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Effects of adding glucosamine or glucosamine combined with chondroitin to exercise on pain and physical function in adults with knee osteoarthritis: a systematic review and meta-analysis

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Abstract

It is well known that different types of exercise significantly improve physical function and relieve pain in knee osteoarthritis (KOA) patients. The aim of this study was to investigate the added effects of glucosamine or glucosamine and chondroitin supplementation in combination with an exercise program in the management of KOA. The randomized controlled trials on adding glucosamine (G) or G combined with chondroitin (C) to an exercise program in the treatment of KOA were searched in the PubMed, Cochrane Central Register of Controlled Trials, PEDro, and Web of Science online databases. The Pedro scale tool was used to assess quality of literature. A meta-analysis was performed using the Review Manager 5.4 software. In total, 6 studies (including 297 participants) were included for the final meta-analysis. According to the PEDro scale, the average quality of the studies was rated as good (mean = 8.2 (2)). The results showed that the effect of G, or G and C, in combination with exercise is not significant, as indicated by the assessed knee pain (WOMAC pain: SMD -0.18, 95% CI -0.47 to 0.11, p = 0.23; and VAS pain: SMD -0.34, 95% CI -0.85 to 0.17, p = 0.20) and physical function (SMD -0.13, 95% CI -0.95 to 0.69, p = 0.76). Adding glucosamine alone or a combination of glucosamine and chondroitin to exercise, has no effect on knee pain and physical function compared with exercise alone in KOA patients..

Key Words: treatment; dietary supplement; physical activity; older adults.

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Osteoarthritis is one of the most common joint disorders[1] affecting especially adults aged > 50 years.[2] According to the Osteoarthritis Research Society International (OARSI) it is defined as a degenerative joint disease characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function causing pain and functional disability.[1] It mainly affects large weight-bearing joints such as hips and knees.[2] The prevalence of knee osteoarthritis (KOA) increases with age, and millions of people worldwide are suffering from it.[3,4] With longer lifetime, the burden of this joint disease will increase globally[1] and management of KOA needs to be researched.

The most widely used KOA treatment is non-steroidal anti-inflammatory drugs (NSAIDs) therapy.[5] Although NSAIDs are effective for alleviation of symptoms, there is evidence for serious adverse effects.[6,7] By contrast, the advantage of commonly used symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) such as glucosamine (G) and chondroitin (C) is that they are not associated with any side effects.[8] G and C have gained wide popularity as alternative treatments for KOA, although clinical benefits have not been established.[9] They were reported to be ineffective or showed arguably clinically unimportant treatment effects. Conversely, some studies have reported that G or C relieve KOA symptoms[10,11] to the same extent as exercise.[12–14] Exercise is a widely researched non-pharmacological treatment for KOA. In older people with KOA, different types of land-based exercise improve balance and fall risk[15], as well as walking function and postural control;[16] physical activity provides pain reduction and improves physical function.[12,13] Additionally, as regards dietary supplements in the treatment of KOA, there are clinical advantages to using C combined with G. The

combination of both is suggested to be more effective than G or C alone in the treatment of KOA.[8,17]
The evidence on the comparative effectiveness of the combination of exercise and dietary supplements in alleviating pain and improving physical function is poor and has not yet been identified. The aim of this systematic review and meta-analysis was to investigate the impact of G alone, or the combination of G and C, both with exercise, on pain and physical function in patients with KOA.

Materials and Methods

Study inclusion and exclusion criteria were structured and organized according to the PICOS tool:[18]

- population (P): adults aged > 50 years with KOA;
- intervention (I): any type of home- or institution-based exercise intervention in duration of at least 4 weeks in combination with G alone or G combined with C;
- comparison (C): control or placebo group (exercise intervention only);
- outcome (O): any tests assessing physical function and pain (instrumented and non-instrumented measures and questionnaires);
- study design (S): interventional clinical trials with at least two groups (exercise + G and/or C and exercise (control/placebo) group).

Search strategy

Multiple databases of scientific literature (PubMed, Cochrane Central Register of Controlled Trials, PEDro, and Web of Science) were searched in February 2023 with no date restrictions. In the databases that enable using Boolean search operators, we used the following combination of search key words: (osteoarthritis of the knee OR knee osteoarthritis OR knee OA) AND (exercise OR strength training OR resistance training OR physical activity) AND (glucosamine OR glucosamine sulfate OR glucosamine hydrochloride OR chondroitin OR chondroitin sulfate) AND (elderly OR older adults OR ageing). Additionally, reference lists of the relevant published systematic reviews and included studies were reviewed. The authors performed a database search in three stages: 1) assessing the eligibility of the papers based on the title, 2) assessing the eligibility of the papers based on the abstract, and 3) assessing the eligibility of the papers based on the full text.

