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Caroline Horton
James Madison University

Ashani Andrews
James Madison University

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Effects of Glucosamine versus Chondroitin Sulfate in Reducing Joint Space Narrowing in Knee Osteoarthritis

Ashani Andrews, PA-S and Caroline Horton, PA-S

James Madison University Physician Assistant Program
December 1, 2016

Abstract

Objective: To determine if over the counter supplements, chondroitin sulfate and glucosamine, in combination or alone, are effective in the treatment of joint space narrowing (JSN) in knee osteoarthritis.

Design: Systematic Literature Review

Methods: Database search of PubMed and MEDLINE using the search terms "glucosamine," "chondroitin sulfate," "osteoarthritis," and joint space narrowing. Filters were implemented to include articles that only dealt with human subjects, that were published in 2000 or later, and were full-text. Articles were excluded if they were cohort studies, reviews, non-English papers, or had pain as the only outcome.

Results: Sawitzke et al.[1] primary outcomes revealed no overall significant difference between mean JSW loss over a two-year period between treatment and placebo groups. Secondary outcomes showed no significant likelihood of radiographic progression with treatment groups versus placebo. Fransen et al.[2] observed a significant decrease in JSN in 2 years with glucosamine and chondroitin sulfate combined but there was no statistical significant in JSN with glucosamine or chondroitin sulfate alone as compared to placebo. There was also a small reduction in knee pain observed versus placebo. The meta-analysis by Lee et. al[3] observed those studies in which there was a small protective effect on minimum JSN with glucosamine and chondroitin individually after two years but there was no statistical significance seen at one year.

Conclusion: Overall, studies showed that chondroitin sulfate, glucosamine, and especially the combination of the two, do have a small protective effect depending on the severity of knee osteoarthritis, the number of years the supplement is utilized, and the drug dosage.

Introduction

Osteoarthritis (OA) is the most common form of arthritis and affects about 27 million Americans, more commonly women. It was once believed that OA was caused by the natural aging progression; however, it now seems to be many factors that lead to OA such as joint integrity, genetics, inflammation, weight, and mechanical forces.[4] While other factors aid in the cause of OA, age still seems to be the most consistent risk factor. Prevalence of radiographic and symptomatic OA rises at the age of 50 for men and 40 in women. It rarely occurs in those less than 35 and is normally due to a secondary cause rather than a primary cause in this age group. It is also evident that knee OA affects women more commonly, while hip OA affects men more.[5] OA of the knee accounts for 1 of 5 leading causes of disability among institutionalized adults with 40% of adults with knee OA reporting their health as "fair" or poor."[6] Due to the high prevalence in which this degenerative disease occurs in the population, effective treatment options are paramount.

Sometimes called degenerative joint disease, OA is characterized by sclerosis, osteophytosis, and joint space narrowing (JSN) and can affect any joint. OA has a common predilection for the knees, hip, lower back, neck, small joints of the fingers and the bases of the thumb and big toe. In OA, matrix degrading enzymes are overexpressed resulting in the loss of collagen and proteoglycans from the matrix. Over time, as the cartilage wears down, pain, inflammation, and swelling begins. Due to this, patients may experience pain that is worse with activity and better with rest and a locking or giving away sensation.[5] Treatment efforts are aimed at limiting symptoms but there is no pharmacological therapy that has been capable of completely stopping OA or the prevention of it.

Evaluating all forms of arthritis begins with measuring the width of the affected joint space. Evaluation of the joint space is important because it allows providers to track the

progression of the cartilage degeneration through scoring and grading. Measurement methods of joint space width (JSW) include using manual calipers against a plain radiographic film, but is more commonly performed using a computer automated caliper system. Based on a study by Anas, et. al, the normal reference range of tibio-femoral medial and lateral joint space width is approximately 4.74 mm ± 0.75 and 5.63 mm ± 0.86 respectively.[7] However, if the rate of degeneration, and therefore joints space narrowing, can be slowed the pain associated with progressive OA and amount of surgeries done due to OA can be reduced.

Pharmacological treatments widely used for OA include acetaminophen, non-steroid anti-inflammatory agents (NSAIDs), COX-2 inhibitors, topical agents and intra-articular injections. Non-pharmacological treatments are aimed at weight reduction and possible surgery. Choice of initial therapy depends on severity, presence or absence of local inflammatory changes, and the efficacy of previous employed therapies. New therapies are now interested in slowing the rate of joint space narrowing as well as pain relief. Glucosamine and chondroitin sulfate (CS) are two dietary supplements available over the counter in the United States. They were initially used for symptomatic relief of OA but have been targeted recently for their use in the treatment of joint space narrowing.[7] Chondroitin sulfate is found naturally in humans, as well as other mammals including bovine and pigs, particularly in the cartilage of the joints.[8] The mechanism of action of CS includes simultaneously promoting stimulation of chondrocytes to produce new extracellular matrix consisting of proteoglycans and hyaluronic acid while inhibiting degeneration of cartilage.[8] Glucosamine is also found in mammalian cartilage, as well as the exoskeletons of arthropods and is typically synthesized from chitin.[8] The mechanism of action of glucosamine is less known compared to chondroitin sulfate, but evidence indicates that glucosamine shows it indirectly inhibits the action of interleukin-1, a pro-inflammatory cytokine, that is locally

stimulated during joint degeneration.[8] Although research is still controversial, the effects of glucosamine and chondroitin sulfate on joint space narrowing may have more benefits on long term improvement in function than previous pharmacological therapies.

Clinical Question

In adults (>18 years old) with knee osteoarthritis, does the use of glucosamine, chondroitin sulfate or combination of glucosamine and chondroitin sulfate compared to placebo have a significant benefit in improving patient's functional outcomes as indicated by a decrease in joint space narrowing?

