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Systematic Review

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Evaluation of efficacy and safety of Glucosamine sulfate, Chondroitin sulfate, and their combination regimen in the management of Knee Osteoarthritis: A systematic review and meta-analysis

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Abstract

Aim: This study was aimed to assess the efficacy and safety of oral Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOAs) such as Glucosamine Sulfate, Chondroitin Sulfate, and their combination regimen in the management of knee osteoarthritis (KOA).

Methods: This systematic review was conducted according to PRISMA 2020 guidelines. A detailed literature search was performed from 03/1994 to 31/12/2022 using various electronic databases including PubMed, Embase, Cochrane Library, and Google Scholar using the search terms- Glucosamine sulfate, Chondroitin sulfate, Knee osteoarthritis, Joint pain, Joint disease, and Joint structure for literature concerning glucosamine, chondroitin, and their combination in knee osteoarthritis treatment. Cochrane Collaboration's Risk assessment tool (version 5.4.1) was used for assessing the risk of bias and the quality of the literature. The data was extracted from the included studies and subjected to statistical analysis to determine the beneficial effect of Glucosamine Sulfate, Chondroitin Sulfate, and their combination.

Results: Twenty-five randomized controlled trials (RCTs) were included [9 RCTs are exclusively for Glucosamine sulfate, 13 RCTs are exclusively for Chondroitin sulfate, and only 3 RCTs can be considered for assessing the possible benefits of the combination of Glucosamine sulfate (GS) and Chondroitin sulfate (CS) versus Placebo]. The results of this meta-analysis revealed the following: (1) Pain intensity: Chondroitin sulfate showed a significant reduction in pain intensity, (2) Physical function: Chondroitin sulphate showed a significant improvement in physical function; (3) Joint space narrowing: Glucosamine sulfate showed a significant reduction in tibiofemoral joint space narrowing. Their combination did not reduce pain intensity and showed no improvement in the physical function, whereas it showed a non-significant reduction in joint space narrowing. In the safety aspect, both compounds have a good safety profile and are well tolerated.

Conclusion: When the overall effect of these SYSADOAs was evaluated, it was seen that they reduced pain intensity and improved physical function showing their symptom-modifying action and decreased the joint space narrowing significantly showing their disease-modifying action. In the safety aspect, both compounds have a good safety profile and are well tolerated. This meta-analysis revealed that as individual drugs glucosamine sulfate showed a significant reduction in the joint space narrowing while chondroitin sulfate showed a significant reduction in pain intensity and improvement in the physical function. This meta-analysis also showed that the combination did not significantly improve the symptoms or modify the disease. This may be because of the availability of limited trials on the combination of the sulfate forms of the intervention. Thus, further trials on the effect of glucosamine sulfate and chondroitin sulfate are required to establish accurate evidence regarding their use in KOA.

Keywords Glucosamine sulfate, Chondroitin sulfate, Knee osteoarthritis, Joint structure

Introduction

Osteoarthritis is a chronic, degenerative joint disease characterized by the gradual loss of articular cartilage in synovial joints which is caused by an imbalance between catabolic and anabolic processes of joints. This is a disease in which tissues in the joint break down over time (1) OA is the most common form of arthritis and is often associated with chronic pain, joint stiffness, joint changes, swelling, disability, functional impairment, and impaired quality of life (1,2). Globally, the prevalence of OA, particularly in large weight-bearing joints such as the knee and hip, is also predicted to grow (3). Knee OA accounts for almost four-fifths of the burden of OA worldwide and increases with obesity and age. Symptomatic KOA is highly prevalent among people aged 60 years and above (4). Approximately 10% of men and 18% of women older than 60 years have KOA (5). OA is the second most common rheumatologic problem and is the most frequent joint disease with a prevalence of 22% to 39% in India (6). The hands, knees, hips, neck, and lower back are the most commonly affected joints in OA. In advanced stages, OA can damage all areas of the joint including the cartilage, tendons and ligaments, synovium, bone, and the meniscus in the knee. Aging, obesity, history of injury or surgery to the joint, overuse from repetitive movements of the joint, genetics, gender and ethnicity, exercise, diet, or family history of OA, are several factors for the development of OA ((1,7). Treatment of OA can be classified as both non-pharmacological interventions including exercises that can reduce joint pain and stiffness and increase flexibility, management of

weight, use of braces and orthotics prescribed by the doctors, etc., and pharmacological therapies which include the use of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), topical creams, intra-articular corticosteroids or hyaluronic acid, etc. (1,3) The limitation with these treatments though is that they are symptom modifying and not disease-modifying treatments along with the increased risk of adverse events including the gastrointestinal and cardiovascular system upon long-term use. Thus, there exists a need for an ideal treatment, which can modify the disease itself and improve the clinical symptoms of OA with better tolerability and safety profiles, such as the symptomatic slow-acting drugs for OA (SYSADOAs), like Glucosamine sulfate and Chondroitin sulfate (3).

Glucosamine, a constituent of glycosaminoglycans in cartilage matrix and synovial fluid, acts as a proteoglycan synthesis precursor promoting the formation of an elastic layer by helping cartilage to capture water and is involved in cartilage formation. It also inhibits the actions of catabolic enzymes and reduces IL-1β levels in synovial fluid (2,8). Chondroitin is a major component of the extracellular matrix of connective tissues and plays a crucial role in creating considerable osmotic pressure that expands the matrix and places the collagen network under tension (8). Multiple RCTs have been conducted previously using GS or CS alone, proving a significant improvement in KOA. However, a huge divergence is seen in the improvement in symptoms of KOA by using the combination of GS and CS (5). Many products or drugs containing a combination of GS and CS have emerged in the market and thus it becomes important for us to understand if the combination proves to be more beneficial than the individual drugs and if they have a disease-modifying effect on KOA. This systematic review and meta-analysis answer this question.

Methodology

Search strategy

Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) 2020 guidelines were followed for this Systematic Review and Meta-Analysis. Electronic databases including PubMed, Embase, Cochrane Library, and Google Scholar were systematically searched based on a logical combination of keywords associated with OA to extract concerned RCTs from inception (1994) to December 31, 2022. The Internet-based search used the following terms: “Glucosamine sulfate”, “Chondroitin sulfate”, “Knee osteoarthritis”, “Joint structure”, and the corresponding free terms. The search was restricted to the English language and only the Randomized Controlled Clinical Trials were chosen. All articles' reference lists

were screened to avoid missing relevant articles. Clinicaltrials.gov was searched for any progressive or ongoing trials. The complete literature search was performed by A.R and G.L.V.

Inclusion and exclusion criteria

The inclusion and exclusion criteria followed a PICO format.

Inclusion criteria:

- Population: Participants of adult (> 18 years) age groups with no gender specifications diagnosed clinically or radiologically with knee osteoarthritis
- Intervention: studies covering intervention such as glucosamine sulfate or chondroitin sulfate or their combination against placebo
- Comparator: studies comparing intervention with placebo group
- Outcomes: Studies reporting pain intensity, stiffness, physical function and tibiofemoral joint space narrowing

Other inclusion criteria are as follows:

Study type: Randomized placebo-controlled trials

Region: Global

Language: all articles published in English language only

Exclusion criteria:

- Population: Participants not diagnosed clinically or radiologically with knee osteoarthritis
- Intervention: studies including the combination of other interventions along with the intervention of interest
- Comparator: studies comparing intervention with any group other than placebo
- Outcomes: Studies reporting outcomes other than those mentioned in the inclusion criteria

Other exclusion criteria are as follows:

Study type: non-Randomized placebo-controlled trials, studies including interventions administered by any route other than oral, studies without numerical data or data in a non-uniform format, studies without full-text available, duplicate studies, observational studies

(cohort, case-control studies etc.), retrospective studies, meta-analysis, reviews, animal studies etc.

