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Review article

Carboxymethyl-Chitosan for Symptomatic Knee Osteoarthritis: A Systematic Review and Meta-Analysis

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Abstract: Intra-articular carboxymethyl-chitosan (CM-chitosan), a novel injectable biopolymer, shows promise for treating knee osteoarthritis. Effectiveness, safety, and how it compares to hyaluronic acid (HA) viscosupplementation are still unclear. We performed a systematic review and meta-analysis to assess intra-articular CM-chitosan in both single-arm and comparative studies. PubMed, Scopus, and Cochrane databases were searched for studies assessing CM-chitosan and comparing it with HA. Comparative studies used risk ratios (RRs) and mean differences (MDs) were pooled, while for single-arm studies, means and proportional meta-analyses were performed. Effects were reported with 95% confidence intervals (CIs). Statistical analyses used RevMan Web and RStudio. Outcomes included: Outcome Measures in Rheumatology – Osteoarthritis Research Society International (OMERACT–OARSI) responder rate, Western Ontario and McMaster Universities Osteoarthritis (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analogue Scale (VAS) score, joint swelling, arthralgia, and adverse device effects (ADEs). We included 264 patients from four studies: two comparative and two single-group cohorts, of whom 180 (68.2%) received CM-chitosan. At 6 months, there was no statistically significant difference between CM-chitosan and HA in (OMERACT–OARSI) responder rate (RR 1.02; 95% CI 0.87 to 1.21; p = 0.79; I^2=0%), mean percentage change from baseline in (WOMAC) total scores (MD 1.42%; 95% CI –6.39 to 9.23; p = 0.72; I^2=0%), and joint swelling (RR 3.88; 95% CI 0.45 to 33.23; p = 0.22; I^2=0%). CM-chitosan showed higher rates of adverse device effects (RR 3.50 higher rates of ADEs (RR 3.50; 95% CI 1.72 to 7.13; p = 0.0006; I^2=0%) and arthralgia (RR 3.01; 95% CI 1.53 to 5.91; p = 0.001; I^2=0%). In single-arm analysis at 6 months, post-treatment KOOS pain score was 60.89% (95% CI 30.01 to 91.77), VAS pain score was 44.57 mm (95% CI –0.71 to 89.86), and OMERACT–OARSI responder rate was 74.44% (95% CI 62.10 to 83.81). Preliminary evidence suggests that CM-chitosan yields functional results similar to those of HA at 6 months, but with a higher incidence of adverse effects. Further larger randomised controlled trials with long-term follow-up are needed.

Keywords: Osteoarthritis, Knee, Chitosan, Hyaluronic acid, Carboxymethyl-chitosan, Patient-Reported Outcome Measure

1. Introduction

Knee osteoarthritis (OA) is a progressive, multifactorial joint disorder characterized by pain, functional loss, and substantial impairment of quality of life [1–3]. Globally, knee OA is a leading cause of disability, with prevalence estimates ranging from approximately 4.9% to 7.6% in adults and exceeding 23% in those aged > 40 years [1,4].

Women are more frequently and severely affected than men, with prevalence and disability rates significantly higher in high-income countries and among individuals with metabolic risk factors [5,6]. The social and economic impacts of knee OA are profound, driving significant healthcare costs and affecting work productivity and daily activities [7].

Treatment paradigms emphasize non-pharmacological strategies, such as physical therapy, alongside pharmacological interventions, including nonsteroidal anti-inflammatory drugs, corticosteroids, and intra-articular therapies [1,6,8,9]. Intra-articular hyaluronic acid (HA) injections are a cornerstone of symptom management due to their viscoelastic, chondroprotective, and anti-inflammatory properties [10–12]. However, persistent pain and poor function in a substantial proportion of patients, including those with advanced radiographic severity, obesity, and complex clinical profiles, highlight the unmet need for new and more effective injectable therapies [1,5].

Carboxymethyl chitosan (CM-chitosan) is a novel injectable biopolymer with demonstrated clinical benefits in various populations with knee osteoarthritis. The clinical mechanism of CM-chitosan is distinct from that of traditional and cross-linked HA formulations, as it offers joint lubrication, free radical scavenging, and modulation of inflammatory processes [13–16]. Clinical studies have suggested rapid pain relief, durable benefit, and good tolerability in both general OA and difficult-to-treat populations, including those with advanced radiographic severity, obesity, and poor responses to previous HA therapies [13–15,17].

Despite these advances, knowledge gaps remain regarding the precise role, magnitude, and durability of the benefits of CM-chitosan compared to competing injectables across diverse patient profiles. Therefore, we performed a systematic review and meta-analysis to evaluate the efficacy, safety, and patient-centered outcomes of CM-chitosan, with a focus on its performance relative to cross-linked HA.

2. METHODS

This systematic review and meta-analysis was performed in accordance with the Cochrane Collaboration Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines [18,19]. This meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the identifier "CRD420251127750". The complete PRISMA checklist is available in the Supplementary Appendix.

2.1 Eligibility criteria

Inclusion criteria were: (1) randomized or non-randomized cohorts; (2) single-arm or comparative designs; (3) adults (≥18 years) with knee osteoarthritis; (4) a single intra-articular knee injection of CM-chitosan; and (5) reporting ≥1 outcome of interest. Exclusion criteria were: (1) chitosan compounds other than CM-chitosan; (2) multi-injection chitosan regimens; (3) cadaveric or in-vitro studies; and (4) non-English publications.