Methods

An initial search of PubMed and MEDLINE was performed in September 2016 using the search terms "glucosamine", "chondroitin sulfate", "osteoarthritis" and "joint space narrowing" that yielded 178 articles (see Figure 1). The articles were further screened and only included if they were studies with human subjects that were published in 2000 or later with full text articles available, which narrowed the results to 23 articles. The 23 full-text articles were assessed for eligibility. Articles were excluded if the study's primary outcome was only measurement of pain management and did not address joint space narrowing. Randomized controlled trials and meta-analyses were the only study types included, while case studies, reviews and cohort studies were excluded. Finally, three articles were chosen, one meta-analyses and two randomized controlled trials, as they were the only studies that addressed disease modifying, or joint space narrowing, effects of both glucosamine and chondroitin as a primary outcome measurement with a follow-up period of two years or greater.

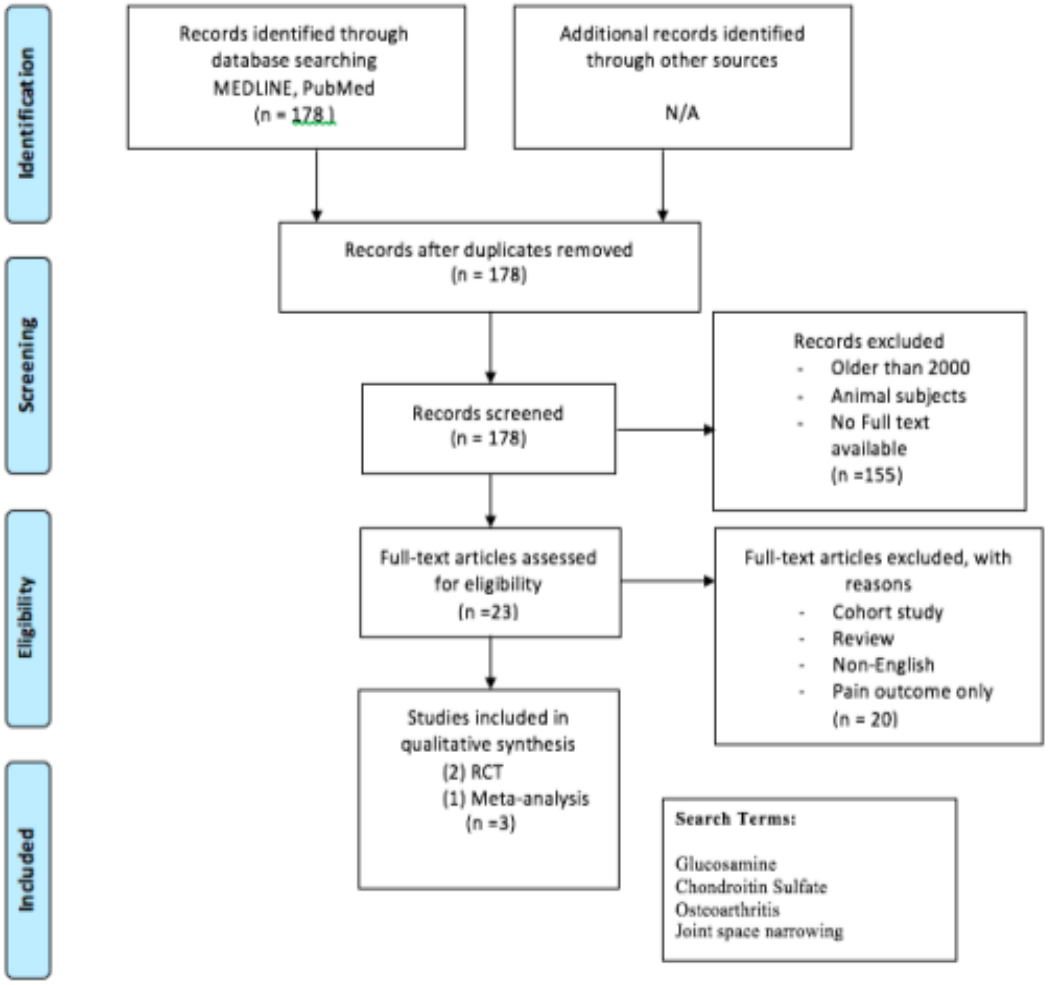


Figure 1. PRISMA flow diagram summarizing the article search process.

Results

Study #1

The effects of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis.

Sawitzke et. al[1]

Objective

The goal of this randomized control trial was to evaluate the effects of glucosamine and chondroitin sulfate, alone or in combination, as well as celecoxib and placebo on the progressive loss of joint space width in patients with knee osteoarthritis.

Study Design

Information was collected from nine out of sixteen Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) centers to assess structural changes in knee osteoarthritis. Eligible patients were at least 40 years of age, had knee pain for at least 6 months occurring on the majority of days in the month preceding enrollment in GAIT, and had Kellgren/Lawrence (K/L) grade two or grade three knee OA determined on screening anterior posterior radiographs of the knee in weight bearing position. The Kellgren/Lawrence is a method of classifying the severity of knee osteoarthritis using a 0-4 grading scale depicted in table 1.