Language: any article published in language other than English

Quality assessment and Risk of bias

Cochrane Collaboration's risk assessment tool (version 5.4.1) was used to evaluate the methodological quality of the included studies. The tool evaluated six potential risks of bias: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each item was judged by the following criteria: low risk of bias, uncertain risk of bias, and high risk of bias. Whenever studies included three or more high risks of bias, it was considered as poor methodological quality. Two reviewers (A.R and G.L.V) checked the profile of each included study independently.

Data extraction

All the studies were assessed for eligibility and extracted data. Two investigators (A.R and G.L.V) independently assessed all the studies for eligibility, and the data was extracted from each study. Any disagreements were resolved through discussion with the reviewers (A.K and K.N). For each study, patients' characteristics including mean age, sex, mean duration of symptom, duration of follow-up, type of outcome (pain, function, stiffness, and AEs), study design, sample size, details of the intervention, treatment duration, and results were individually extracted.

Outcome measures

The primary outcomes of this systematic review and meta-analysis were pain intensity, stiffness score, function improvement, and joint space narrowing from the baseline to the end of the treatment. The safety of the studies was the secondary outcome.

Main outcomes

The aforementioned outcomes were measured using the following scales:

(1) The Western Ontario and McMaster Universities Osteoarthritis Index, WOMAC
    Three subscales of the WOMAC were used in order to measure pain, stiffness, and function.
(2) Visual Analog Scale, VAS (0 – 100mm) to measure pain intensity.

(3) Lequesne Index to measure pain intensity.

Safety outcomes

The most common adverse events reported in all the studies were combined. These were gastrointestinal disturbances like diarrhea, constipation, headache, skin allergies like rashes, pruritis, urinary tract infections, and respiratory tract infections.

Statistical analysis

Review Manager (RevMan, version 5.4) was employed for the meta-analysis. The random and fixed-effects models were used to estimate the inverse variance (IV) for continuous variables using a mean difference (MD) as an impact measure. The effect size measure for the dichotomous variables was the odds ratio (OR) or risk difference (RD), and the Mantel-Haenszel (M-H) statistic was calculated using the random-effects (RE) and fixed-effects (FE) models. Random-effects model was utilised to get the pooled effect, and a 95% confidence interval (CI) was used. Heterogeneity was determined using the I^2 statistic. I^2 values below 40% were considered insignificant. However, for I^2 values greater than 40%, moderate to high heterogeneity was considered.

Results

Literature search

A total of 613 articles were identified by using electronic databases including 236 from PubMed, 182 from Embase, and 192 from Google Scholar. In addition, 3 articles were found from other sources.

Screening

Out of the 613 studies, 355 duplicate records were excluded. The remaining 258 records were screened manually for titles and abstracts from which 119 records were excluded which did not meet the eligibility criteria. The remaining 139 full-text articles were assessed for eligibility from which 114 articles were excluded with proper reasons. 25 studies were included in the qualitative synthesis. 9 articles compared the glucosamine sulfate group with the placebo, 13 articles compared the chondroitin sulfate group with the placebo, and 3 articles compared the combination with the placebo. Refer Figure 1 PRISMA flowchart for study selection.

Study characteristics

The characteristics of all the twenty-five included studies are summarised in Table 1. All the studies were Randomized Controlled Trials (RCTs) which included intervention (either glucosamine sulfate or chondroitin sulfate or their combination) group and placebo group. The number of participants ranged between 36 and 622, and the articles were published between 1994 and 2019.

Risk of bias

The Risk of bias in the included studies is summarized in Figure 2. 22 out of 25 studies were double-blind. One was a single-blind, another one did not mention any blinding and in the third, the nature of blinding was not clear. Random sequence generation was unclear in 5 studies and was high risk in 3 studies. Allocation concealment was unclear in 2 studies and 2 studies showed high risk. 24% of the studies showed incomplete outcome data while 24% of the studies did not show selective reporting. One study was found to have poor methodological quality (24).

Effect on evaluation parameters

1. Pain intensity

All twenty-five studies included in this review reported pain intensity in both groups (Table 1).

A. WOMAC

1.1.1 Placebo vs Glucosamine sulfate (GS)

Four out of nine studies of GS (9–12) reported pain intensity using the WOMAC pain subscale. Glucosamine sulfate showed a decrease in pain intensity (Inverse variance (IV): -0.10 (-0.25 to 0.05) at 95% CI, $p = 0.19$, I-square = 7%) but was statistically not significant. (Figure 3).

1.1.2 Placebo vs Chondroitin sulfate (CS)

Three out of thirteen studies of CS (11,13,14) reported pain intensity using the WOMAC pain subscale. Chondroitin sulfate showed a decrease in pain intensity (Inverse variance (IV): -0.76 (-0.90 to -0.62) at 95% CI, $p < 0.00001$, I-square = 99%). This decrease in the pain intensity was statistically significant and thus CS can be considered a symptom-modifying agent in the management of knee osteoarthritis. (Figure 3).

1.1.3 Placebo vs GS + CS

Two out of three studies of the combination (11,15) reported pain intensity using the WOMAC pain subscale. The combination did not show any decrease in pain intensity (Inverse variance (IV): 0.42 (0.22 to 0.62) at 95% CI, $p < 0.0001$, I-square = 98%), and the results favored the placebo group. (Figure 3).

Overall

The overall effect (Inverse variance (IV): -0.27 (-0.36 to -0.18) at 95% CI, $p < 0.00001$, I-square = 98%) was significantly favouring the experimental group compared to the placebo group showing an overall decrease in the pain intensity in patients with knee osteoarthritis. (Figure 3).

B. VAS

1.2.1 Placebo vs Glucosamine sulfate (GS)

Three out of nine studies of GS (16,17) reported pain intensity using VAS (0 – 100) mm. Glucosamine sulfate showed a decrease in pain intensity but was insignificant (Inverse variance (IV): -5.10 (-14.49 to 4.30) at 95% CI, $p = 0.29$, I-square = 99%) (Figure 4).

1.2.2 Placebo vs Chondroitin sulfate (CS)

Nine out of thirteen studies of CS (13,18–25) reported pain intensity using VAS (0 – 100) mm. Chondroitin sulfate showed a statistically significant decrease in pain intensity (Inverse variance (IV): -9.40 (-15.05 to -3.76) at 95% CI, $p = 0.001$, I-square = 99%) (Figure 4).

Placebo vs GS + CS: Meta-analysis was not performed due to availability of single study assessing this parameter.

Overall

The overall effect (Inverse variance (IV): -8.37 (-11.14 to -5.60) at 95% CI, $p < 0.00001$, I-square = 99%) was significantly favoring the experimental group compared to the placebo group showing an overall decrease in the pain intensity in patients with knee osteoarthritis (Figure 4).