2.2 Search strategy and data extraction

We systematically searched PubMed, Scopus, and the Cochrane Library from inception to August 2025. Two researchers (M.A.M. and L.S.) independently selected records using the Rayyan software [20]. We also extracted data with authors blinded to each other's decisions (M.A.M. and L.S.). Disagreements were resolved through discussions with a third researcher (R.M.M.). Our search strategy included the following medical subject heading terms: "kiomedine," "chitosan," "carboxymethyl-chitosan," "CM-chitosan," "osteoarthritis," and "knee osteoarthritis." The complete search strategy is presented in the Supplementary Appendix. Additionally, the references of previous reviews were manually searched for eligible studies.

2.3 Endpoints

Outcomes included clinical assessments such as (1) Western Ontario and McMaster Universities Osteoarthritis (WOMAC) score, (2) Knee Injury and Osteoarthritis Outcome Score (KOOS), (3) Osteoarthritis Research Society, (3) Osteoarthritis Research Society International (OARSI) Standing Committee for Clinical Trials Response Criteria Initiative, and the Outcome Measures in Rheumatology (OMERACT) responder rates [21], (4) Visual Analogue Scale (VAS) pain score. The safety analysis included (1) adverse device effects (ADEs), (2) arthralgia, and (3) joint swelling.

2.4 Quality assessment

Quality assessment of the included RCTs was performed using the revised Cochrane risk of bias tool for randomized trials (RoB-2) [37], in which studies were scored as having high, some concerns, or low risk of bias in five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. (Supplementary Table 1A). The quality assessment for observational studies was performed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) [38], which scores the studies as having low, moderate, serious, or critical risk of bias, evaluating seven domains: confounding, selection of participants, classification of interventions, deviations from the intended intervention, missing data, measurement of outcomes, and selection of reported results (Supplementary Table 1B). Two researchers (M.A.M. and L.S.), blinded to each other's decisions, independently performed a quality assessment. In case of disagreement, a third researcher was consulted (R.M.M.).

2.5 Statistical analysis

For pairwise analyses, we pooled risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes using the Mantel-Haenszel method with a fixed-effects model, given the small number of studies. Single-arm meta-analyses of continuous outcomes pooled study-level post-treatment means using inverse-variance random-effects models. Proportional meta-analyses used events/total with logit transformation in a generalized linear mixed model (GLMM), reported as percentages. Where pooling was not possible, results were presented qualitatively with descriptive study-level estimates. Comparative pooling was limited to the two RCTs, whereas single-arm pooling combined randomized treatment arms with observational cohorts; with fewer than 10 studies, design subgroups or meta-regressions could not be examined.

Heterogeneity was assessed using the Cochran's Q test and I^2 statistics, with thresholds of p-value ≤ 0.10 and I^2 interpreted according to the overlapping ranges in the Cochrane Handbook [18], with values of 50–90% regarded as potentially substantial. Leave-one-out sensitivity analyses were used to assess the effects of influential studies on pooled analyses only for endpoints with N > 3 studies. Studies were sequentially removed one at a time, and the data were reanalyzed to evaluate the stability of the pooled effects.

Due to the expected limited nature of this analysis, robustness was also assessed by comparing alternative meta-analytic methods (fixed-effects versus random-effects Hartung-Knapp-Sidik-Jonkman (HK-SJ) models). When studies reported different metrics, absolute post-treatment means (±SDs) were converted to change-from-baseline using the Cochrane within-participant correlation approach, and a sensitivity analysis using different Rs was performed to assess robustness.

All analyses used 95% confidence intervals (CI), and a two-sided p-value below 0.05 was set as statistically significant for the estimated effect sizes. Analyses were performed using Review Manager Web (version 9.10.0, Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), and R Studio (version 4.5.0, R Foundation for Statistical Computing, Vienna, Austria) was used with the "meta" package [22].

3. RESULTS

3.1 Study selection and characteristics

As detailed in Figure 1, the initial search yielded 761 records. After removing duplicate records and ineligible studies, 17 records were reviewed in full-text. Of these, four studies [13–15,17] met all inclusion criteria, representing 264 patients, of whom 180 (68.2%) were assigned to the CM-chitosan group with a mean age ranging from 60 to 80 years. Population characteristics are presented in Table 1. We reported baseline characteristics stratified using CM-chitosan versus HA among studies that reported such data.