Study quality assessment

Study quality was assessed using the PEDro Scale,[19] which assesses study quality based on a ten level scale. A higher score indicates a higher quality of the study. Studies scoring 9–10 were considered as excellent, 6–8 as good, 4–5 as fair, and less than 4 as poor quality. The PEDro Scale was chosen because it was developed specifically to assess the quality of randomized controlled trial studies evaluating physical therapist interventions. According to the PEDro Scale, study quality was assessed for the following domains: 1) random allocation; 2) concealed allocation; 3) groups similar baseline; 4) subjects blinding; 5) therapists blinding; 6) assessors blinding; 7) adequate follow-up; 8) intention-to-treat analysis; 9) between-group comparisons; 10) point estimates and variability.

Data extraction

Data extraction included: a) baseline and post-intervention means and standard deviations (SD) for all outcome measures for the intervention and control groups; b) patients' demographics (age, sex, body mass index, radiographic classification (Kellgren and Lawrence score); c) intervention characteristics (duration of intervention, weekly frequency, duration of sessions, supervision during intervention, type of exercise program, and dietary supplements); d) exercise characteristics (number of exercises, sets, and repetitions, breaks between exercises and sets, intensity of exercise (a percentage of one-repetition maximum or heart rate, type of used load (machines, bodyweight, free weights); e) outcomes, and f) main conclusions of studies. In cases where the data were reported in mean (SEM) or median and interquartile ranges (IQR), means and standard deviations were accurately estimated using the methods of Luo et al.[20] and Wan et al.[21] Data were carefully inserted into Microsoft Excel 2013 (Microsoft Corporation).

Data synthesis and analysis

The main data analyses were carried out in Review Manager (RevMan, Version 5.4, The Cochrane Collaboration, 2020). Before the results were entered into the meta-analytical model, the pre-post differences and pooled standard deviations were calculated according to the following formula $SD = \sqrt{[(SDpre^2 + SDpost^2) - (2 \times r \times SDpre \times SDpost)}$. The correction value (r), which represents the pre-test–post-test correlation of outcome measures, was conservatively set at 0.75. It should be noted that a change in the correction value in the range between 0.5 and 0.9 had little effect on the pooled SD and would not change the outcomes of the meta-analysis. For the meta-analysis, the inverse variance method for continuous outcomes with a random-effects model was used. The effect sizes were expressed as standardized mean difference (SMD). For SMD, the respective 95% confidence intervals were also calculated and reported. Statistical heterogeneity among studies was assessed by calculating I^2 statistics. According to Cochrane guidelines, the I^2 statistics of 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% indicates considerable heterogeneity.[22] Statistical significance threshold was set at $p \leq 0.05$ for all analyses.

Results

Search results

The search process is presented in a flowchart in Figure 1. 118 articles were identified in the initial database search. After removing the duplicates, 90 titles were identified as potentially relevant for our meta-analysis.

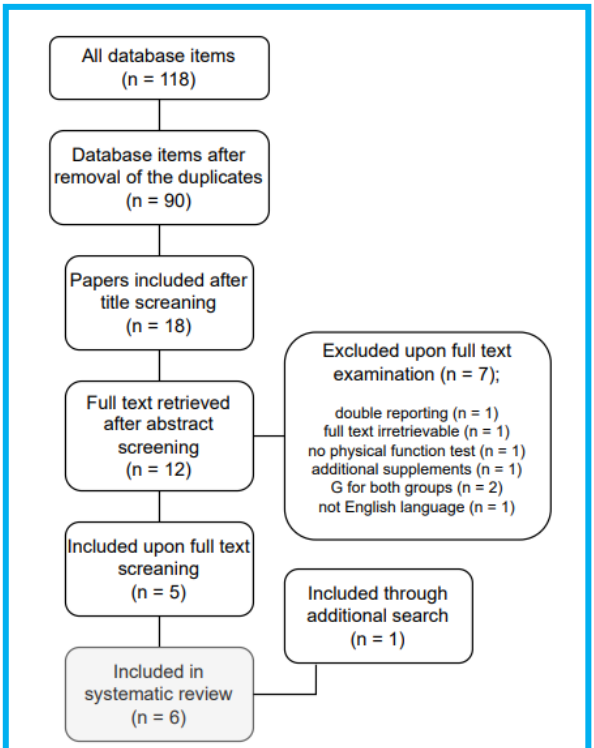

Fig 1. *Summary of search results.*

Based on the screening of the title, 18 papers were included for abstract examination, after which 12 papers remained as potential candidates for the meta-analysis. After full-text examinations, 5 studies were included for the final meta-analysis. In addition, 1 study was found through screening the reference lists of existing systematic reviews. Therefore, our meta-analysis included 6 studies.[23–28]

Study quality assessment

According to the PEDro scale, the average quality of the studies was rated as good (mean = 8.2 (2); median = 9.0; range = 5–10). One study was rated as being of fair quality, satisfying 5 items. One study scored 7 and was rated as being of good quality, whereas the remaining four studies with excellent quality scored 9–10. Results from the PEDro scale are summarized in Table 1.