C. VAS Resting Pain

1.3.1 Placebo vs Glucosamine sulfate (GS)

Two of the nine studies of GS (27,28) reported resting pain using VAS (0 – 100) mm. Glucosamine sulfate showed a statistically significant decrease in the resting pain intensity (Inverse variance (IV): -8.58 (-15.69 to -1.47) at 95% CI, p = 0.02, I-square = 71%) (Figure 5).

1.3.2 Placebo vs Chondroitin sulfate (CS)

Three of the thirteen studies of CS (29–31) reported resting pain using VAS (0 – 100) mm. Chondroitin sulfate though not statistically significant showed a decrease in resting pain intensity favouring the experimental group (Inverse variance (IV): -2.01 (-5.74 to 1.72) at 95% CI, p = 0.29, I-square = 0%) (Figure 5).

Placebo vs GS + CS: Meta-analysis was not performed as none of the studies reported this parameter.

Overall

The overall effect (Inverse variance (IV): -3.43 (-6.73 to -0.13) at 95% CI, p = 0.04, I-square = 39%) was significantly favoring the experimental group compared to the placebo group showing an overall decrease in the resting pain intensity in patients with knee osteoarthritis. (Figure 5)

D. VAS Moving Pain

1.4.1 Placebo vs Glucosamine sulfate (GS)

Two of the nine studies of GS (27,28) reported moving pain using VAS (0 – 100) mm. Glucosamine sulfate though not statistically significant showed a decrease in moving pain intensity as compared to the placebo group (Inverse variance (IV): -5.37 (-12.45 to 1.71) at 95% CI, p = 0.14, I-square = 55%)(Figure 6).

1.4.2 Placebo vs Chondroitin sulfate (CS)

Three of the thirteen studies of CS (29–31) reported moving pain using VAS (0 – 100) mm. Chondroitin sulfate showed a statistically significant decrease in the moving pain intensity when compared to the placebo group (Inverse variance (IV): -5.86 (-10.07 to -1.65) at 95% CI, p = 0.006, I-square = 0%) (Figure 6).

Placebo vs GS + CS: Meta-analysis was not performed as none of the studies reported this parameter.

Overall

The overall effect (Inverse variance (IV): -5.73 (-9.35 to -2.11) at 95% CI, p = 0.002, I-square = 0%) was significantly favouring the experimental group compared to the placebo group showing an overall decrease in the moving pain intensity in patients with knee osteoarthritis (Figure 6).

E. Lequesne Index

Lequesne algo functional index is a questionnaire consisting of 10 questions reporting pain as well as physical function as a single unit.

1.5.1 Placebo vs Glucosamine sulfate (GS)

Three of the nine studies of GS (9,10,32) reported pain intensity and physical function using Lequesne algo functional index. All the studies showed a significant reduction in pain intensity and improvement in physical function favouring the experimental group (Inverse variance (IV): -1.15 (-1.79 to -0.51) at 95% CI, p = 0.0004, I-square = 0%) (Figure 7).

1.5.2 Placebo vs Chondroitin sulfate (CS)

Eight out of thirteen studies of CS (18,20,22,24,25,29–31) reported pain intensity and physical function using Lequesne algo functional index. All the studies showed a significant reduction in pain intensity and an improvement in physical function favouring the CS group (Inverse variance (IV): -1.50 (-2.11 to -0.88) at 95% CI, p < 0.00001, I-square = 59%) (Figure 7).

Placebo vs GS + CS: Meta-analysis was not performed as none of the studies reported this parameter.

Overall

The overall effect (Inverse variance (IV): -1.37 (-1.81 to -0.94) at 95% CI, p < 0.00001, I-square = 47%) was significantly favouring the experimental group compared to the placebo group showing an overall decrease in the pain intensity and improvement in the physical function in patients with knee osteoarthritis (Figure 7).

2. Stiffness

Meta-analysis of this parameter was not performed due to the availability of only a smaller number of studies reporting stiffness. Out of the nine studies comparing GS with a placebo, only two reported stiffness (10,12). Both studies reported a significant effect of GS in improving stiffness against a placebo. Only one study out of thirteen comparing chondroitin

sulfate with placebo reported stiffness and the result was insignificant (14). None of the combinations versus placebo studies reported stiffness.

3. Function

Physical function was reported using the WOMAC function subscale having 17 questions.

1.6.1 Placebo vs Glucosamine sulfate (GS)

Four out of nine studies of GS (9–12) reported function as a parameter using the WOMAC function subscale. Out of these, three studies favored the experimental group whereas one study showed no effect favouring neither placebo nor the GS group. The overall effect was not significant (Inverse variance (IV): -0.11 (-0.25 to 0.04) at 95% CI, p = 0.16, I-square = 0%) (Figure 8).

1.6.2 Placebo vs Chondroitin sulfate (CS)

Two out of the thirteen studies of CS (11,14) reported function using the WOMAC function subscale. Both the studies favoured the CS group and were shown to significantly improve physical function (Inverse variance (IV): -0.79 (-1.00 to -0.59) at 95% CI, p < 0.00001, I-square = 100%) (Figure 8).

1.6.3 Placebo vs GS + CS

Two of the three studies of the combination (11,15) reported function using WOMAC function subscale. One study favoured the placebo group while the other study showed no effect. Thus, the combination favoured the placebo group significantly (Inverse variance (IV): 0.43 (0.23 to 0.63) at 95% CI, p < 0.0001, I-square = 99%) (Figure 8).

Overall

The overall effect (Inverse variance (IV): -0.14 (-0.25 to -0.04) at 95% CI, p = 0.007, I-square = 98%) was significantly favouring the experimental group compared to the placebo group indicating an overall improvement in the physical function in patients with knee osteoarthritis (Figure 8).

4. Joint Space Narrowing (JSN)

Radiological measurement of the tibiofemoral joint space width is a crucial parameter to assess the progression of the disease. For this Joint Space Narrowing (JSN) is measured in mm.

1.7.1 Placebo vs Glucosamine sulfate (GS)

Three of the nine studies (10–12) reported JSN in mm. Out of which two studies favoured the experimental group while one study favoured the control group. The overall effect was significantly favouring the GS group (Inverse variance (IV): 0.29 (0.15 to 0.42) at 95% CI, $p < 0.0001$, I-square = 85%) indicating the disease-modifying effect of Glucosamine sulfate (Figure 9).

1.7.2 Placebo vs Chondroitin sulfate (CS)

Three of the thirteen studies (11,14,18) reported JSN. Out of which two studies favoured the experimental group while one study favoured the control group. The overall effect though favoured the treatment group was insignificant (Inverse variance (IV): 0.11 (-0.01 to 0.24) at 95% CI, $p = 0.08$, I-square = 42%) indicating no significant disease-modifying effect of CS (Figure 9).

Placebo vs GS + CS: Meta-analysis was not performed due to availability of single study assessing this parameter.

Overall

The overall effect (Inverse variance (IV): 0.19 (0.10 to 0.29) at 95% CI, $p < 0.0001$, I-square = 76%) was significantly favouring the experimental group compared to the placebo group indicating an overall decrease in the joint space narrowing in patients with knee osteoarthritis. This indicates the disease-modifying effect of the intervention (Figure 9).