Table 1. Kellgren/Lawrence Osteoarthritis grading.[9]

Grade	**Classification**
Grade 0	no radiographic features of OA are present
Grade 1	doubtful joint space narrowing (JSN) and possible osteophytic lipping
Grade 2	definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph
Grade 3	multiple osteophytes, definite JSN, sclerosis, possible bony deformity
Grade 4	large osteophytes, marked JSN, severe sclerosis and definite bony deformity

Qualifying patients received a blinded study treatment for a total of 24 months. Treatment consisted of glucosamine 500 mg 3 times a day, chondroitin sulfate 400 mg three times daily, combination of glucosamine and chondroitin sulfate, celecoxib 200 mg daily, or placebo. Patients were not eligible if they had a concurrent medical conditions that could potentially hinder the evaluation of the knee joint or disease that would limit their successful completion of the trial. Certain knees were also excluded if they had a minimum baseline medial tibiofemoral JSW of <2 mm, predominant lateral compartment OA on any film, and a history of significant trauma or surgery to the knee. All inclusion and exclusion criteria is summarized in table 2.

Table 2. Patient Inclusion and Exclusion Criteria; *Sawitzke* et. al[1]

Inclusion Criteria
· At least 40 years old · Knee pain ³ 6 months occurring on majority of days in the month preceding enrollment in GAIT · K/L grade of 2 or 3
Exclusion Criteria
· Any concurrent disease or medial conditions that could hinder evaluation of the knee joint · Any disease or medical condition that could limit their completion of the trial · Minimum baseline medial tibiofemoral JSW of <2mm · Predominant lateral compartment OA · History of significant trauma or surgery to the knee

All radiology technicians were experienced skeletal radiology technicians. Technicians were trained at a two-day session on performing nonfluroscopic weight bearing radiographic assessment of the knee joints. Radiographs were obtained at baseline, 12 months, and 24 months. The final sample size included 357 subjects with 581 qualifying knees. Analysis was done on a modified intention to treat basis. Baseline characteristics were compared using a chi-square test which compares the different treatment groups for heterogeneity. Statistical testing of treatment

differences was adjusted for the comparison amongst the four treatment groups, with the control being the placebo, with calculation of 95% confidence intervals. The primary longitudinal analysis compared mean change in JSW in each intervention group compared to placebo. The secondary longitudinal analysis compared occurrence of disease progression with a JSW loss exceeding 0.48 mm over a two-year period.

Study Results

The primary outcomes focused on mean change in joint space narrowing over two years. Eligible patient treatment group distribution, of those who consented to participate, is shown in table three. There was no significant difference in baseline characteristics in those patients who were randomized.

Table 3. Distribution of patients randomized to the treatment groups

	Glucosamine	**Chondroitin sulfate**	**Glucosamine + Chondroitin sulfate**	**Celecoxib**	**Placebo**
Patients					
Initial	134	123	128	143	134
Eligible	119	107	110	122	114
Withdrawal	33	30	40	32	36
Inadequate film quality	9	6	11	10	8
Assessable	77	71	59	80	70
Knees	123	116	94	135	113
Single knee	31	24	25	25	27
Both knees	46	46	34	55	43

Primary outcomes showed that overall there was no significant difference in mean JSW loss over 2 years between the treatment and placebo groups. The glucosamine sulfate group had the least mean loss in JSW with 0.013 mm at 2 years whereas the glucosamine plus chondroitin sulfate had the greatest mean loss of 0.194 mm at 2 years. It was also observed that JSW loss was greater in knees with K/L grade 3 radiographic OA than knees with K/L grade 2 radiographic OA. Originally, a JSW loss of 0.40 mm was anticipated in the placebo group but it was observed that there was only a JSW loss of 0.34 mm unadjusted with 0.273 mm JSW loss in K/L grade 2 knees and 0.523 mm in K/L grade 3 loss (see Table 4).

Secondary outcomes showed that overall there was no significant likelihood of radiographic progression in any treatment group compared to placebo. Radiographic progression, defined as JSW loss exceeding 0.48mm was more frequent in the group treated with combination of glucosamine and chondroitin sulfate (24.4% progression at two years). Progression was less frequent in the group treated with glucosamine alone (18.6% at two years). These changes are seen in table 5.

Table 4. Loss in JSW over 2 years by treatment group

Therapy	**No. of subjects**	**Mean JSW loss over 2 years, mm**	**Difference from placebo (95% CI)%**
Glucosamine	77	0.013	-0.153(-0.379, 0.074)
Chondroitin sulfate	71	0.107	-0.059(-0.287, 0.169)
Glucosamine + Chondroitin sulfate	59	0.194	0.028(-0.214, 0.271)
Celecoxib	80	0.111	-0.055(-0.279, 0.170)
Placebo	70	0.166	

Table 5. Disease progression over 2 years by treatment group

Therapy	**No. of subjects**	**Progression, % of patients**	**OR versus placebo (95% CI)**
Glucosamine	77	18.6	0.79(0.48-1.3)
Chondroitin sulfate	71	21.4	0.94(0.57-1.55)
Glucosamine + chondroitin sulfate	59	24.4	1.12(0.67-1.88)
Celecoxib	80	20.2	0.87(0.53-1.43)
Placebo	70	22.4	

Although not statistically significant all treatment groups showed less JSW loss than placebo for knees with K/L grade 2 radiographic knee OA but showed more JSW loss compared to placebo for knees with K/L grade 3 radiographic OA (see figure 2). Estimated odds ratio for radiographic progression compared to placebo group was <1 (intervention being better than the control) in patients with K/L grade 2 knees, whereas the odds ratio was >1 (control is better than the intervention) in patients with K/L grade 3 knees (see figure 3). Overall, the study showed no statistical or clinical significance and the effect of glucosamine plus chondroitin sulfate, rather than the two alone, may be less effective in JSW loss and OA progression.