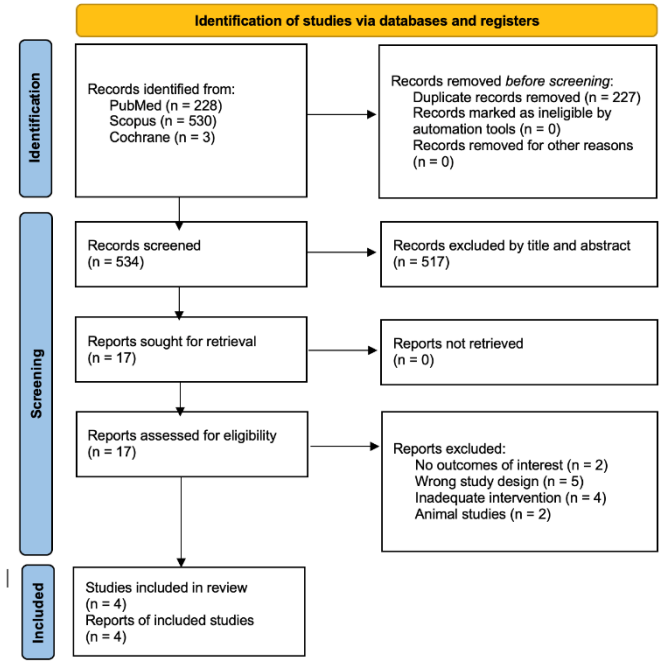

Figure 1. PRISMA 2020 flow diagram for study screening and selection

Table 1. Baseline characteristics of included studies.

Study	Design	HA type	Patients (n) CM-C/ HA	Age† (years) CM-C/ HA	Female (%) CM-C/ HA	BMI†(kg/m²) CM-C/ HA	KL Grade (%) CM-C/ HA	Follow-up
Emans 2022 (APROOVE)	comparative, RCT	Durolane®	63 / 32	61.9 / 59.8	74.6% / 53.1%	28.9 / 29.1	II: 61.9% / 65.6% III:38.1% / 34.4%	2 wks. 1, 3, 6 mos.
Van Overschelde 2025 (PIONEER)	comparative, RCT	Hylan G-F 20 (Synvisc-One)	52 / 52	61.9 / 61.7	69.2% / 73.1%	28.8 / 28.3	III and IV‡ TKA eligible	2 wks. 3, 6, 9, 12 mos.
Lynen 2024	single-arm, pro-spective	NA	49	65.6	71.4%	30.1	II: 46.9%, III: 53.1 %	1 wk. 3, 6, 9 mos.
Manocchio 2025	single-arm, retro-spective	NA	16	79.6	56.3%	NA	III and IV‡	1, 3, 6, 12 mos.

† mean or median, ‡ number of patients not available

Abbreviations: CM-C: Carboxymethyl-chitosan, HA: Hyaluronic Acid, NA: Not available; wks: Weeks; mos: Months

3.2 **Pair-wise pooled analysis of studies**

The two RCTs involving 199 patients performed a comparative analysis between CM-chitosan and HA [13,15]. At 6 months, there was no statistically significant difference between CM-chitosan and HA for OMERACT-OARSI responder rates (RR 1.02; 95% CI 0.87 to 1.21; p = 0.79; I^2 = 0%; Figure 2) and mean percentage change from baseline in WOMAC total scores (MD 1.42%; 95% CI -6.39 to 9.23; p = 0.72; I^2 = 0%; Figure 3). In addition, the groups were similar in terms of joint swelling (RR 3.88; 95% CI 0.45 to 33.23; p = 0.22; I^2 = 0%; Figure 4A). However, HA was associated with lower rates of ADEs (9.63% vs 28.44% with CM-chitosan) (RR 3.50; 95% CI 1.72 to 7.13; p = 0.0006; I^2 = 0%; Figure 4B) and arthralgia (10.84% vs 31.00%) (RR 3.01; 95% CI 1.53 to 5.91; p = 0.001; I^2=0%; Figure 4C).

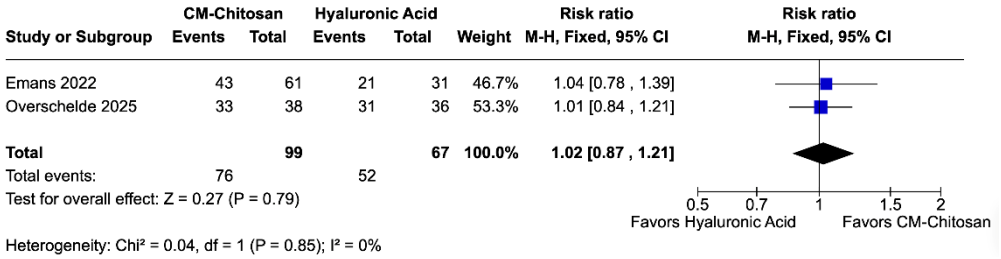

Figure 2. There was no statistically significant difference in OMERACT-OARSI responder rates at 6 months between CM-Chitosan and Hyaluronic Acid

CI, Confidence interval; M-H, Mantel–Haenszel; CM-Chitosan, Carboxy-methyl Chitosan; SD, Standard deviation

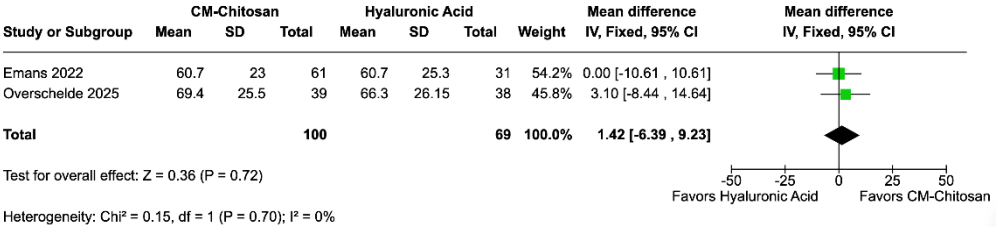

Figure 3. There was no statistically significant difference in WOMAC scores at 6 months between CM-Chitosan and Hyaluronic Acid