Participant data and intervention characteristics

The total number of participants finally included in the review was 297 (150 in intervention groups and 147 in control groups), with samples ranging in size from 12 to 45 patients. Four studies included participants of both sexes, and two studies included females only. The total number of women participants was 226. The severity of KOA was assessed using the American College of Rheumatology clinical[29] and radiographic classification criteria and the Kellgren-Lawrence grading system;[30] the severity score was assessed to be 2–3 (mild to moderate) in three studies, 1–3 (mild to moderate) in two studies, and 1–4 (mild to severe) in one study. The studies were conducted in Japan,[24] Turkey,[23] Italy,[28] United States,[25] Denmark,[27] and Pakistan.[26]

In three studies, the duration of the interventions was 12 weeks, one intervention was shorter (4 weeks) and two interventions were longer (12 months and 18 months). Most interventions included 3 sessions per week, while two studies included daily sessions (in one of them, the sessions were held twice daily); the duration of intervention sessions varied. In 5 studies, the exercises were conducted under supervision, while in one study they were home-based and participants were provided with instructions in the form of a brochure.

All interventions focused on the lower limb muscles in various types of exercise, such as strength training, aerobic training, active and active-assisted range of motion (ROM) exercises, and mixed training approaches (combined aerobic and strength exercise, or strength training and stretching). In three studies, the intervention group used only G (1500 mg daily), while in two studies G and C were used (1500 mg and 1200 mg daily, respectively), and in one study the intervention group received a combination of G, C and Bio-Curcumin. In two of the studies, the participants in the experimental group were given G tablets of 500 mg 3 times daily,[26,27] while in one study they were given a choice of either once-daily or thrice-daily regimens.[25] In a study by Sterzi et al.[28] patients received two tablets of agent daily, while the remaining two studies did not provide details on the daily supplement regimen. The control group received the same exercise program as the intervention group, while participants were also given placebo tablets in three of the included studies.

The interventions included a combination of single-joint and multi-joint exercises. The volume of exercise varied between studies, with the number of exercises ranging from 3 to 8, the number of sets ranging from 1 to 4, and the number of repetitions in sets ranging from 10 to 20. Most of the studies did not report the intensity of exercise; one study assessed intensity through heart rate (between 50% and 70% of heart rate reserve) and two as percentage of repetition maximum. Breaks between sets were only determined in one study. Two exercise programs included machines and cuff weights.

Outcomes

In total, 4 studies measured quadriceps muscle strength and power (maximal isokinetic and isometric strength, isometric muscle force of knee extension, knee concentric extension and flexion strength, modified sphygmomanometer test for isometric muscle strength in knee flexion and extension). Visual analogue scale (VAS) for pain was reported in four studies (pain scoring during the strength measurements, actual pain level, pain during normal daily living and pain during rest). The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used in four studies, while the WOMAC total score was reported only in two studies. Two studies included the performance of the 6-min walk test (6MWT), knee ROM in flexion and extension, blood markers using C-reactive protein (CRP), the Knee Injury and Osteoarthritis Outcome Score (KOOS

Table 1. *Assessment of the methodological quality of the included studies by the PEDro scale.*

Reference	1	2	3	4	5	6	7	8	9	10	total
Durmus et al., 2012[23]	yes	yes	yes	no	no	no	yes	yes	yes	yes	7
Kawasaki et al., 2008[24]	yes	no	yes	no	no	no	no	yes	yes	yes	5
Messier et al., 2007[25]	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	9
Osama et al., 2022[26]	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	9
Petersen et al., 2011[27]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	10
Sterzi et al., 2016[28]	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	9

questionnaire), and MRI. Due to substantial discrepancy in outcome measures among the studies, only meta-analysis was performed. Supplementary Materials Table 1 presents all the details regarding the participants, interventions and outcomes of individual studies.