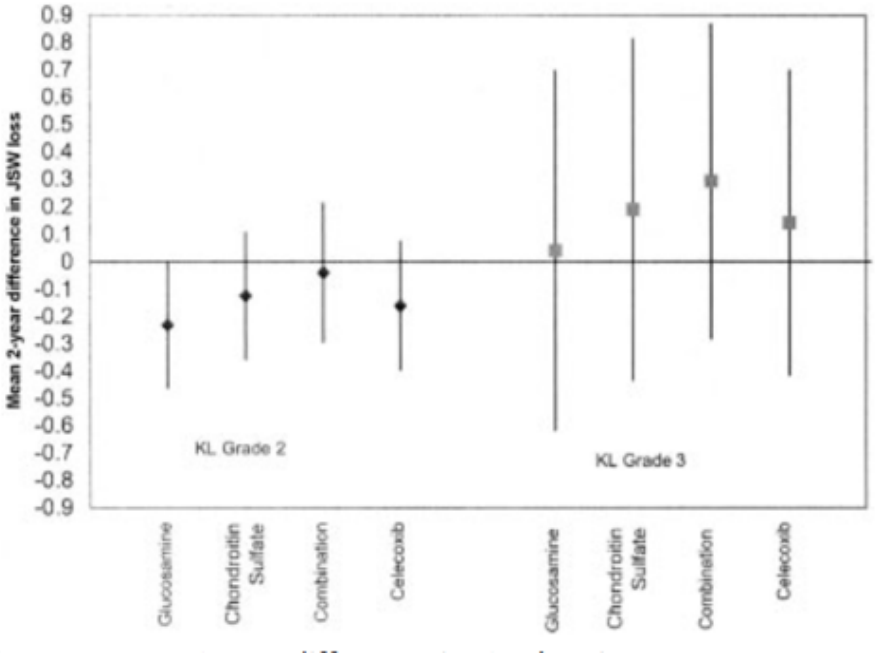


Figure 2. Mean 2-year difference in JSW loss in treatment groups relative to placebo group according to K/L radiographic severity

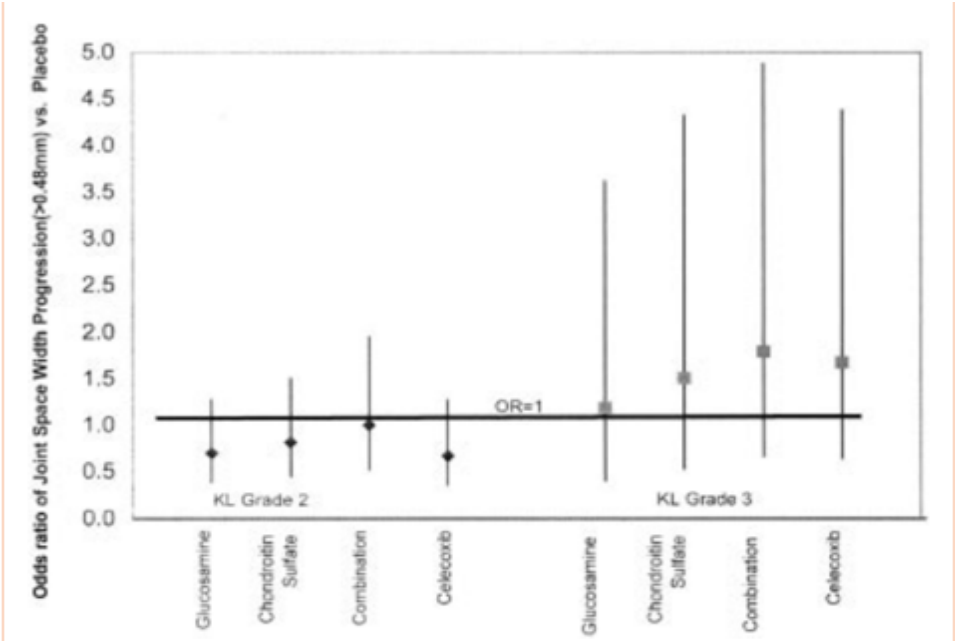


Figure 3. Odds ratio for likelihood of progression of JSW loss in treatment groups relative to the placebo group.

Study Critique

One of the strengths of this article is the use of statistical analyses such as the chi-square to assess the baseline heterogeneity characteristics between the treatment groups. A mixed effect regression model, containing both fixed and random effects, was also used to carry out comparisons amongst the treatment and control groups for mean JSW progression. Another strength in this article is the amount of detail the researchers used obtaining the knee radiographs of all the participants. They had strict protocols that had to be followed such as foot mapping, a "drawing" of the subject's foot to allow for consistent positioning during subsequent radiographs, was used at each radiographic assessment. The article was easy to follow and all the charts and tables made it very simple to follow the study results for each treatment group.

One drawback of the study was that the power of the study was limited because the sample size was so small. Decreased statistical power due to a small sample size leads to a type II error, making it difficult to stratify the study results into the general population of patients dealing with osteoarthritis as the treatment may be effective in a larger population despite the results from this small study. Power of the study was also limited because the number of qualifying individuals whose follow up films were considered were less than expected, the magnitude of JSW loss in the placebo group was less than anticipated and the variability of JSW measurement was larger than expected. There is increased variability associated with multicenter trials which may have aided in the smaller effect size seen in the study. Weight bearing PA based films at the time of this study was believed to have the best overall performance there is now evidence that fluoroscopic methods may be more advantageous because of the increased sensitivity for detection of JSW loss. Finally, the researchers stated they used a "modified" intention to treat analysis, but this method was not elaborated on. Despite the study's

conclusions that there is no statistical significance on the efficacy of glucosamine and chondroitin sulfate on JSN, it may be skewed with the inclusion of those participants who did not fully comply with the study requirements.

Study #2

Glucosamine and chondroitin for knee osteoarthritis: a double-blind randomized placebo-controlled clinical trial evaluating single and combination regimens.