CI, Confidence interval; IV, Inverse variance; CM-Chitosan, Carboxy-methyl Chitosan, SD, Standard deviation

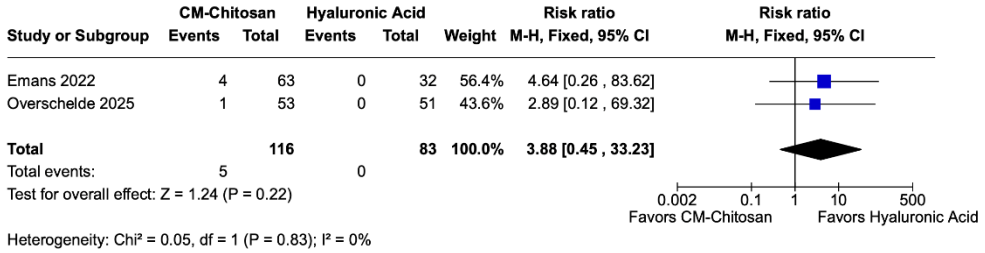

Figure 4A. There was no statistically significant difference in joint swelling rates between CM-Chitosan and Hyaluronic Acid

CI, Confidence interval; M-H, Mantel–Haenszel; ~~NA-TKA,~~ CM-Chitosan, Carboxy-methyl Chitosan, SD, Standard deviation

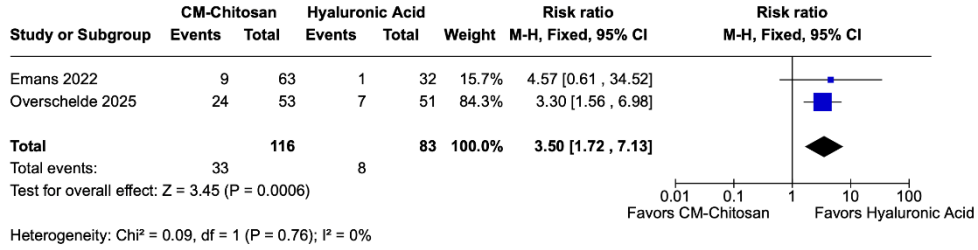

Figure 4B. Adverse device effects were significantly decreased after Hyaluronic Acid compared with CM-Chitosan

CI, Confidence interval; M-H, Mantel–Haenszel; CM-Chitosan, Carboxy-methyl Chitosan, SD, Standard deviation

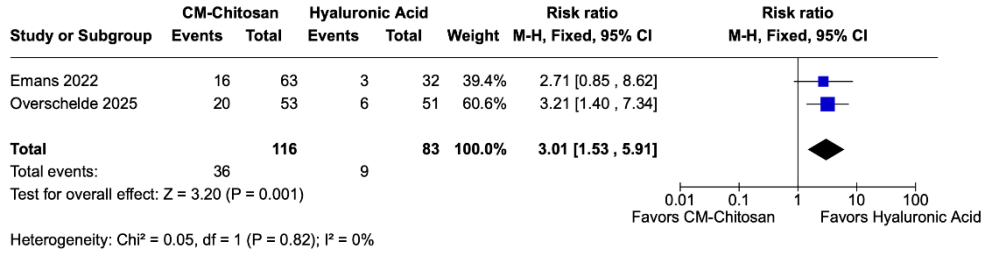

Figure 4C. Arthralgia was significantly decreased after Hyaluronic Acid compared with CM-Chitosan

CI, Confidence interval; M-H, Mantel–Haenszel; CM-Chitosan, Carboxy-methyl Chitosan, SD, Standard deviation

Single-arm pooled analysis

The overall OMERACT–OARSI responder rate of CM-chitosan at 6 months was 74.44% (95% CI 62.10 to 83.81; I^2 = 64%; Supplementary Figure 5). KOOS pain was 62.54% at 3 months (95% CI 40.51 to 84.57; I^2 = 94%; Supplementary Figure 6A) and 60.89% at 6 months (95% CI 30.01 to 91.77; I^2 = 96%; Supplementary Figure 6B). VAS pain was 42.95 mm at 3 months (95% CI 16.73 to 69.17; I^2 = 93%; Supplementary Figure 7A) and 44.57 mm at 6 months (95% CI −0.71 to 89.86; I^2 = 98%; Supplementary Figure 7B). Mean KOOS scores for symptoms, activities of daily living (ADL), sports and recreation (sport/rec), and quality of life (QoL) subscales are shown in Supplementary Appendix (Figures 8 and 9A, B, C, D).