Effects of intervention

Pain was assessed using WOMAC pain and VAS pain. The meta-analysis showed no significant pain decrease through WOMAC (SMD -0.18, 95% CI -0.47 to 0.11, p = 0.23) and no heterogeneity (I^2 = 0%) when comparing the glucosamine and exercise group and the exercise-only group (Figure 2). Similarly, compared to controls for pain reduction on the VAS pain score, the group who received the glucosamine supplement in combination with exercise did not present any significant differences (SMD -0.34, 95% CI -0.85 to 0.17, p = 0.20) while showing moderate heterogeneity (I^2 = 60%) (Figure 2).

Three included studies assessed physical function through WOMAC. The meta-analysis showed no significant physical function improvements (SMD -0.13, 95% CI -0.95 to 0.69, p = 0.76) with considerable heterogeneity (I^2 = 86%) between groups (Figure 3). Stiffness was evaluated using WOMAC stiffness. Compared to the control group, there was no statistically significant reduction of stiffness in intervention groups across the studies (SMD -0.13, 95% CI -0.95 to 0.69, p =

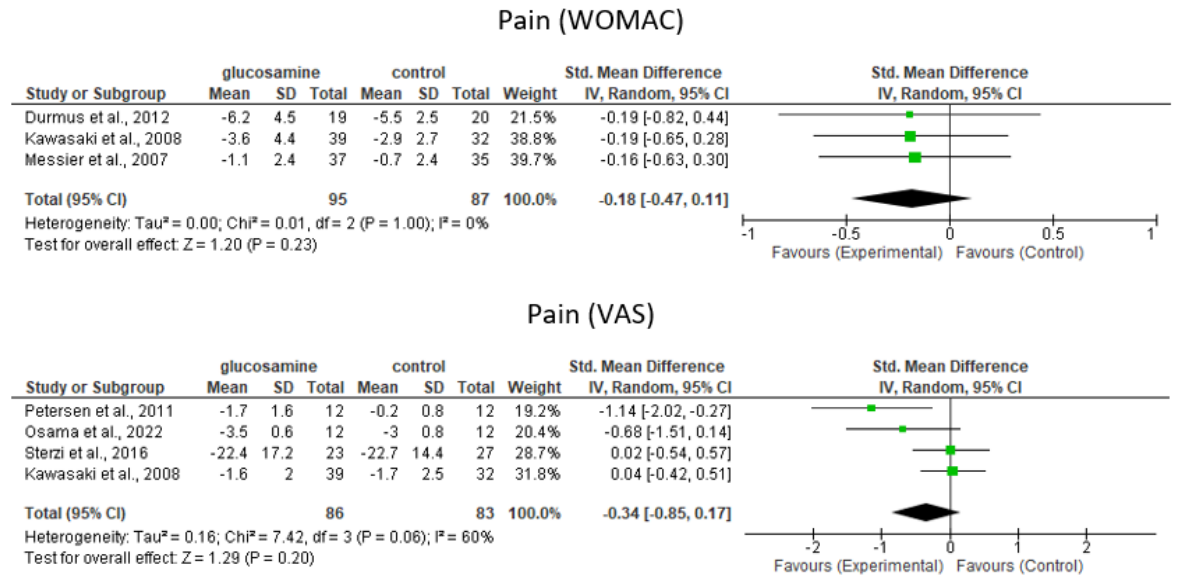

Fig 2. *The effect of G or G and C in combination with exercise vs. exercise-only group on pain.*