Fransen, et. al.[2]

Objective

The Long Term Evaluation of Glucosamine Sulfate (LEGS) study was performed to evaluate the effects of glucosamine sulfate, chondroitin sulfate and their combination on the reduction and limitation of structural disease progression as well as pain relief and improvement in functional status in patients with chronic knee pain due to osteoarthritis over a two year period.

Study Design

The LEGS study is a double blinded randomized placebo controlled clinical trial with participant recruitment from primary care facilities in New South Wales, Australia. During a 2-year period, 605 males and females were selected for randomization based on telephone screenings. Inclusion and exclusion criteria for participants are outlined in Table 6**.** Participants were randomized to one of the following study treatments: (1) glucosamine sulfate potassium chloride 753 mg water-soluble white powder capsule and matching placebo capsule; (2) chondroitin sulfate 400 mg bovine derived capsule and matching placebo capsule; (3) glucosamine sulfate capsule and chondroitin sulfate capsule; or (4) two placebo capsules. Participants were instructed to take both capsules once daily for the two years of study with participation in three clinical assessments at baseline, year one and year two.

Table 6. Inclusion and Exclusion Criteria for participants.

Inclusion Criteria	Exclusion Criteria
· Age >45 and <75 years · Knee pain >6 months · Knee pain on most days of the past month · "Worst pain" experienced in the left and right knee over the past week rated as 4+ on a scale of 0-10 · Reduced medial tibio-femoral compartment JSW, compared with the lateral compartment, but retain $\geq$ 2.0 mm minimum medial JSW · Distance between the anterior and posterior rims of the medial tibial plateau $\leq$1.7 mm on radiograph.	· History of rheumatoid arthritis · History of unstable diabetes mellitus · Allergy to shellfish · Lower limb surgery in the past 6 months · Intra-articular injection for knee pain · History of bilateral knee replacements · Knee replacement planned in the next year · in the past 3 months

The main outcome assessed was medial tibio-femoral joint space narrowing evaluated from three annual weight-bearing, semi-flexed bilateral knee radiographs. Foot maps were used to allow for standardization of each image. The medial tibio-femoral joint space width was measured using image analysis software, such as Holy's software, and assessed by a radiologist blinded to the treatment allocation. X-rays were considered valid and included in JSN analysis if there was a medial tibial inter-rim distance (TIRD) of $\leq$1.7 mm at each time point and $\leq$0.2 mm difference in TIRD between two x-rays at different assessment times.

The secondary outcomes assessed in the study were symptomatic benefits of the treatments including knee pain and physical and mental functional status over two years. Participants were required to submit bimonthly diary entries with self-reported symptoms. Knee pain was reported as the mean of the maximum knee pain score, on a scale from 0-10, for each bimonthly diary collected during the first year only. Pain and function were also assessed based on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) with a function scale of 0 to 68 and pain scale of 0-20. During annual clinical assessments, participants also

performed a medical outcomes study short form questionnaire (SF-12 version 2) that assessed the physical and mental well-being of the participants. Both outcomes of JSN and knee pain were analyzed by intention-to-treat and 95% confidence intervals were included when appropriate.

Study Results

Of the 605 participants selected for randomization, 449 reported at least 90 percent compliance with treatment and of those, 34 participants withdrew through the two year period for possibly related medical events, which are not elaborated on in the study. There was a statistically significant ($p=0.046$) decrease in two year JSN of 0.10 mm with combination glucosamine and chondroitin sulfate treatment (see Table 7). There were no significant differences in JSN for single glucosamine or single chondroitin treatment compared to placebo. There was a 7% absolute risk reduction for $\geq$7 percent JSN, as a JSN greater than 7 percent is highly predictive of knee replacement treatment and the number needed to treat (NNT) is 14, so fourteen people will need to take a chondroitin and glucosamine combination for two years for prevention of one knee replacement surgery in one patient.

There was a small reduction in maximum knee pain over the second year but not the first year of treatment among all three treatment allocations compared to placebo (see Table 8). Knee pain and physical function measured by the WOMAC scale improved between the baseline and year one but had no further improvements at year two among the three treatment allocations compared to placebo. At baseline, approximately 17 percent were using opioids or daily NSAIDs for relief of pain. After treatment with daily glucosamine and/or chondroitin for two years, there was no reduction in the use of NSAIDs or opioids for pain relief.

The LEGS study concluded that taking both glucosamine sulfate and chondroitin sulfate together daily for a period of at least two years will aid in the reduction of tibio-femoral joint

space narrowing, compared with placebo. However, there are no significant symptomatic benefits to taking glucosamine and chondroitin individually or in combination on a daily basis over a two year period.

Table 7. Joint space width by x-ray measurement.

	Placebo	Glucosamine	Chondroitin	Glucosamine + Chondroitin
Baseline, mm (SD)	3.81 (0.96) n=151	3.78 (1.06) n=152	3.71 (0.97) n=151	3.81 (0.95) n=151
Year 1, mm (SD)	3.75 (1.03) n=127	3.70 (1.18) n=131	3.61 (1.00) n=129	3.76 (0.96) n=132
Year 2, mm (SD)	3.70 (1.04) n=121	3.62 (1.22) n=125	3.63 (1.06) n=117	3.80 (1.03) n=121

Table 8. Mean maximum knee pain (0-10) by participant diaries year 1 and 2.