3.3 Qualitative synthesis

Our quantitative synthesis results are limited to a 6-month follow-up due to variability of reported results. Long-term results (9 and 12 months) were not powered for between-group comparisons and are presented qualitatively (Table 2). At 9 months of follow-up, Lynen et al. reported that baseline VAS pain was 49 mm and fell to 18 mm, and KOOS pain subscale score rose from 58.3% at baseline to 86.1%. In Manocchio et al.'s 12-month cohort, baseline VAS pain was 73.75 mm and decreased to 70 mm, and KOOS Pain increased from 37.80% at baseline to 40.22%. Likewise, at 12 months, Van Overschelde et al. reported numerically greater WOMAC pain reduction of 73.5% with CM-chitosan versus 62.0% with HA. OMERACT-OARSI responder rates were 93.8% for CM-chitosan and 82.8% for HA. The incidence of total knee arthroplasty (TKA) was lower in the CM-chitosan group (2/24 patients) than in the HA group (4/20 patients). However, these statistics were not tested between groups and should not be extrapolated.

Table 2. Long-term results of CM-Chitosan.

Study	Van Overschelde 2025 (PIONEER)			Lynen 2024		Manocchio 2025	
Timepoint/ Outcome	WOMAC pain† (%) CM-C/ HA	OMERACT-OARSI (%) CM-C/ HA	Eligible for TKA (%) CM-C/ HA	VAS pain (mm) CM-C	KOOS pain (%) CM-C	VAS pain (mm) CM-C	KOOS pain (%) CM-C
Baseline	NA	NA	76.5/ 78.8	47.3	56.2	73.7	36.6
Month 9	NA	87.9/ 72.4	4.2/ 27.3	25.4	74.1	NA	NA
Month 12	–73.5/ –62	93.8/ 82.8	8.3/ 20	NA	NA	70	40.2

† change from baseline,

Abbreviations: TKA: Total knee arthroplasty, CM-C: Carboxymethyl-chitosan, NA: Not available; mm: Millimeters;

3.4 **Sensitivity analysis**

Due to N < 3 studies, a leave-one-out sensitivity analysis was conducted only on the outcome of OMERACT-OARSI responders at 6 months (Supplementary Figure 5). This analysis revealed that the effects remained unchanged. To further assess the robustness of the findings, we compared fixed-effect with random-effects Hartung-Knapp-Sidik-Jonkman (HK-SJ) models; results were consistent. For the WOMAC score at 6 months, varying the within-participant correlation coefficient (R = 0.2–0.8) did not materially change the estimates.

3.5 **Quality assessment**

Supplementary Appendix Tables 1A and 1B present an individual appraisal of each study using the Cochrane Collaboration's RoB2 and ROBINS-I tools. The two randomized trials exhibited some concerns regarding missing outcome data and a low risk of bias in the remaining domains. The non-randomized studies showed a moderate risk of bias in confounding, participant selection, and selection of reported results. Both studies had a low risk of bias in the classification of interventions and deviations from intended interventions. Lynen et al. showed low risk of bias in missing data and outcome measurement, while Manocchio et al. showed moderate risk.

4. DISCUSSION

In this systematic review and meta-analysis of four studies involving 264 patients, we assessed the safety and efficacy of intra-articular CM-chitosan injection and compared it with cross-linked HA for knee OA. Our main findings include: (1) at 6 months of follow-up, there was no statistically significant difference in WOMAC scores, OMERACT-OARSI responder rates, and joint swelling rates between CM-chitosan and HA; (2) HA was associated with a reduction in ADEs (9.63% vs. 28.44%) and arthralgia (10.84% vs. 31%); (3) single-arm mean KOOS pain subscale scores decreased from 62.54% at 3 months to 60.89% at 6 months; (4) single-arm mean VAS pain scores slightly rose from 42.95 mm at 3 months to 44.57 mm at 6 months; (5) qualitative analysis may indicate that the benefits of CM-chitosan could persist up to 9-12 months, with VAS, KOOS, WOMAC, OMERACT–OARSI improvements and potentially fewer TKAs compared to HA. To the best of our knowledge, this systematic review is the first to evaluate CM-chitosan and compare it with HA, as previous studies have focused on other chitosan formulations [23].

Management of knee OA with conservative measures includes options like HA, a high-molecular-weight polysaccharide, essential in synovial fluid and articular cartilage [24]. HA injection into the knee joint lubricates the surface, reduces erosion,

nourishes cartilage, and stimulates endogenous HA production [25]. However, systematic reviews and RCTs show inconclusive results regarding its efficacy for pain relief and functional improvement [26–28]. These variations may be due to factors like HA molecular weight, OA stage, BMI, age, female sex, and different patient-reported outcome measures (PROMs) [29]. The molecular weights of HA provide different biomechanical profiles. Ultra-high and high molecular weight polymers offer better joint lubrication and mechanical support in joints with less severe inflammation. Both RCTs included in this systematic review used cross-linked high-molecular-weight HAs: Durolane and Hylan G-F 20 (Synvisc-One) [26–28].

CM-chitosan has promising mechanistically regenerative long-term properties in knee OA. It modulates inflammation by inhibiting pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-17, while stimulating extracellular matrix component production [13,17,30]. Furthermore, chitosan-based hydrogels exhibit sustained release properties and remain in the joints for extended periods. This prolonged release enhances therapeutic efficacy and may reduce the need for frequent injections [17]. Preclinical models have suggested that chitosan-based hydrogels can effectively alleviate cartilage destruction and reduce pain compared to traditional HA [17,31]. Our quantitative comparative findings at 3-6 months do not indicate early superiority of CM-Chitosan versus cross-linked HA, which is compatible with an inflammatory mechanism that may not yield short-term separation. The clinically consequential question is whether CM-chitosan offers a more durable trajectory or differential benefit in "difficult-to-treat" phenotypes.