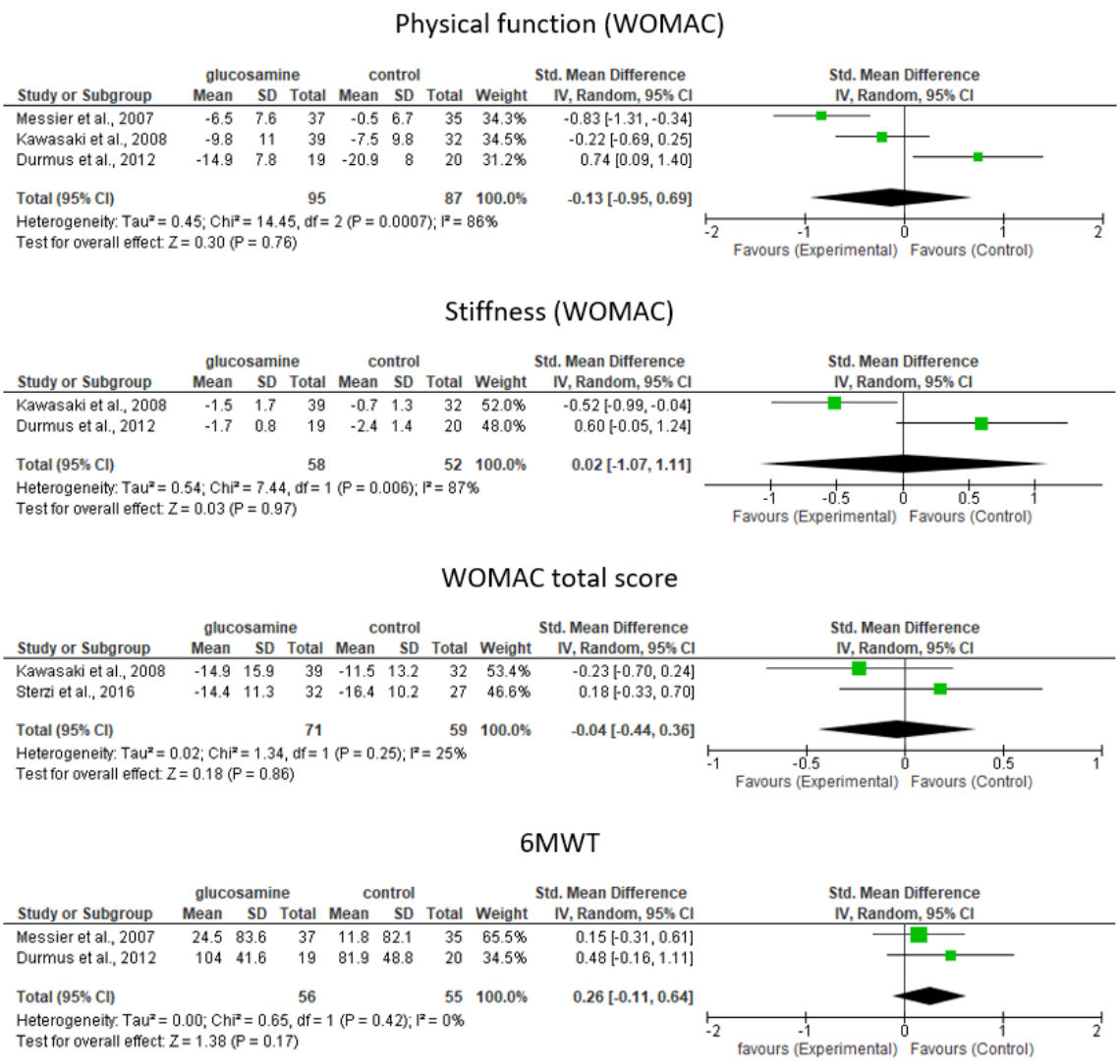

Fig 3. *The effect of G or G and C in combination with exercise vs. exercise-only group on WOMAC score and 6MWT.*

0.97), while a very high heterogeneity was observed (I^2 = 86%) (Figure 3). The WOMAC total score was reported in two studies. The meta-analysis demonstrated no significant differences between groups (SMD -0.04, 95% CI -0.44 to 0.36, p = 0.86) and no important heterogeneity (I^2 = 25%) (Figure 3). 6MWT was performed in two studies; results are summarized in Figure 3. There were no significant differences between intervention and control group (SMD 0.26, 95% CI -0.11 to 0.64, p = 0.17) without heterogeneity (I^2 = 0%).

Discussion

The aim of this systematic review with meta-analysis was to investigate the effects of G or G and C in combination with exercise on pain and physical function in patients with KOA. The main findings are: 1) knee pain was assessed through the WOMAC pain score in three studies and through the VAS pain score in four studies. The effect of G, or G and C, in combination with exercise was in both cases small and not significant (effects on VAS pain were unclear due to the heterogeneity and assessment during different daily activities); 2) physical function was assessed through the WOMAC score only in three studies and G has been shown to have no effect on it; 3) G, or G and C, in combination with exercise have been shown to have no effect on stiffness, the WOMAC total score, and 6MWT. It is possible that some of the other variables, such as duration of treatment, frequency, type of exercise program, age of participants, sex, BMI and type of dietary supplements, have influenced the results. Exercise program is recommended as first-line treatment for KOA patients.[31] Different types of physical activity alone have been considered very beneficial as a conservative therapy for OA patients, showing significant improvements especially in pain and physical function.[32–36] Our meta-analysis does not show