Adverse effects

Seven out of nine studies of GS (9,10,12,16,17,28,32) while eight of the thirteen studies of CS (13,14,20–22,25,29,31) reported adverse events. None of the combination studies reported any adverse events. The most common adverse events reported among these studies were gastrointestinal disturbances including diarrhea, headache, skin allergies, urinary tract infections, and upper respiratory tract infections. Three studies from GS versus the placebo group (12,16,28) whereas three studies from CS versus the placebo group (25,29,31) reported diarrhea in both groups. One study from GS versus placebo reported diarrhea in just the placebo group (10). Four GS versus placebo studies (12,16,28,32) while one CS versus placebo study (14) reported headache. Skin allergies like pruritis were reported in both the groups of two GS versus placebo studies (10,32) whereas it was only reported in the placebo group in one study

(16) and only in the GS group (28) in the other. Two CS versus placebo studies (20,25) reported the occurrence of skin allergies. Urinary tract infections occurred in the GS group of 2 studies (10,16) while only in the placebo group of one study (10) whereas UTI occurred in just one CS versus placebo study (14). Five GS versus placebo studies (10,12,16,17,28) and two CS versus placebo studies (14,20) reported the occurrence of upper respiratory tract infections. No AEs were reported in any of the combination versus placebo studies. Though these were the adverse events reported, no significant difference was found in the AEs reported in the intervention group and the placebo group suggesting a good safety profile of the SYSADOAs. (9,10,12,16,32)

Discussion

In this study, we performed a systematic review and meta-analysis of twenty-five randomized controlled trials assessing the effectiveness and safety of glucosamine sulfate, chondroitin sulfate, and their combination for the treatment of knee osteoarthritis, selected based on their high methodologic quality, The primary efficacy outcome measures considered consists of 4 core domains: pain intensity, stiffness, physical function, and joint space width (JSW). A decrease in pain intensity, stiffness and improvement in physical function indicates the symptom-modifying effect of these SYSADOAs. Whereas decrease in the joint space narrowing (JSN) indicates the disease-modifying effect. All the twenty-five trials included in this study reported pain and function using different scales. Joint structural changes were assessed on radiographs and represented by mean JSW changes of the tibiofemoral joint in seven trials.

The WOMAC index was used to measure the severity of knee OA symptoms in the 3 trials, but alternative forms (i.e., VAS and Likert scale) were applied. These different versions were then converted into a standard format and the data was extracted. Not enough articles were available which reported stiffness and thus a meta-analysis of the effect of the intervention on stiffness was not possible.

For reduction in pain intensity using all the different pain scales (i.e., WOMAC, VAS, and LI), our results suggested that the overall effect showed a significant reduction in pain favouring the experimental group. The physical function was evaluated using the WOMAC function subscale and the results suggested an overall significant improvement in the physical function favouring the experimental group. The reduction in the JSN was evaluated and our results suggested that the overall effect showed a significant reduction in JSN favouring the

experimental group. Stiffness was not considered in this meta-analysis, and results of the systematic review revealed that GS may reduce stiffness in KOA patients, but CS and combination did not show this reduction.

In this study, it was seen that GS reduced pain when measured with WOMAC, VAS scales, and Lequesne Index, whereas no reduction was seen in moving pain using VAS. Based on the results of the systematic review, GS showed a significant reduction in stiffness. GS statistically showed a significant reduction in the joint space narrowing. However, it did not improve the physical function significantly.

CS showed a significant reduction in pain intensity, and JSN and an improvement in physical function. The combination of GS and CS did not show any significant reduction in pain intensity, JSN and improvement in physical function.

Previously only one systematic review and meta-analysis was performed on the efficacy and safety of the combination of GS and CS by Zhengyuan Meng et. al. This study included all the articles in English and Chinese unlike our study which excluded articles in any language other than English. Also, their study did not include articles in which GS and CS were given individually against placebo unlike our study which included all the articles following the inclusion criteria. They concluded that the combination showed a statistically significant effect and that it is effective and superior to other treatments in KOA which is not the case in our study. This may be because of the exclusion of other RCTs which were not published in the English language. (5)

2 meta-analyses were performed previously by Young Ho Lee et. al. (8)and Xiaoyue Zhu et. al. (3) on the effectiveness of glucosamine and chondroitin on KOA. Young Ho Lee et. al. included all the articles in which GS and CS were given as an intervention whereas Xiaoyue Zhu et. al. included articles in which different salt forms of the intervention such as Glucosamine Hydrochloride (GH) and Chondroitin Hydrochloride (CH) were also used. However, in our study in which we considered articles that included only the sulfate salt forms of the intervention. This makes our study more homogenous as different salt forms have different characteristics e.g., the sulfate form of glucosamine has higher oral bioavailability and lesser clearance as compared to the hydrochloride form. Also, Young Ho Lee et. al. focused only on the radiological progression of KOA and did not consider any other parameters like pain, stiffness, or function whereas Xiaoyue Zhu et. al. did not consider radiological

progression and thus JSN as a parameter in their analysis. Our study covered both symptoms as well as the disease-modifying actions viz. pain, stiffness, function, and JSN.

Thus, it is worth mentioning that our systematic review and meta-analysis include all the parameters and efficacy of intervention both individually as well as in combination. This study has also considered articles with sulfate salt form of the drug, making it homogenous. The literature search was done thoroughly and systematically using all the possible databases which leave us with no chance of missing out on any articles. The search did not have any time constrain and all the available articles were included in this study. Also, this study considered only the oral route of administration of this intervention, and thus the data obtained was homogenous. Even though different scales were used in different articles for the evaluation of the same parameter, we standardized them to one single unit thus not missing out on relevant data.

Limitations of this study include:

(1) The literature search was restricted to English language only, thus missing out on data of the trials which are published in other languages. This may have an impact on the results, (2) Inclusion of RCTs only to have as low risk of bias as possible, (3) Inclusion of placebo-controlled trials, (4) This study included articles with only the sulfate salt form of the drugs, and thus any other RCTs where other salt forms were used, are excluded leaving a very limited number of studies in the combination versus the placebo group, (5) As this study evaluates the efficacy of oral SYSADOAs, RCTs having the same intervention but using a different route of administration were excluded, (6) The efficacy of the combination on pain intensity using VAS scale and Lequesne index and joint space narrowing was not quantitatively analysed due to unavailability of sufficient studies on the combination.

Authors prospectives

The main objectives of this study were to assess the disease-modifying effects of glucosamine sulfate and chondroitin sulfate when given individually and in combination and to assess their safety. With the available moderate weight of evidence it can be concluded that both the interventions when given individually showed an overall reduction in pain intensity and an improvement in the physical function suggesting symptom-modifying effect and showed a significant reduction in the tibiofemoral joint space narrowing suggesting a disease-modifying effect. But this this was not seen when the interventions were given in combination. Due to the

limited availability of the studies reporting stiffness in joints in the patients with KOA, a meta-analysis could not be performed for this parameter. Thus, we conclude that more multicentric RCTs are needed to be conducted using glucosamine sulfate and chondroitin sulfate in combination in order to obtain a more evident conclusion.

Conclusion

This study aimed to assess the efficacy and safety of oral SYSADOAs, viz.- glucosamine sulfate and chondroitin sulfate on symptoms and structure in KOA. We performed meta-analyses on twenty-five randomized clinical trials which were selected based on pre-defined inclusion criteria. According to our results, oral SYSADOAs are more effective and superior to placebo and thus can be used in the management of KOA.