Long-term outcomes (9-12 months) were reported in three included studies [14,15,17]. These suggest that symptom improvement can be maintained in selected populations, with a possible divergence in the longer-term trajectory that cannot be confirmed quantitatively. This is supported by Van Overschelde et al. [15], where the direction of effects at 12 months (greater WOMAC pain reduction, higher OMERACT-OARSI responder rates, and decreased need for TKA for CM-chitosan) aligns with our qualitative inference that any advantage would plausibly emerge after an early window, when both injectables perform similarly. The high-risk viscosupplementation failure population [15,17,32,33] (Kellgren–Lawrence III–IV, and/or obesity) may have partial attenuation by 12 months (Table 2), indicating that in advanced, refractory disease, CM-chitosan may provide modest symptomatic relief rather than sustained remission.

Our results showed that ADEs decreased significantly after HA compared with CM-chitosan. Treatment-related adverse events are induced by a physiological macrophage reaction required to degrade CM-chitosan implants [13,16]. Local reactions following CM-chitosan injection are typically due to its biomaterial response and should not be mistaken for hypersensitivity reactions [15,31]. Patients experience transient arthralgia lasting 3 days, as reported by Van Overschelde et al., which responds to anti-inflammatory drugs without impacting clinical benefit [15]. Emans et al. showed that CM-chitosan had more treatment-related adverse events (30.2%) than Durolane, but fewer than Hylan G-F 20 (Synvisc-One) and Gel-One [13,34]. To address these initial side effects, Van Overschelde et al. administered an intra-articular corticosteroid (CS) injection at screening, which resulted in an initial decrease in pain before randomization [15]. According to the Brazilian consensus group, CS injection improves pain and function for 2-4 weeks [15,35], raising the question of whether injecting CS or anti-inflammatory drugs before CM-chitosan would be potentially beneficial, but this warrants prospective evaluations.

From a rehabilitation standpoint, CM-chitosan should be regarded as an adjunct within the multidisciplinary, conservative management of knee OA, in which patient

education, structured exercise, and weight management remain the core treatments and intra-articular therapies serve as complementary options [8,9,39]. By providing a window of symptom relief, it may facilitate engagement in physiotherapy and exercise-based rehabilitation within an individualized care pathway, although its optimal timing and combination with rehabilitation interventions remain to be defined [40].

This meta-analysis has limitations. Firstly, there was substantial variability in OA severity and HA formulation among included studies. Secondly, CS injection at enrollment to reduce joint inflammation may have acted as a confounder affecting PROMs. These factors, together with the variability inherent to single-arm pooling, contributed to substantial statistical heterogeneity, with I^2 exceeding 90% for the pooled single-arm estimates of KOOS pain and VAS pain; however, the I^2 statistic can often be high due to the nature of proportional data, which does not necessarily indicate data inconsistency [36]. Thirdly, heterogeneity in follow-up durations and results also prevented long-term comparisons. Fourthly, publication bias could not be properly assessed due to the limited number of studies. Finally, having only two comparative RCTs precluded robust pooled estimates, and single-arm designs required longitudinal comparisons, preventing quantitative synthesis of all studies. These findings should be regarded as exploratory and hypothesis-generating rather than definitive estimates of treatment effect. Future RCTs with standardized protocols stratified by OA stage, standardized comparators, long-term follow-up, and use of minimal clinically important difference-validated scores are required to confirm these findings.

5. CONCLUSION

This systematic review and meta-analysis suggest that CM-chitosan may provide early, satisfactory relief with moderate mid-term results, but does not demonstrate superiority to HA at 6 months. Further research is necessary to confirm its long-term efficacy. Although CM-chitosan demonstrates a favorable safety profile, it is associated with a slightly higher risk of adverse events than HA. From a physical and rehabilitation medicine standpoint, CM-chitosan may serve as an adjunct to conservative, multidisciplinary management, alongside exercise-based physiotherapy and patient education.

6. Declations

Ethics approval and consent to participate: This is a meta-analysis; ethical approval and consent to participate were not required to commence the study.

Consent for publication: All authors consented to the publication of this paper.

Availability of data and materials: Extracted data are available for future use and can be obtained by contacting the corresponding author.

Competing interests: All authors report no relationships that could be construed as conflicts of interest.

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Credit author statement:

R.M.M.: study screening, data extraction, quality assessment, Writing – review & editing

L.S.: study screening, data extraction, quality assessment, Writing – review & editing

A.J.: Investigation, Data curation, Resources

B.V.: Investigation, Formal analysis, Software

A.N.M.: Resources, Original draft, Project administration

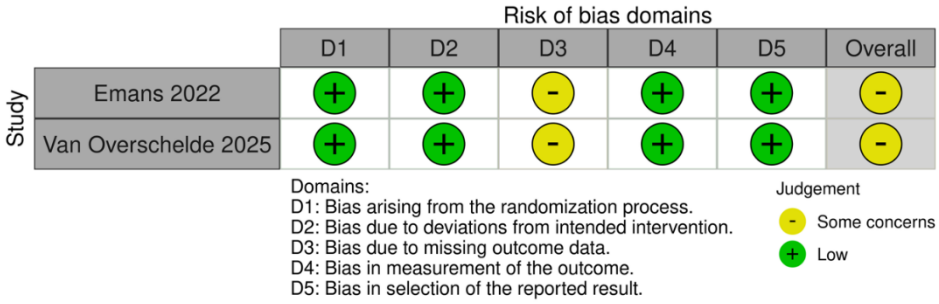
M.A.M.: Conceptualization, study screening, Data curation, Methodology, Writing – review & editing, Supervision,

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretations.