	Placebo	Glucosamine	Chondroitin	Glucosamine + Chondroitin
Baseline	4.75	4.72	4.61	4.71
Year 1 (diaries 1-6)	4.14	4.02	4.01	3.94
Difference (95% CI)		-0.01 (-0.34 to 0.31) p=0.93	-0.10 (-0.43 to 0.22) P=0.53	0.02 (-0.31 to 0.34) p=0.92
Year 2 (diaries 7-12)	4.03	3.86	3.76	3.58
Difference (95% CI)		-0.13 (-0.52 to 0.27) p=0.53	-0.12 (-0.51 to 0.28) p=0.57	-0.27 (-0.67 to 0.13) p=0.19

Study Critique

A significant flaw in LEGS study is that the majority of participants had early and mild radiographic osteoarthritic disease based on the Kellgren and Lawrence (KL) system for

classification of osteoarthritis of the knee. Approximately 53% of the 605 participants had KL grade 1 or 2, or mild to moderate, osteoarthritis and therefore this study is less applicable to those with moderate to severe osteoarthritis (KL grade 3+) and more severe pain. It's possible that people with severe joint space narrowing were excluded from the study because they had a medial compartment JSW that was <2.0 mm. There is also limited information for the effects of glucosamine and chondroitin over a period of use greater than two years but the majority of other studies that have focused on JSN have also been limited to two years or less of follow up.

Despite the requirement of a two-year commitment, this study had a large participant population with a high rate of compliance with two-year follow up. Originally, there was an even number of participants allocated to the four treatment groups and drop out numbers were fairly equal among all four groups as well. Compliance may be an important factor in the findings of decreased JSN in the combination group as this study only required participants to take the allocation daily, while these dietary supplements are typically taken two to three times per day. Joint space narrowing in the three treatment groups were adjusted for varying demographics including gender, baseline BMI, baseline tibio-femoral joint space width, KL grade and presence of Heberden's nodes when compared to placebo so that treatment groups were compared as equally as possible.

The calculated number needed to treat of 14 for prevention of knee replacement surgery is clinically significant as knee replacement surgery is such a common operation in those with severe osteoarthritis but is not always effective in improving functional status. It is important to consider glucosamine and chondroitin in patients who may have a high risk of knee replacement in the future.

Study #3

Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis.

Lee et. al.[3]

Objective

The goal of this meta-analysis was to assess the structural efficacies of daily glucosamine sulfate and chondroitin sulfate in patients with knee osteoarthritis.

Study Design

Literature searches were performed using MEDLINE and Cochrane Controlled Trials Register to identify available articles. "Glucosamine," "chondroitin," "knee," "cartilage," "structure," and "osteoarthritis" were the keywords used to narrow the literature search. Results were limited to English language papers. All randomized controlled studies were considered eligible if they compared glucosamine sulfate or chondroitin sulfate with placebo in patients with OA with joint space narrowing as the outcome. Studies were excluded if they did not contain a placebo group, the OA site was not the knee joint, they did not contain adequate data, and if it was a cross-sectional study (see table 9). Jadad scores, a scale used to quantify the quality of randomized controlled clinical trials, were considered in the selection process.

Table 9. Inclusion and Exclusion Criteria; *Lee et. Al.*[3]

Inclusion Criteria
· English language papers · Randomized Controlled Studies
Exclusion Criteria
· Non-English language papers · No placebo group · OA site was not the knee · Didn't contain adequate data · Cross-sectional Study

Information extracted from each study was the author, year of publication, dose of glucosamine or chondroitin, length of follow-up, intention to treat analysis, mean standard deviation (SD) of JSN, and number of patients who experienced a clinically relevant (>0.5mm) mean JSN. Funnel plots were used to detect any publication bias and was evaluated using Egger's linear regression test which measures funnel plot asymmetry using a natural logarithm scale of odds ratios.

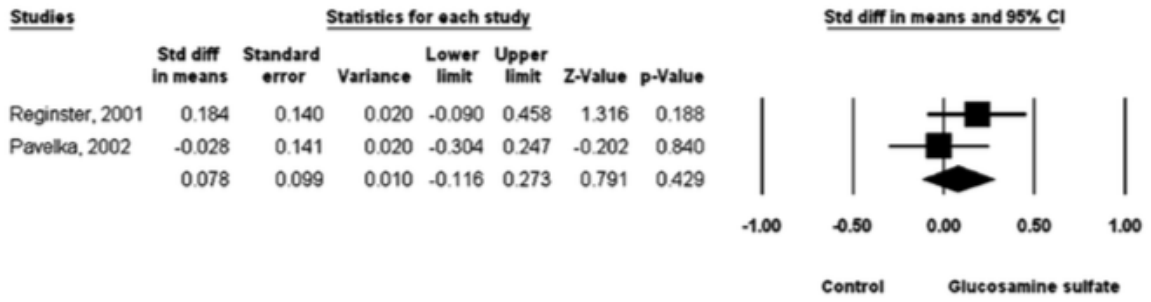
Standardized mean differences (SMD) were used for JSN analysis and odds ratios were used to analyze severe narrowing. Within and between study variations and heterogeneities were assessed using Cochran's Q –statistics. If the Q-statistics indicates heterogeneity across studies, a random effects model was used considering both inter and intra study variations. In this particular study the fixed effect model was performed because heterogeneity was not identified. I^2 was also measured to assess the degree of inconsistency between studies to determine if variation across studies was due to heterogeneity or chance. Statistical manipulations were evaluated using a comprehensive meta-analysis computer program.