significant additional effects of G or G/C, compared to exercise only. Some studies that have compared G intake to the control group in KOA patients have shown no clear effects in terms of reducing pain and improving physical function,[37,38] which is in accordance with our findings. On the other hand, a meta-analysis including 54 studies showed that glucosamine alone or G with C were effective in terms of reduced pain, compared to placebo, while only G with C showed significant improvement in function in KOA patients.[39] Based on these findings, a combination of G and C seems a better choice in the treatment of knee OA than G only. Due to lack of studies or similar outcomes, it was not possible to perform subgroup analyses to confirm this in our study. It is important to emphasize that there are multiple formulations of SYSADOAs available. Known are prescription-grade products and among patients high popular an over-the-counter agents.[40] G and C are natural products, various glucosamine-containing product is usually derived from shells of shellfish. Exogenous glucosamine is administered as a salt, glucosamine hydrochloride (GH) is obtained by extraction, while glucosamine sulfate (GS) is complex molecule and is found only in the prescription drug product as prescription crystalline glucosamine sulfate (pCGS).[41] pCGS is the only pharmaceutical product that has demonstrated consistently that it is effective against the symptoms and the progression of the KOA.[42] In addition to pCGS the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases strongly support the use of chondroitin sulfate (CS) as background pharmacological treatment in the first step of the knee OA management algorithm and also paracetamol as needed.[41] It is a common practice to add sodium sulfate to GH for the misleading use of the term sulfate. The meta-analysis by Runhaar and colleagues confirm that GH and non-characterised GS products are ineffective in osteoarthritis.[43] Our review included a mix of different supplements and none of the studies is it explained sources, process for extraction or purity of molecules. In two studies, the intervention group received GS[23,27] and GH combined with CS,[25,28] while Kawasaki et al.[24] and Osama et al.[26] decided to include GH and G combined with CS, respectively. The therapeutic regimens and the dosage administered were similar. The dose of G was 1500 mg daily in 5 studies and the dose of C was 1200 mg daily in two studies. With the exception of the study by Sterzi et al.,[28] where patients received 2 tablets of agent (doses of GH and CS are unknown), the administered doses were equivalent to those reported by Hochberg et al.[44] There were no notable differences in the frequency of glucosamine intake. Three studies did not report the administration frequency; participants in the studies by Osama et al.[26] and Petersen et al.[27] received glucosamine 3 times daily, while patients in the study by Messier et al.[25] were given a choice of either once-daily or thrice-daily regimen. Significant and clinically important reduction in the VAS pain intensity in the affected knee was identified in all the three groups and without differences among them (500 mg GS/400 mg CS as capsules three times daily vs. sachet once daily vs. 500 mg GH/400 mg CS three times daily).[45] Persiani et al. confirmed that the bioavailability after once-daily therapeutic dose of 1500 mg was effective.[46] It remains questionable if the difference in daily regimen (smaller and more frequent doses) effects in lower bioavailability. Conversely, Messier et al. report that multiple doses may make C more bioavailable.[25] Short term exercise therapy alone improved clinical symptoms in the KOA patients,[47–50] while for dietary supplements it seems long term interventions are needed. Systematic review of randomized controlled trials of glucosamine long-term treatment limited to studies that lasted at least one year showed moderate effect in improving symptoms of KOA.[51] Pavelka et al.[52] showed significant improvement in the WOMAC total index and pain, function, and stiffness subscales after 3-year treatment with GS compared to placebo. There is good safety profile of dietary supplement (G and C) without differences in adverse effects compared to placebo after two or three years.[38,52] Symptom changes as previously mentioned were evident in the patients with mild to moderate disease according to Kellgren and Lawrence scoring system for classification of knee OA. Most of our studies involved patients with mild to moderate KOA and one study involved patients with mild to severe conditions. The benefits in KOA symptoms in those with severe KOA are questionable, surgery is only suitable for patients with end-stage KOA.[14] There are numerous risk factors for the development and progression of the KOA such as age, gender, and obesity.[53] It is interesting to note that in the present review there was only one study which included obese people.[28] Participants of Kawasaki et al.[24] were normal weight, and in other studies subjects were overweight. To our knowledge, an association between weight loss and knee OA exist and weight loss is considered a treatment strategy in KOA patients. Obese KOA patients with muscle weakness experience more pain compared with KOA patients who are non-obese.[54] Despite regular exercise intervention in different duration none of the studies confirmed a reduced BMI in any of groups and there is no possible pain relieve. Although not explained in the studies, there is a possibility that the high prevalence of overweight participants encompasses sarcopenic individuals with poor exercise capacity who may not benefit from 4 weeks of training. Additionally, from the standpoint of resistance training, benefits in muscular strength cannot be expected in just 4 weeks. In the included studies a sex misbalance was noted, 24% of analyzed subjects were male and 76% were female. Women have higher KOA prevalence with higher VAS pain score and more impaired function compared to men.[55] Based on these findings, the results cannot be generalized to both sexes. Our review found no significant effects of G or G with CS on WOMAC pain

