Fransen M, Agaliotis M, et al. Glucosamine and chondroitin for knee osteoarthritis: a double-blind randomised placebo-controlled clinical trial evaluating single and combination regimens. Ann Rheum Dis 2015;74:851-858.

Design: randomized clinical trial

Purpose of study: to estimate the effectiveness of glucosamine alone, chondroitin alone, and a combination of both for treating osteoarthritis (OA) of the knee

Population/sample size/setting:

- 605 patients (about 50% women, mean age 60) treated for OA of the knee the University of Lidcombe in Australia
- Eligibility criteria were knee pain for at least six months, knee pain on most days of the last month, and worst pain during the last week rated as 4 or more on a 0-10 point scale
- Exclusion criteria were rheumatoid arthritis, bilateral knee replacements, unstable diabetes, allergy to shellfish, no lower limb surgery in the past six months, not planning to have knee replacement in the coming year, and no knee injections in the past 3 months
- An additional criterion was radiographic: every patient had a weight-bearing film of both knees in a semi-flexed posture at 4 specific imaging centers, showing a medial tibial inter-rim distance (TIRD) of at least 2.0 mm, and reduced in width compared with the lateral side of the same joint in order to assess and follow joint-space narrowing (JSN)

Interventions:

- All patients had a run-in period in which they were given a 14 day supply of placebo capsules and a 7 day symptom diary; only those who completed the diary were randomized in a manner concealed to allocation
- Randomization was to one of four groups: glucosamine alone (G, n=152), chondroitin alone (C, n=151) , a combination of both (G+C, n=151) or placebo (P, n=151)
    - The glucosamine capsules contained 753 mg of glucosamine sulfate; the chondroitin capsules contained 400 mg of bovine-derived low molecular weight chondroitin sulfate, and the placebo capsules appeared identical to the active capsules
    - The chondroitin capsules were made by a firm in Australia with standards that minimize the transmission of bovine spongiform encephalopathy; all other capsules, including placebo, were made by Sanofi-Aventis in accordance with standards of the US Pharmacopeia

- All patients took two capsules daily of the assigned medication

Outcomes:

- The 7 day symptom diary was sent every 2 months along with the study capsules for 2 years
    - The diary asked patients to report on the worst pain they had had that day, and the maximum score during those 7 days was recorded as an outcome
    - The diary also asked the patients to rate their knees each day as excellent=0, very good 1, good 2, fair 3, or poor 4, and asked if they had exercised more than 20 minutes that day; less than 5 of the 7 days recording exercise was considered "inadequate " exercise
- JSN was evaluated from 3 annual knee radiographs and read by a radiologist blinded to treatment allocation but not to the sequence of the films; for a film to be included in JSN analyses, the TIRD had to be <=1.7 mm at each time point and had to show a difference of <= 0.2 mm between two x-ray time points
    - Severity of OA was also assessed with the Kellgren-Lawrence system, and about half of the patients had KL grade less than 2, indicating mild radiographic disease
- During the 2 year followup, 126 (24%) of the patients withdrew, but only 34 for possibly-related medical events there were no major differences between groups
- For the structural outcome of JSN, there were 303 sets of x-rays evaluated as valid for the 2-year followup, and the four treatment groups had equal rates of completing the followup films
- `A difference was reported in the degree of JSN between the P group and the G+C group at 2 years; the P group had 0.22 mm of JSN while the G+C group had only 0.12 mm of JSN; the difference in the amount of JSN between the two groups was 0.10 mm with a 95% confidence interval between 0.0 and 0.2 mm, with a p value of 0.046
    - No other differences in the amount of JSN was observed between any of the other treatment groups
- With respect to the clinical outcomes, the groups had equal pain scores after the end of two years; neither the G+C group, the G group, or the C group differed from the P group on knee pain or on any of several secondary outcomes such as the Western Ontario and McMaster Osteoarthritis (WOMAC) pain and physical function scores; the groups had some improvements in pain between baseline and year 1 but not between year 1 and year 2

- A subgroup analysis of patients with more severe pain at baseline (>=6/10) also did not show differences in knee pain and global assessment between the treatment groups

Authors' conclusions:

- Taking chondroitin plus glucosamine for two years provided a meaningful reduction in JSN among people with symptomatic OA of the knee with mostly mild radiographic disease
- The amount of JSN in the chondroitin plus glucosamine group was about half that in the placebo group after two years of treatment; if this were sustained over a period of 10 to 15 years, there could be a very significant clinical impact on the progression of OA of the knee
    - In contrast to other studies which have not found a significant influence of chondroitin plus glucosamine on the progression of JSN, this study had only5% with KG grade 3 OA, while the other studies had a higher percentage of patients with more severe radiographic disease at the time of study enrollment
- The pain outcome (worst knee pain in the past 7 days using a 7 day diary which was sent out every two months) was selected in order to have a better chance of detecting a pain-relieving effect than would have been possible with a pain outcome which would have lower average expected values, which could miss an actual analgesic effect of treatment

Comments:

- The influence of chondroitin plus glucosamine on JSN was statistically better than seen with placebo, but the 0.1mm difference between the two groups had a 95% confidence interval between 0.0 and 0.2 mm; the inference that the rate of narrowing is cut in half with chondroitin plus glucosamine is somewhat speculative, considering the possibility that measurement error affects the resolution of the digitized images used to measure JSN

- The lack of influence of chondroitin plus glucosamine on knee pain and function scores over a two year period, even when the scoring system was set up in a way which had a good likelihood of detecting pain score changes, makes the JSN results of uncertain importance, since it is pan and loss of function which mainly lead to the decision to perform surgery; JSN is an ancillary consideration in this decision making

- With a large enrollment and a large number of patients in each group, the study was adequately powered to detect any clinically meaningful benefit on pain and function, and such an effect was not missed because the study suffered from a lack of power

- It would apparently require daily use of chondroitin plus glucosamine for a period of many years to manifest a therapeutic effect, even assuming that the authors are

correct in their inference that the combination of agents has a large effect on the radiologic progression of knee OA

- However, the assertion that there is an absolute risk reduction of 7% in the percentage of patients who would have a 7% amount of JSN (which has been reported to predict the need for joint replacement within two to five years), is the basis for their conclusion that one would need to treat 14 patients with chondroitin plus glucosamine for two years to prevent a single joint replacement
- This is based on the difference between the percentages of placebo patients who had a 7% reduction in JSN (29%) and those taking chondroitin plus glucosamine (22%)
- The 65% confidence interval for this 7% risk reduction can be calculated, and is quite wide, from -6.5% to 20.7%; this means that the risk difference could lie between 6.5% in favor of placebo to 20.7% in favor of chondroitin plus glucosamine
- Thus, the statistically marginal difference in JSN with chondroitin plus glucosamine was not reported with an adequate reporting of the uncertainty in the estimate of its effectiveness, and the conclusion that it has an important benefit on the progression of knee OA cannot be sustained
- The study was partly funded by the maker of the tested compounds and the medication was of pharmaceutical grade; quality control issues are not likely to explain the lack of a major effect clinically or radiographically

Assessment: Inadequate for the conclusion that pharmaceutical grade chondroitin plus glucosamine reduces the progression of knee OA. Adequate for the conclusion that chondroitin plus glucosamine has no clinically important effect on knee pain and function when taken for two years. An effect of slowing of the progression of joint space narrowing cannot be ruled out.