Study Results

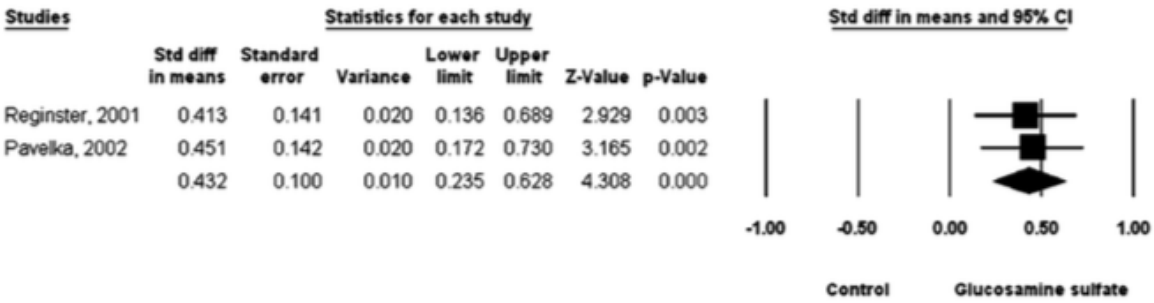
A total of six studies were reviewed in this meta-analysis that met the inclusion criteria - two on the effects of glucosamine sulfate on knee JSN and four on the effects of chondroitin sulfate on knee JSN - that consisted of a total of 749 participants in the treatment groups and 753 participants in the control groups. The two studies evaluating glucosamine sulfate on the effects of knee JSN showed no significant effect versus controls on minimum JSN after one year of treatment with glucosamine sulfate. However, there was a small to moderate protective effect on minimum JSN after three years of treatment with glucosamine sulfate (see figure 4).

Similar results with chondroitin sulfate were summarized (see figure 5). After one year of treatment with chondroitin sulfate, there was no significant effect versus controls on minimum JSN. There was a small protective effect on minimum JSN after two years of treatment with chondroitin sulfate. Therefore, the study concluded that both glucosamine sulfate and chondroitin sulfate inhibit the progression of knee OA with long-term daily use of at least three and two years, respectively.

No publication bias was evident per Egger's regression test ($p>0.1$) however, the authors state it was difficult to correlate the funnel plot associated with the regression test as the number of studies was too small. No heterogeneity was noted between studies, therefore a fixed effect model was used in this meta-analysis.



(A)



(B)

Figure 4. Standard differences in the mean values and 95% CI of individual studies and pooled adate for the structural effect of glucosamine sulfate on minimum JSN in knee OA after 1 year (A) and 3 years (B) of treatment.[3]

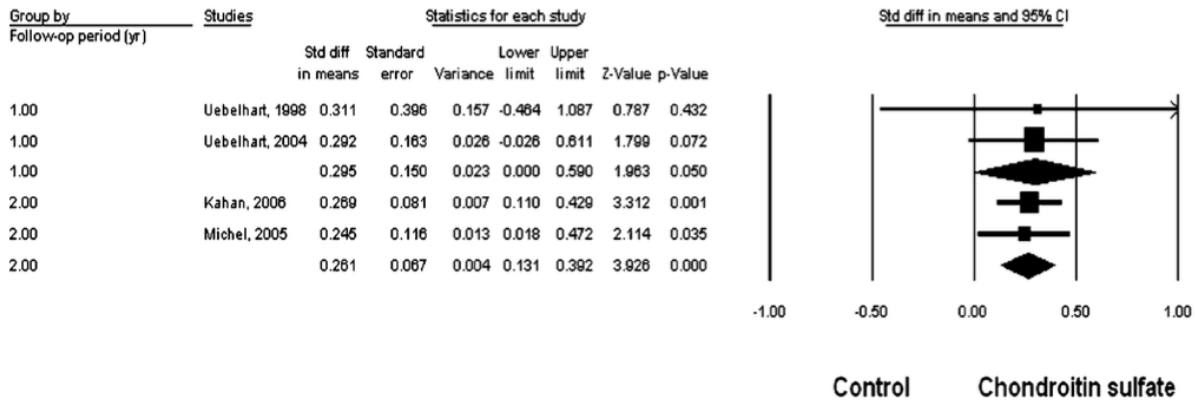


Figure 5. Standard differences in the mean values and 95% CI of individual studies and pooled adate for the structural effect of chondroitin sulfate on minimum JSN in knee OA at 1 and 2 years of treatment.[3]

Study Critique

There are multiple concerns with this meta-analysis' inclusion of articles and the varying study methods. Out of the five articles included, the over the counter preparations of both glucosamine sulfate and chondroitin sulfate were not controlled and therefore, it is unknown if one preparation had a higher efficacy than others. Two of the studies used glucosamine sulfate produced by the same pharmaceutical company but is a prescription form from Italy, not an over the counter preparation that is available in the United States. The prescription formulation is also taken once a day instead of the typical two to three times a day dosing of over the counter glucosamine formulations, which may contribute to a higher compliance rate and therefore, a more efficacious outcome. The meta-analysis does address these concerns with formulations and dosages briefly, stating the nonprescription and prescription formulations had no statistically significant difference in pain.

It is unfortunate that only five studies, two on glucosamine and three concerning chondroitin on knee OA, were included in this meta-analysis. There is a lack of data on long term use of glucosamine and chondroitin for limiting joint space narrowing of the knee in OA

patients and the authors of the article address this limited pool of resources. There is interest in the use of glucosamine and chondroitin in combination for knee OA structural changes and this meta-analysis does not address studies testing the combination formulations.

Overall, the meta-analysis suggests that use of glucosamine and chondroitin may delay the natural progression of joint space narrowing of the knee in OA if these medications are taken daily for greater than two to three years. However, the conclusions this study makes are less reliable given the varying formulations of drugs used in the studies as well as the small number of studies included that only studied glucosamine and chondroitin individually.

Discussion

The use of glucosamine and chondroitin sulfate as disease modifying therapy in knee osteoarthritis is still fairly unknown. Two articles reviewed each make a conclusion that the combination of glucosamine and chondroitin sulfate may limit narrowing of the medial tibio-femoral compartment of the knee but this combination must be taken daily for at least two years to produce this result. The overview of the studies, including demographics, results and limitations, included in this systematic review is summarized in Table 10.