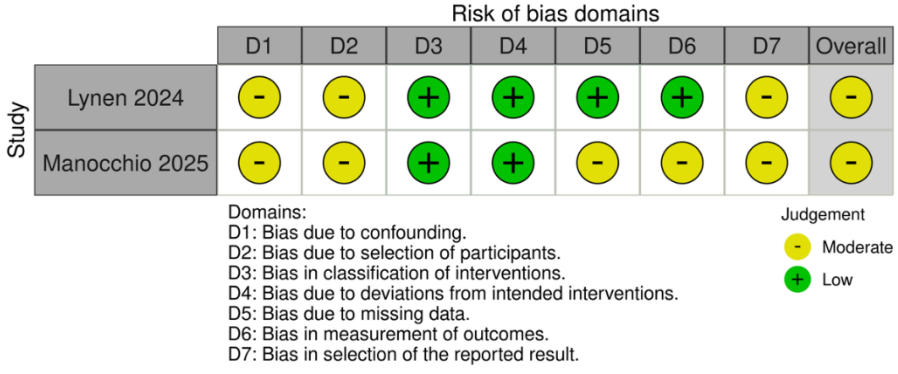
Appendix A

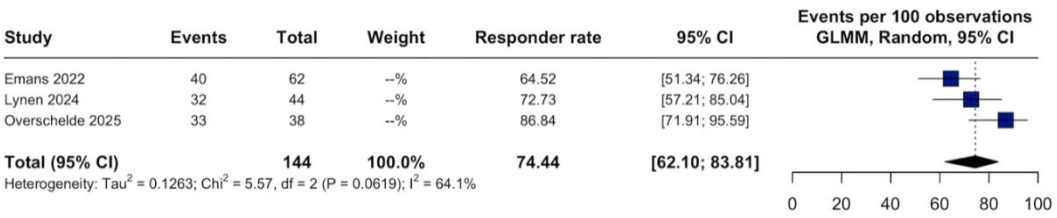
Search strategy: ("KiOmedine" OR chitosan OR "carboxymethyl-chitosan" OR "CM-chitosan") AND ("osteoarthritis" OR "knee osteoarthritis")

Supplementary Table 1A. Critical appraisal of individual studies according to the Cochrane Collaboration's RoB 2 tool for assessing the risk of bias in randomized trials.

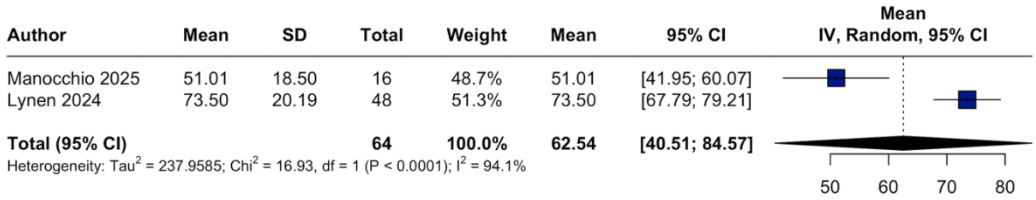


Supplementary Table 1B. Critical appraisal of individual studies according to the Cochrane Collaboration's ROBINS- I tool for assessing the risk of bias in non-randomized trials.

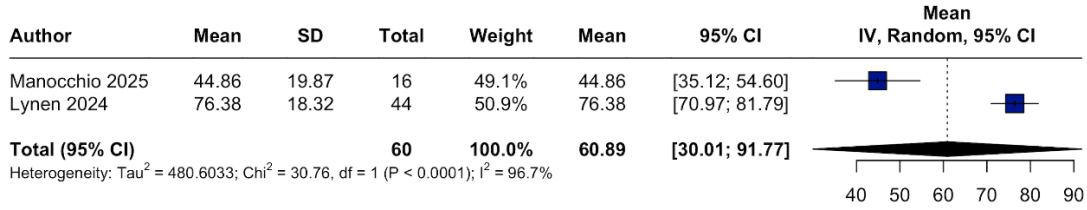




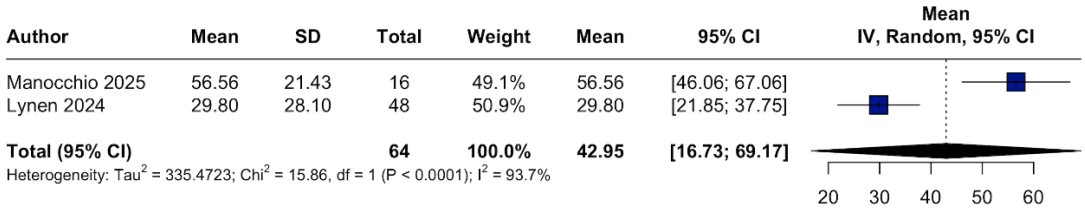
Supplementary Figure 5. Proportion of OMERACT-OARSI responders at 6 months
CI, Confidence interval; GLMM, Generalized Linear Mixed Model