or other WOMAC's subscales. To relief knee pain, it can be expected that functional performance should increase. Our findings suggest that patients have not been able to show greater exertion in everyday life without reduction in pain. In the intervention group, no effects exist compared to the control group, which suggests that the knee exercise program included in the studies in this review was well designed, and changes from baseline can be attributed to exercise only. On the other hand, a long-term study without supervised training session and without progression in 3 studies has been conducted. One study treatment duration was only 4 weeks, which is less than the shortest duration of the study included in systematic review and meta-analysis of randomized placebo controlled trials to investigate the efficacy of G and CS on KOA symptoms.[56] In accordance with this study, there is no additional effect using both oral supplements on KOA symptoms using WOMAC pain or VAS pain. Runge et al.[57] reported very low to moderate certainty of evidence that adding manual therapy to an exercise program may benefit pain and the WOMAC global scale in patients with KOA in the short term. We have thus included a study of Osama et al.,[26] where a four-week manual therapy was used as an adjunct to resistance exercise and glucosamine. We do not believe that a manual therapy effect could have changed our results.

Some limitations to the present study need to be noted. There were 2 studies,[25,28] in which the exclusion criterion was the use of glucosamine and/or chondroitin, while in one study,[27] a one-month washout period was conducted. In three other studies,[23,24,26] there is no report about exclusion criteria or specific monitoring of participants who were using dietary supplements prior to their inclusion in the research. We cannot exclude that some of these subjects might not have been totally clear of dietary supplements or even of NSAIDs. This could be the reason why there were no differences between the groups. The review includes studies with varying intervention durations and a relatively small sample size. Further studies on a larger population for a longer period would be necessary. The sample size might not be sufficient, affecting the reliability of our study. Moreover, due to choosing literature only in aforementioned databases and only in English, selection bias exists. Due to the smaller number of included studies, the subgroup analyses were not possible, and further comparisons were not possible for all outcome measures. 29 different tests and outcomes were used across the studies. The major limitation of the present review is an unbalanced representation of different outcomes and a smaller number of included studies. From the methodological viewpoint, the study protocol is not registered on PROSPERO platform.

Regardless the results we have to be cautious in clinical practice giving instruct to patients not to take G and/or C. This may lead to resistance to therapy. Considering the results and current understanding of the benefits of taking G and/or C it is important to be aware that additional benefits of combining exercise with the consumption of G and/or C cannot be achieved. This raises the question of whether there is limited benefit of different therapy combination in KOA management.

In conclusion, overall, we observed a high variability among study designs, which made it difficult to assess with certainty the effect that glucosamine and chondroitin may have on KOA symptoms. Conclusions should be viewed with caution, since there are a few questions that remain open. More high-quality studies are needed to explore the role of G and/or C combining with exercise in the treatment of KOA. However, the inclusion of glucosamine alone or in combination with chondroitin in a KOA exercise program did not seem to make exercise therapy more effective.

List of acronyms

BMI – body mass index
C – chondroitin
CRP – C-reactive protein
CS – chondroitin sulfate
G – glucosamine
GH – glucosamine hydrochloride
GS – glucosamine sulfate
KOA – knee osteoarthritis
KOOS – Knee injury and Osteoarthritis Outcome Score
NSAIDs – non-steroidal anti-inflammatory drugs
pCGS – prescription crystalline glucosamine sulfate
ROM – range of motion
SD – standard deviation
SMD – standard mean difference
SYSADOAs – symptomatic slow-action drugs for osteoarthritis
VAS – visual analogue scale
WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index
6MWT – six minute walk test

Contributions of Authors

TC and NS conceived the original idea of the manuscript. TC and NS participated to the writing of the text. TC and NS reviewed the manuscript and have approved the final edited typescript.

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Conflict of Interest

The authors declare no conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supplementary Materials Table 1. *Overview of the studies included into the meta-analysis.*