The GAIT study by Sawitzke, et. al.[1] is one of the first studies to address glucosamine and chondroitin sulfate for the use of more than just pain relief in osteoarthritis. The GAIT study suggested that more research should be performed to evaluate the effect of G and CS on joint space narrowing and yet the majority of studies, such as the two included in this systematic review, also suggest further research is still necessary to make a definite conclusion about the effects of these two supplements. The GAIT study concluded that neither glucosamine or chondroitin sulfate individually or in combination had a significant clinical effect on limiting joint space narrowing in knee OA when compared to placebo.

The LEGS study did find a significant decrease in joint space narrowing in those with knee OA who took glucosamine and chondroitin sulfate in combination once a day for two years, but not at one year of use. The LEGS study is the only study included in this systematic review that measured pain and physical function using the WOMAC index and basic 0-10 pain scale. Effects of G and CS on pain were similar to the results on joint space narrowing where only combination of G and CS daily for two years showed any improvement in pain.

The meta-analysis by Lee, et. al.[3] did not include studies that measured structural changes in knee OA treatment with combination G and CS. The authors concluded that chondroitin sulfate had a minimal protective effect on JSN compared to placebo if taken for three years and glucosamine had similar benefits if taken for at least two years, however, these significant protective effects were very minimal. The small group of studies included in this meta-analysis were inconsistent in their methods, including the varying formulations and frequency of dosing of the oral supplements, and despite the homogeneity between studies, conclusions may be unreliable

All three studies used intention to treat analysis. It is important to recognize that with intention to treat analysis, the study conclusions may be distorted as the efficacy of the treatments on JSN are based on both the data from the patients who fully complied with treatment and from those who did not. There is also minimal information on reasons for loss to follow up and noncompliance. If any safety issues were of concern of the researchers, they were not included in the reports. Glucosamine and chondroitin sulfate are both supplements with minimal known side effects, other than possible mild gastrointestinal upset, or drug-drug interactions.

The first two studies, Sawitzke et al[1] and Fransen et al[2], both addressed the significance of osteoarthritis severity on the response of structural changes to glucosamine and chondroitin sulfate. The majority of participants had a KL grade one or two and had mild to moderate osteoarthritis of the knee with only minimal joint space narrowing at baseline. The authors of both of these articles believe that the combination of glucosamine and chondroitin sulfate would be more beneficial to those with severe osteoarthritis, or KL grade 2-4. The other limitation of these studies in regards to the conclusions made is that follow up period did not exceed two years, except for the studies on chondroitin sulfate included in the meta-analysis, and effects were not statistically significant until at least two years of daily use. Therefore, more research on the use of these two oral supplements in combination over more than two years in patients with severe osteoarthritic joint changes and severe pain is necessary.

Table 10. Summary of methods, results (joint space width loss and pain) and limitations of the three reviewed studies.

	***Sawitzke, et. al.*[1] (Study #1)**	***Fransen, et. al.*[2] (Study #2)**	***Lee, et. al.*[3] (Study #3)**
Sample Size	357	605	1,502
Study Treatments	Glucosamine 500 mg TID Chondroitin sulfate 400 mg TID Combination G + CS Celecoxib 200 mg QD	Glucosamine 753 mg QD Chondroitin sulfate 400 mg QD Combination G + CS	Glucosamine 1,500 mg QD Chondrotin sulfate 800 mg QD OR CS 400 mg QD
Comparison	Placebo	Placebo	Placebo
Follow Up Periods	2 years	1 year, 2 years	G: 1 year, 3 years CS: 2 years
Female (%)	63%	56%	67%
BMI, mean (kg/m^2) or %	25-30 kg/m^2= 34.7% >30 kg/m^2= 53.2%	28.9	27.4
K/L Grade of 3 (%)	23%	47%	n/a
Pain Scale at baseline and at the end of follow up period (0-10, mean)	n/a	G = 4.7, 3.86 C = 4.6, 3.76 G + C = 4.7, 3.58 Placebo = 4.8, 4.03	n/a
Mean joint space narrowing at end of follow up period in (mm or SMD with 95% confidence interval)	G = 0.013 mm CS = 0.107 mm G + CS = 0.194 mm Celecoxib = 0.111 mm Placebo = 0.166 mm	G = 0.24 mm CS = 0.20 mm G + CS = 0.12 mm Placebo = 0.22 mm	G (SMD) = 0.432 (0.235 - 0.628) CS (SMD) = 0.261 (0.131-0.392)
Conclusion	No statistically significant effects on JSN in all treatment allocations	Statistically significant effect on JSN in combination G + CS at 2 years of daily use	Statistically significant effect on JSN in chondroitin and glucosamine individually with long-term daily use of at least three and two years, respectively
Limitations	- Small sample size - Small group of qualifying follow up x-ray films - Intention to Treat	-Minimal number of participants with severe JSW or KL grade 3-4. - Intention to Treat	- Small number of studies - Varying formulations and dosage frequencies - Intention to Treat

Conclusion

There is a potential protective effect of glucosamine and chondroitin sulfate, especially if used in combination, on joint space narrowing in patients with knee osteoarthritis with at least two years of daily use. The safety of these two supplements seems to be minimal, but is not well documented in the included studies. Patients with a KL grade of one or two are more likely to benefit from these two supplements. However, more research over a longer duration of time, greater than two years, is needed to definitively conclude that glucosamine and chondroitin sulfate are effective in limiting joint space narrowing in patients with knee osteoarthritis.

Acknowledgements

We would like to thank Dr. Erika Kancler, Carolyn Schubert and the JMU Communication Center for their time and assistance with this research project.

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