When given individually, Glucosamine sulfate was more effective than placebo; it reduced pain intensity and improved physical function though that was insignificant and decreased joint space narrowing significantly. Chondroitin sulfate on the other hand reduced pain intensity and improved physical function significantly, while the reduction in JSN was insignificant. When given in combination, these SYSADOAs did not reduce pain intensity or improve physical function. Reduction seen in JSN was insignificant. When the overall effect of these SYSADOAs was evaluated, it was seen that they reduced pain intensity and improved physical function which shows their symptom-modifying action and decreased the joint space narrowing significantly exhibiting their disease-modifying action. In the safety aspect, both the compounds have a good safety profile and are well tolerated.

Combination therapy is frequently used in clinical practice, but this meta-analysis shows that the combination has not significantly improved the symptoms or modified the disease. This may be because of the limited trials on the combination of the sulfate forms of the interventions. Therefore, further trials on the effect of glucosamine sulfate and chondroitin sulfate are required to establish accurate evidence regarding their use in KOA.

Conflicts of interest state: Authors declare no conflict of interest.

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Table 1 Description of included studies

Sr. No.	Author Name	Dose, route, and duration of treatment	Parameters	Scales used	Safety	Outcomes and conclusion
Glucosamine sulfate						
1	R. Hughes and A. Carr, (2002)	1500mg/day (500mg x 3 times/day), orally for 6 months	Pain intensity	VAS (0-100) mm	Diarrhoea, Headache, Skin allergy, UTI, RTI	GS was no more effective than placebo in KOA patients.
2	Wolfgang Noack et.al. (1994)	1500mg/day (250mg x 2 tablets, 3 times a day), orally for 4 weeks	Pain and function	Lequesne Index	Headache, Skin allergy	GS was significantly more effective than placebo in improving pain and movement limitation.
3	Gabriel Herrero-Beaumont et. al. (2007)	1500mg/day, powder sachets orally for 6 months	Pain and function	WOMAC, Lequesne index	NA	GS was significantly more effective for KOA symptoms, compared to placebo.

Sr. No.	Author Name	Dose, route, and duration of treatment	Parameters	Scales used	Safety	Outcomes and conclusion
Glucosamine sulfate						
4	Karel Pavelka et. al. (2002)	1500mg/day, powder sachets daily for 3 years	Pain, stiffness, function, and JSN	WOMAC, Lequesne Index	Diarrhoea, Skin allergy, UTI, RTI	Long-term treatment with GS retarded the progression of KOA, possibly determining disease modification.
5	Reginster et. al. (2001)	1500mg/day, for 3 years	Pain, stiffness, function, and JSN	WOMAC, Lequesne Index	Diarrhoea, Headache, RTI	Long-term treatment with GS showed structure- and symptom-modifying effects in KOA.
6	Susanne G. Petersen et. al. (2011)	1500mg/day for 12 weeks	Pain	VAS (0-10) cm	NA	No significant beneficial effects of GS were found.

Sr. No.	Author Name	Dose, route, and duration of treatment	Parameters	Scales used	Safety	Outcomes and conclusion
Glucosamine sulfate						
7	Joseph P Rindone et. al. (2000) (27)	500mg x 3 times a day for 2 months	Pain intensity	VAS (0-10) cm	NA	GS was no better than a placebo in reducing pain from KOA in this group of patients.
8	K. Madhu et. al. (2013) (17)	750mg x 2 times/day for 42 days	Pain and total WOMAC	VAS (0-100) mm, WOMAC	RTI	A significant reduction in pain was observed in the GS group as compared to the placebo.
9	Nicola Giordano et. al. (2009) (28)	1500mg/day for 12 weeks	Pain	VAS (0-100) mm	Diarrhea, Headache, Skin allergy, RTI	A significant reduction in pain was observed in the GS group.

Chondroitin sulfate						
1	Beat A. Michel et. al. (2005) (14)	800mg/day tablet for 2 years [Condrosulf]	Pain, stiffness, function and JSW	WOMAC score, range 0-10	Headache, UTI, RTI	No appreciable change in pain, stiffness, and function was seen.
2	Jean-Yves Reginster et. al. (2017) (21)	800mg/day capsule for 6 months	Pain and function	VAS (0-100) mm, Lequesne Index (0-24)	NA	CS showed significant improvement in pain and function and was superior to PBO.
3	Bernard Mazie`res et. al. (2007) (29)	1000mg/day (500mg x 2 times/day) hard capsules orally for 24 weeks	Mean variation of pain on activity, mean variation of LI score at end of 24 weeks.	VAS (0-100) mm, Lequesne Index (0-24)	Headache	This study failed to show the efficacy of CS although it was slightly more effective than PBO on pain.

Sr. No.	Author Name	Dose, route, and duration of treatment	Parameters	Scales used	Safety	Outcomes and conclusion
Chondroitin sulfate						
4	I. Möller et. al. (2010) (20)	800mg/day (400mg x 2 times/day) capsules orally for 3 months	Pain and function	VAS, Lequesne index (1-14)	Skin allergy, RTI	Daily administration of CS for 3 months improved OA-associated pain and physical function.
5	Mariangela Rondanelli et. al. (2019) (23)	600mg/day tablet orally, for 12 weeks	Pain and function	WOMAC, VAS	NA	CS showed significant improvement in pain, and function.
6	Pierre Bourgeois et. al. (1998) (25)	1200mg/day oral gel, for 3 months	Pain and function	VAS (0-100) mm, Lequesne Index	Diarrhea, Skin allergy	LI and VAS scores decreased significantly in the treatment group at day 91 as

						compared to the placebo group.
7	Laszlo Bucsi et. al. (1998) (22)	800mg/day orally for 6 months	Pain and function	VAS (0-100) mm, Lequesne Index	NA	CS 800mg/day for 6 months is an effective and safe SYSADOA in patients with KOA.
8	Daniel Uebelhart et. al. (2004) (18)	800mg/day sachet orally, from entry to month 3 and from month 6 to 9. **No treatment to any group between months 3-6 and 9-12.**	Pain, function, JSN	VAS (0-100) mm, Lequesne algo functional Index	NA	Condrosulf is effective in reducing pain and improving function but was not able to prove its structure-modifying effects.

Sr. No.	Author Name	Dose, route, and duration of treatment	Parameters	Scales used	Safety	Outcomes and conclusion
Chondroitin sulfate						
9	Andre´ Kahan et. al. (2009) (13)	800mg/day sachet, orally for 2 years	Pain and JSN	VAS (0-100) mm	NA	Long-term combined structure- and symptom-modifying effects suggest that it could be a disease-modifying agent.
10	Bernard Mazieres et. al. (2001) (30)	500mg x 2 times/day gel caps for 90 days	Pain and function	VAS, Lequesne AFI	NA	AFI showed greater but non-significant improvement in the CS than in PBO.
11	J-J. Railhac et. al. (2012) (31)	500mg x 2 times/day for 48 weeks	Pain and function	VAS (0-100) mm, Lequesne Index	Diarrhea	No statistically significant

						improvement was seen.
12	Mohammad H. Elgawish et. al. (2015) (24)	2 capsules of 500mg Structum capsule once daily for 6 months.	Pain and function	VAS (0-100) mm, Lequesne Index	NA	No statistically significant difference in terms of VAS, but a highly significant difference in terms of LFI score.
13	Daniel Uebelhart et. al. (1998) (19)	400mg sachet x 2 sachets/day, orally for 1 year **(Condrosulf® IBSA)**	Pain and JSN	Huskisson VAS (0-10) cm	NA	Significant improvement was seen in pain and JSN.

