heterogeneity indicated that joint function was improved by administrating GS for more than 6 months. The pooled estimate of trials lasting less than 24 weeks showed a nonsignificant effect with a high degree of heterogeneity with pooling deemed inadvisable due to marked heterogeneity.
- Subgroup analyses of pain reduction in GS trials revealed different results. The joint affected by OA had an impact on the heterogeneity. Although both the knee alone group, and the knee or hip group had nonsignificant pooled effect sizes, heterogeneity was absent in the knee or hip group, suggesting that this pooled effect was valid.

Comments:

- The meta-analysis pooled effect size of -0.36 (95% CI -0.56, -0.17) favoring GS for improved function indicates a small, (rather than a moderate effect size claimed by the author) statistically significant, but clinically unimportant effect size. Even though this analysis showed no heterogeneity and suggests improved joint function by administrating GS for more than 6 months, the results should be interpreted with caution since this analysis was based on only 2 trials with a treatment duration of more than 24 weeks.

- Trials with poor methodology have been associated with inflated treatment effects, especially in trials with inadequate allocation concealment and absence of ITT analysis. When stratified by allocation concealment and ITT analysis, no superiority of GS over placebo for pain reduction was identified for trials with inadequate allocation concealment or trials without ITT analysis.
- A Cochrane Review by Towheed (2005) concluded that pooled results from studies using a non-Rottapharm product or adequate allocation concealment failed to show benefits in terms of pain reduction or functional improvement, whereas those studies evaluating the Rottapharm product showed that glucosamine was superior to placebo for the treatment of pain and functional impairment. Rottapharm is an Italian pharmaceutical company that is supported by a continued focus on research and development and extensive clinical validation demonstrating the strength, effectiveness and safety of its products. However, eligible trials in this study included non-placebo-controlled and single-blinded trials.
- Wandel and colleagues also concluded in an earlier meta-analysis that glucosamine did not reduce joint pain and had no impact on narrowing of the joint space compared with placebo, with no evidence for time-dependent effect.
- The methodological quality of the 2 trials with a duration of more than 24 weeks evaluating function for GS was moderate to high, scoring 3 and 5 on the 5 point Jadad scale. Both studies incorporated allocation concealment and ITT analysis, thus reducing a high risk of bias.
- Assessments of other methodological flaws, other than allocation concealment and ITT analysis, among all trials to help judge methodological quality and risk of bias were not included, just the Jadad score.
- Smaller studies usually show larger effect sizes and this held true in this review, since the smallest studies in this review had the largest effect sizes. Small studies showing no effect often do not get published and this leads to publication bias. The smaller studies in this review most certainly contributed to the publication bias found in this review.
- The stratified analyses for allocation concealment and ITT analysis included 4 small trials for inadequate allocation concealment and 3 small trials not conducting ITT analysis. As smaller studies usually show larger effect sizes, these small studies contributed to the inflated effect sizes observed in these sub-groups analyses.
- When homogeneity was present among trials, the authors suggested that this validated the summary effect. Homogeneity is not equated with validity, but rather with similar characteristics among studies, such as similar doses or study duration, or patient characteristics.
- The difference in sample size between studies was large ranging from 20 to 630, which may have contributed to the heterogeneity. Subgroup analysis should have been performed by stratifying the studies according to sample size to see if sample size contributed to the heterogeneity.
- The use of different instruments to measure pain and function outcomes could be a potential factor leading to variation among studies and causing a high degree of heterogeneity.

- The number of times of administration for the daily glucosamine dose also differed among these studies ranging from once to 3 times a day, even though the total daily dose was similar. It is possible that this added to the large heterogeneity among included studies.
- The fact that heterogeneity was large among trials may reflect large variations in patient characteristics which the authors did not describe or address, except for BMI.
- Biases relating to participant compliance, or truthfulness in patient reporting are both possible and could contribute to variation among the effect sizes.
- The authors accurately report the number of studies and patients that each comparison and result is based on. The addition of this information improves the quality of this review.
- The results of this review include both short-term and long-term effects and this adds to the quality of the review.
- For many patients with osteoarthritis of the knee, pain relief is accompanied by improvements in functioning, and this is not confirmed in this review, since only the effect size for physical function was significant, and not for pain. This is somewhat disconcerting.
- No adverse effects were reported by the authors.

Assessment:

- An adequate meta-analysis which supports good evidence that glucosamine sulfate and glucosamine hydrochloride are ineffective for relieving pain in patients with knee or hip OA, but glucosamine sulfate treatment for more than 6 months shows a small improvement in joint function compared to placebo controls in people with osteoarthritis of the knee or hip.

References:

- Towheed T, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev 2005: Issue 2. Art. No.:CD002946.
- Wandel S, Juni P, Tendal B et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ 2010; 341: c4675.