Reference	Intervention characteristics	Participant data (EG; CG)	Exercise characteristics	Outcome measures	Main conclusion
Petersen et al., 2011[27]	12 weeks 3 times/week 45 min/session supervised: yes strength training + GS 1500 mg daily vs. strength exercise + placebo	n = 24 (12; 12) n female = 14 (7/12; 7/12) age = 62.2 ± 11.8; 63.1 ± 16.3 BMI = 27.3 ± 11.4; 28.3 ± 11.1 K/L grade = 1–4	3 exercises, from 4 sets of 15 RM to 4 sets of 8 RM	quadriceps muscle strength and power, habitual walking speed on a 10-m track, stair-climbing time (13 steps), chair stands (30 s), pain during the strength measurements (VAS), KOOS questionnaire, muscle biopsy, CRP, total cholesterol, creatinine, and alkaline phosphatase, MR	Similar gains in functional performances were obtained in both groups. Beneficial effects were not convincing enough to recommend treatment with GS.
Durmus et al., 2012[23]	12 weeks 3 times/week 45 min/session supervised: yes aerobic exercise + GS 1500 mg daily vs. aerobic exercise	n = 39 (19; 20) n female = 39 (19/19; 20/20) age = 57.,7 ± 1,4; 57.1 ± 1,3 BMI = 27.7 ± 1.0; 28.6 ± 0.8 K/L grade = 1–3	4 exercises (active ROM, strength, stretching, flexibility)	WOMAC, 6MWT, quadriceps muscle strength, quality of life (SF-36), depression, MR	No statistically significant between-group differences were found in any outcome measures. Exercise alone is effective in improvement of clinical symptoms in a short period in KOA.
Kawasaki et al., 2008[24]	18 moths twice a day supervised: no home-based training + GH 1500 mg daily vs. home-based training	n = 71 (39; 32) n female = 71 (39/39; 32/32) age = 68.5 ± 7.3; 69.5 ± 7.1 BMI = 23.9 ± 2.5; 24.0 ± 3.0 K/L grade = 2–3	4 exercises (isometric muscle strength + active ROM) 1 set, 20 repetitions	JOA score, actual pain level (VAS), WOMAC, tibiofemoral joint space width	No statistically significant difference between groups was observed in any outcome measures.
Messier et al., 2007[25]	6 months 3 times/week (twice facility-based, once home-based) supervised: yes aerobic and strength exercise program + GH/CS 1500/1200 mg daily vs. aerobic and strength exercise + placebo	n = 89 (45; 44) n female = 63 (34/45; 29/44) age = 70.0 ± 8.6; 74.1 ± 8.8 BMI = 30.7 ± 6.2; 27.3 ± 4.8 K/L grade = 2–3	2x15 min walking (50–70% HR reserve), 4 strength exercises 2 sets, 10–12 repetitions cuff weights and machines progression	WOMAC, 6MWT, mental status, knee concentric extension and flexion strength, balance	No statistically significant between-group differences were found in function, pain, or mobility.

Supplimentary Materials Table 1. *Overview of the studies included into the meta-analysis. CONTINUE.*

Reference	Intervention characteristics	Participant data (EG; CG)	Exercise characteristics	Outcome measures	Main conclusion
Sterzi et al., 2016[28]	12 weeks 3 times/week supervised: yes mixed exercise program + CartiJoint daily (GH, CS, Curcumin) vs. mixed exercise program + placebo	n = 50 (23, 27) female = 33 (14/23; 19/27) age = 71.3 ± 8.8; 71.0 ± 8.1 BMI = 34.8 ± 6.4; 34.3 ± 7.5 K/L grade = 2–3	active and active-assisted ROM, stretching and strength exercises	pain (VAS 0-100) during normal daily living and during rest, WOMAC, Lequesne Index, flexion and extension ROM, inflammation assessment using CRP and ESR measurements	Treatment with Curcumin, GH and CS, accompanied by physical therapy, may improve pain symptoms during the activities of daily living and reduce the Lequesne Algofunctional Index values in KOA.
Osama et al., 2022[26]	4 weeks 3 times/week with manual therapy + 4 times/week home-based exercise supervised: yes resistance exercise training + G/CS 1500/1200 mg daily vs. resistance exercise training	n = 24 (12, 12) n female = 6 (3/12; 3/12) age = 57 ± 9.2; 57 ± 7.6 BMI = 27.4 ± 3.4; 27.4 ± 1.6 K/L grade = 1–3	8 exercises 3 sets of 8 repetitions 1–2-minute rest between the sets 80% of 8 RM was used as training intensity (reassessed every week)	Pain (VAS), KOOS, isometric muscle strength in knee flexion and extension, 5XRSS, knee ROM in flexion and extension, fall risk score, body composition analysis	Physical therapy and resistance exercise training are effective in KOA management; short-term supplementation of G and CS showed no additional benefits after 4 weeks of treatment.

EG: experimental group; CG: control group; BMI: body mass index; K/L: Kellgren/Lawrence; KOOS: Knee Injury and Osteoarthritis Outcome Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ROM: range of motion; MR: magnetic resonance; 6MWT: 6-minute walk test; JOA: Japan Orthopaedic Association; 5XRSS: 5-repetition sit-to-stand test; HR: heart rate; G: glucosamine; GS: glucosamine sulfate; CS: chondroitin sulfate; GH: glucosamine hydrochloride.