Sr. No.	Author Name	Dose, route, and duration of treatment	Parameters	Scales used	Safety	Outcomes and conclusion
Glucosamine sulfate + Chondroitin sulfate						
1	Jorge A. Roman-Blas et. al. (2016) (15)	(1500mg crystalline GS + 1200mg CS)/day, sachet, orally for 6 months	Pain and function	VAS version of WOMAC	NA	CS/GS combination therapy was not superior to placebo.
2	Andri M.T. Lubis et. al. (2017) (26)	1500mg of GS + 1200mg of CS + 500mg of saccharumlactis, once daily for 3 months	Pain	VAS, WOMAC	NA	Our findings indicate that glucosamine-chondroitin sulfate was not effective in reducing joint pain in OA

						compared to placebo.
3	Marlene Fransen et. al. (2014) (11)	(753mg of GS capsule + 400mg of CS capsule) once daily, for 2 years	Pain, function, and JSN	WOMAC	NA	There was no significant symptomatic improvement, but the combination achieved a significant reduction in tibiofemoral JSN over 2 years, compared with the placebo.

Figure 1 PRISMA Flowchart for study selection

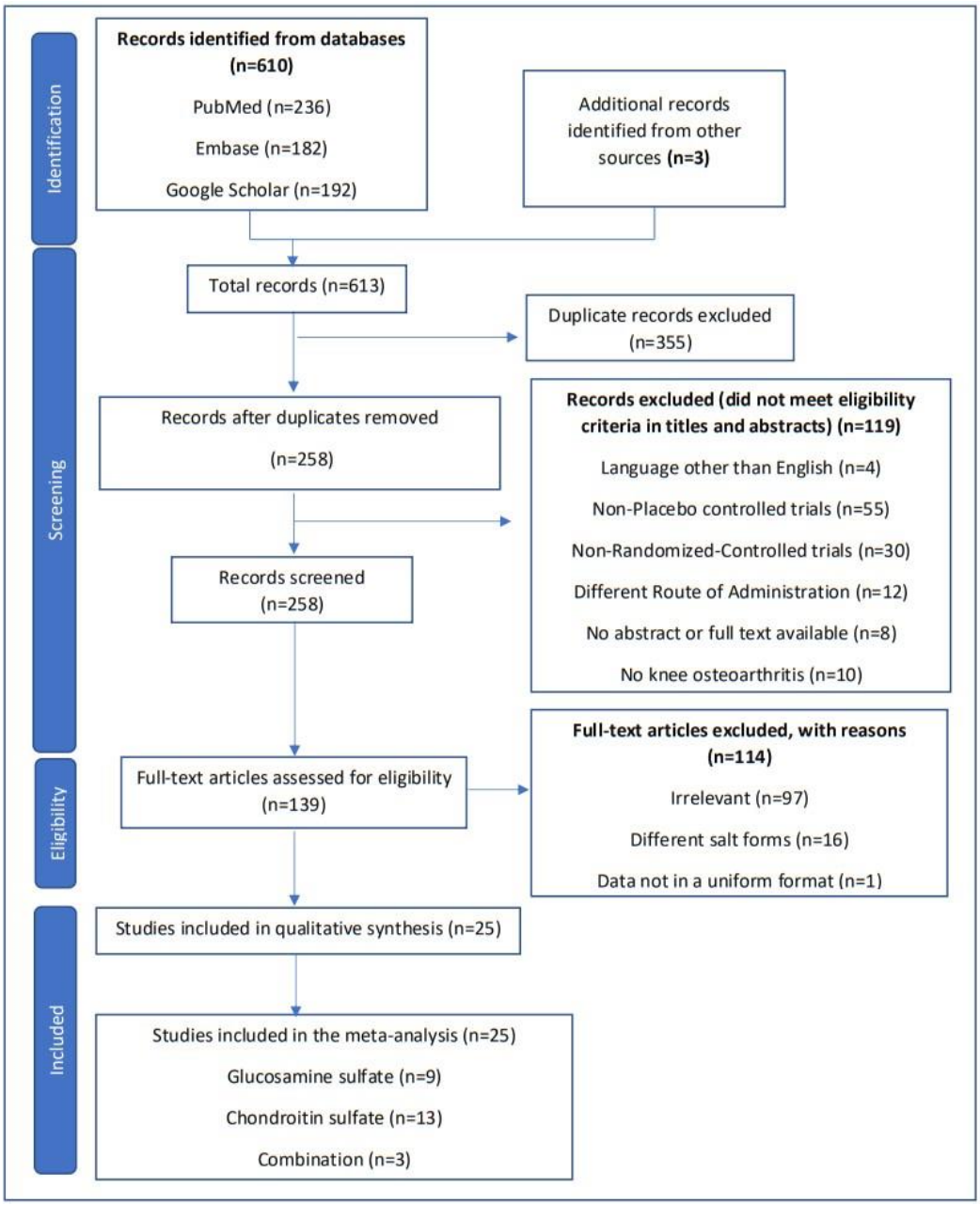

Figure 2 Risk of bias summary

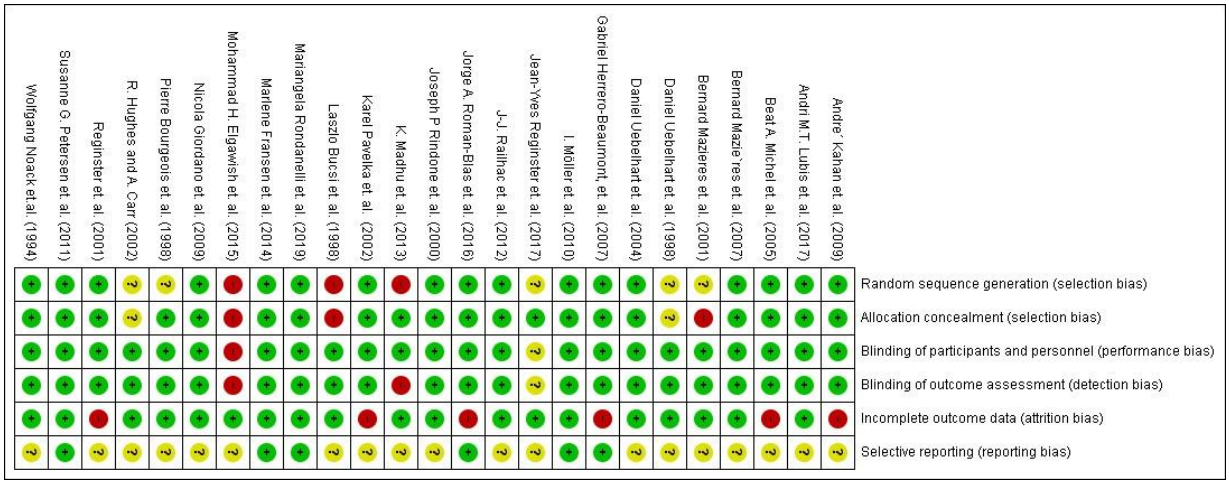

Figure 3 Pain intensity: WOMAC Forest Plot

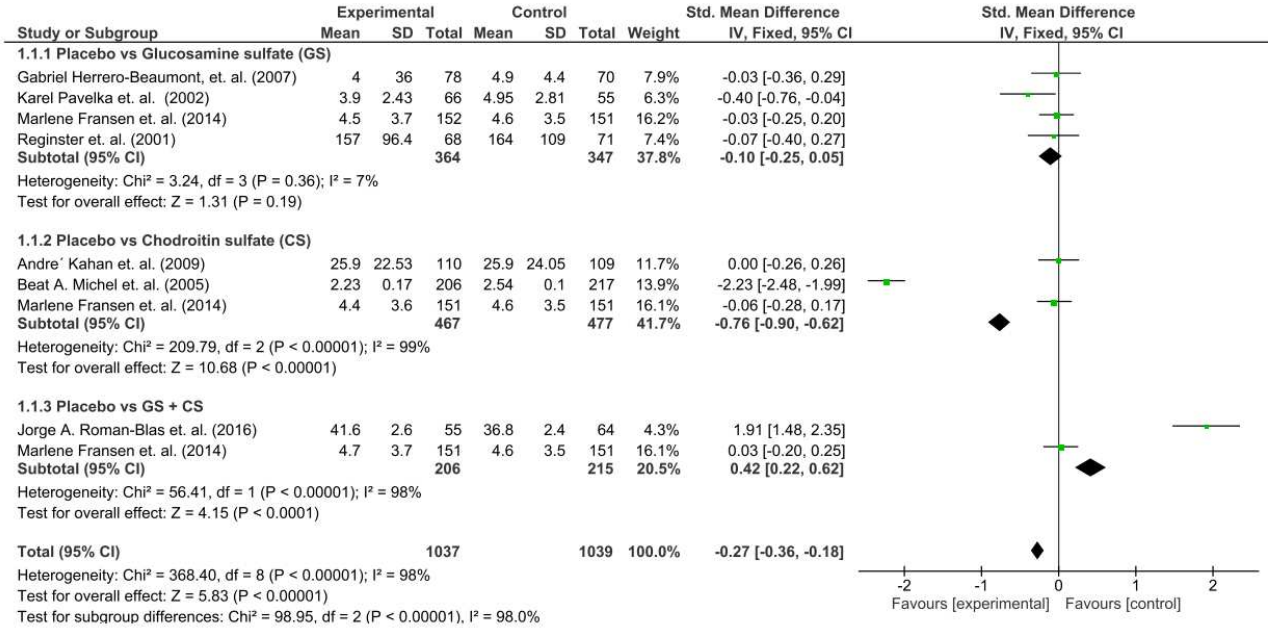

Figure 4 Pain intensity: VAS Forest Plot

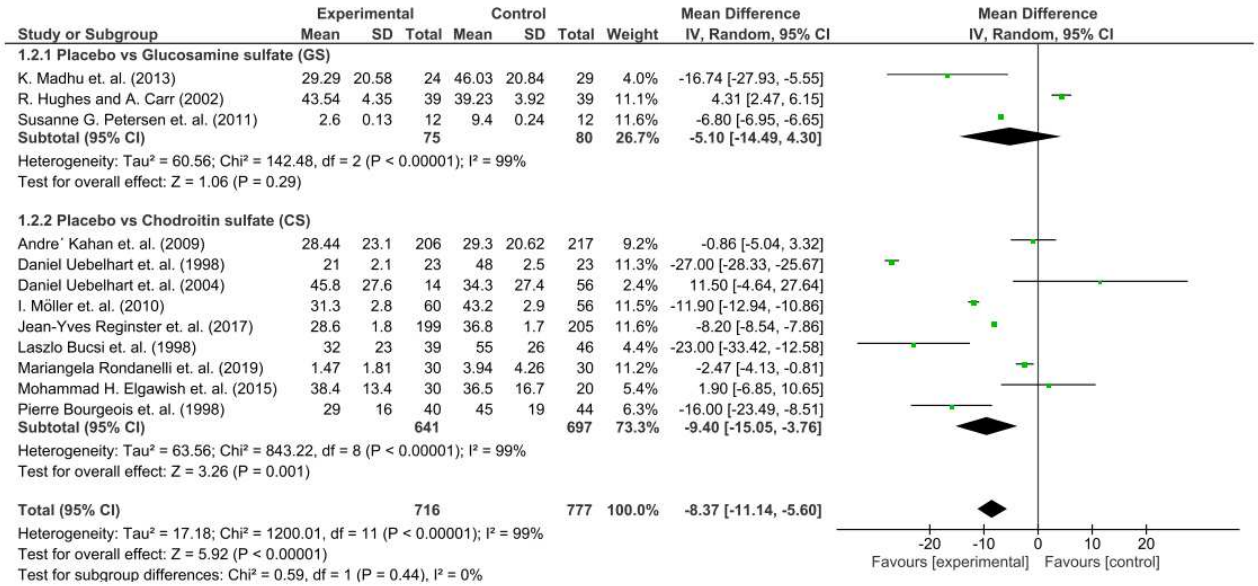

Figure 5 Pain intensity: VAS Resting Pain Forest Plot

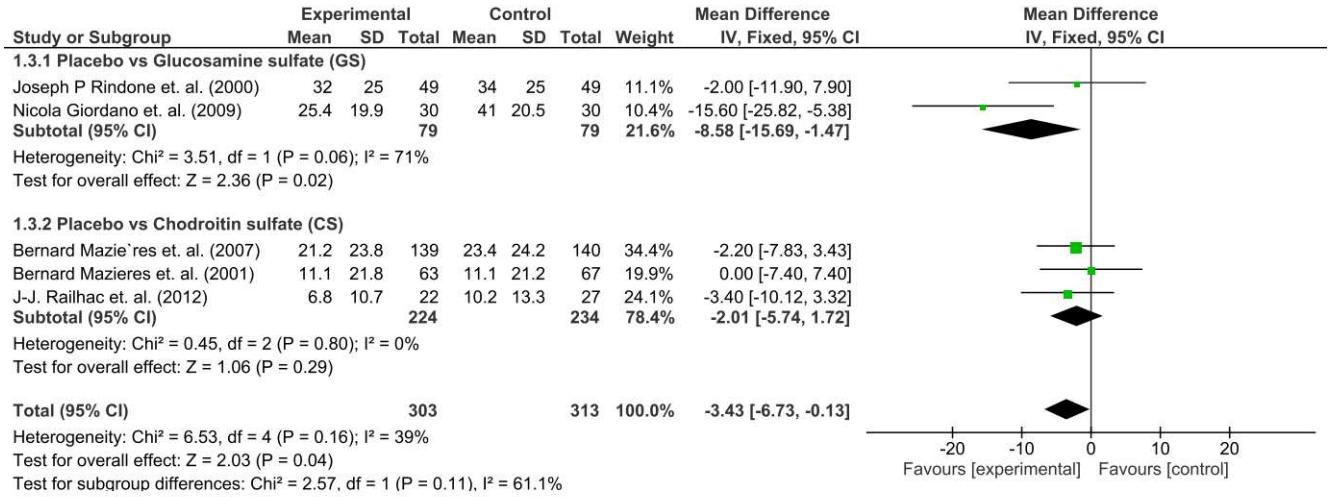

Figure 6 Pain intensity: VAS Moving Pain Forest Plot

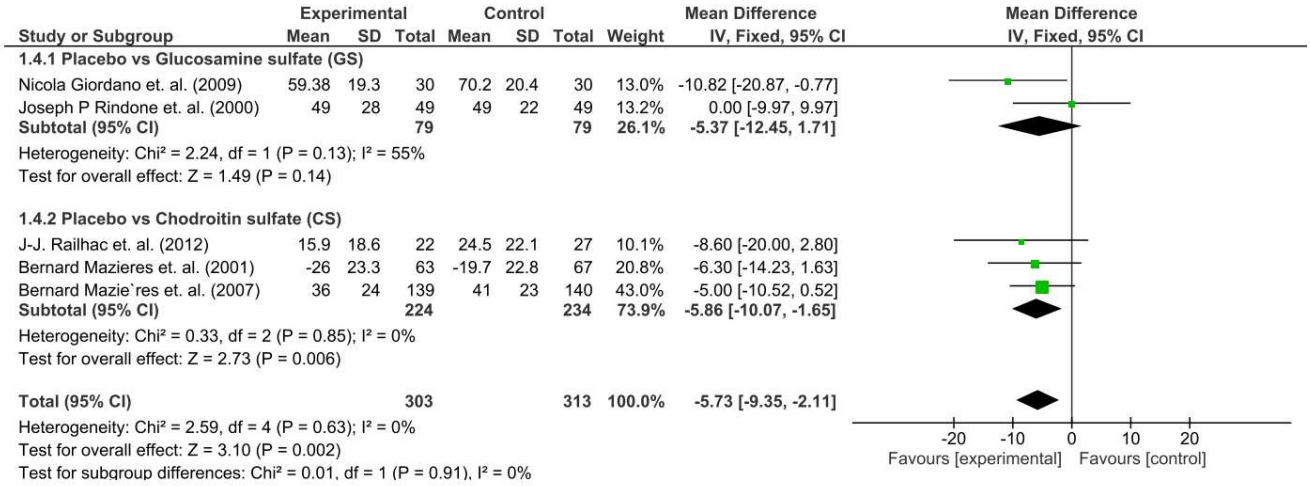

Figure 7 Pain intensity: Lequesne Index Forest Plot

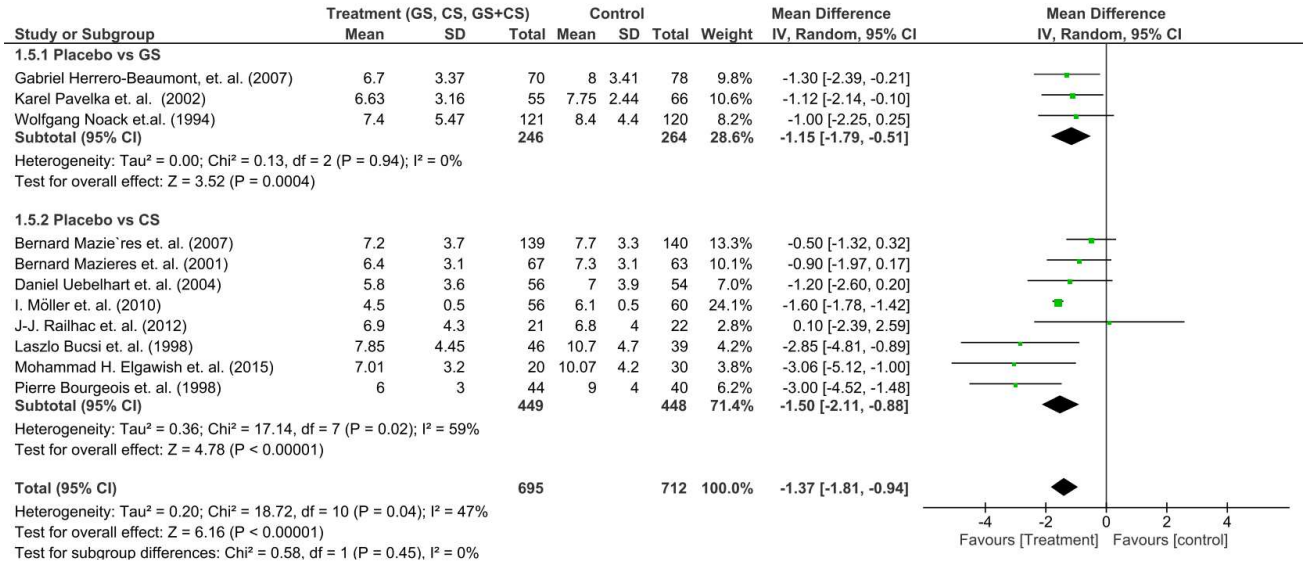

Figure 8 Physical Function: WOMAC Forest Plot

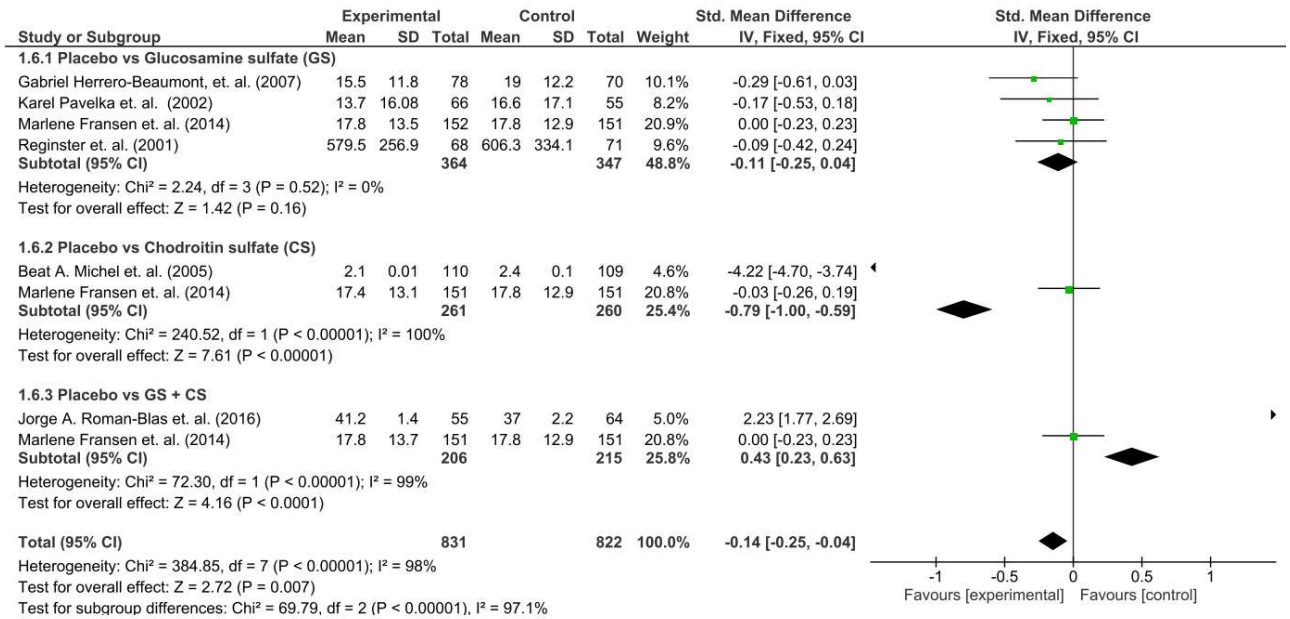

Figure 9 Joint Space Narrowing Forest Plot