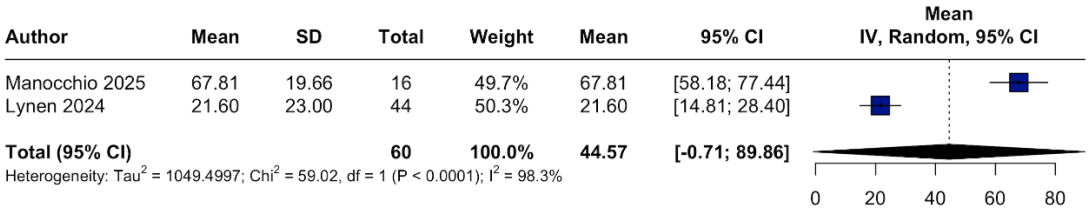
Supplementary Figure 6A. Mean KOOS pain subscale score at 3 months after CM-Chitosan injection
CI, Confidence interval; IV, Inverse variance; SD, Standard deviation



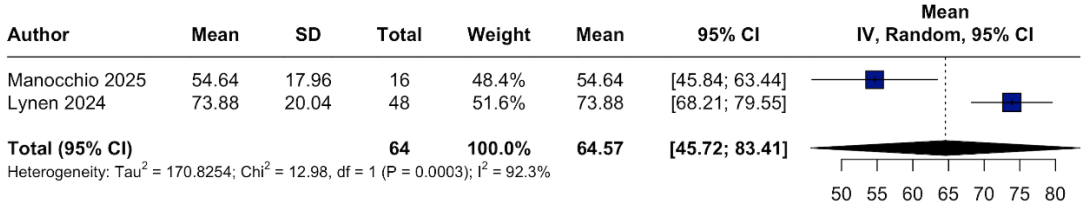
Supplementary Figure 6B. Mean KOOS pain subscale score at 6 months after CM-Chitosan injection
CI, Confidence interval; IV, Inverse variance; SD, Standard deviation



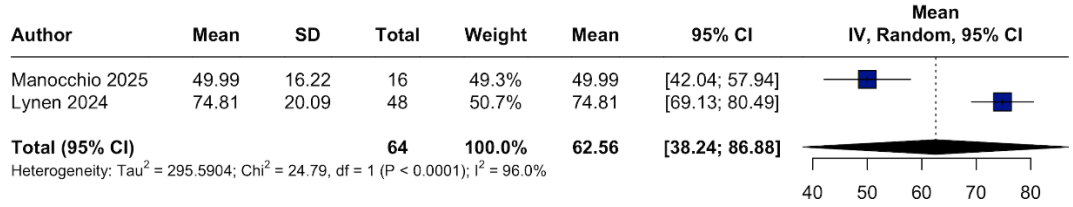
Supplementary Figure 7A. Mean VAS pain score at 3 months after CM-Chitosan injection
CI, Confidence interval; IV, Inverse variance; SD, Standard deviation



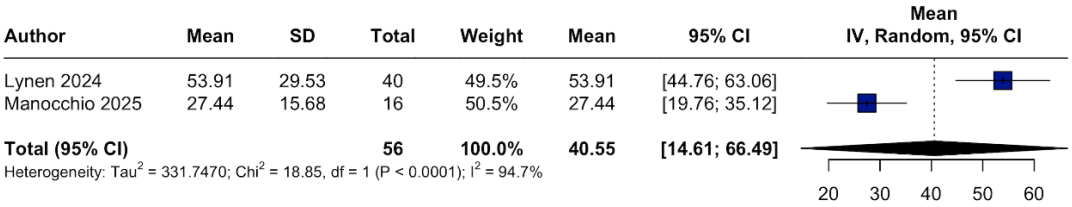
Supplementary Figure 7B. Mean VAS pain score at 6 months after CM-Chitosan injection
CI, Confidence interval; IV, Inverse variance; SD, Standard deviation



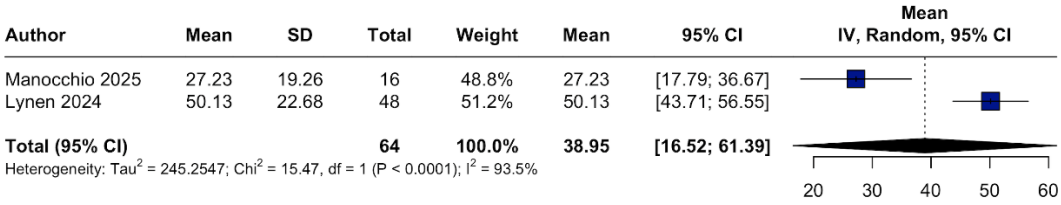
Supplementary Figure 8A. Mean KOOS symptoms subscale score at 3 months after CM-Chitosan injection.
CI, Confidence interval; IV, Inverse variance; SD, Standard deviation



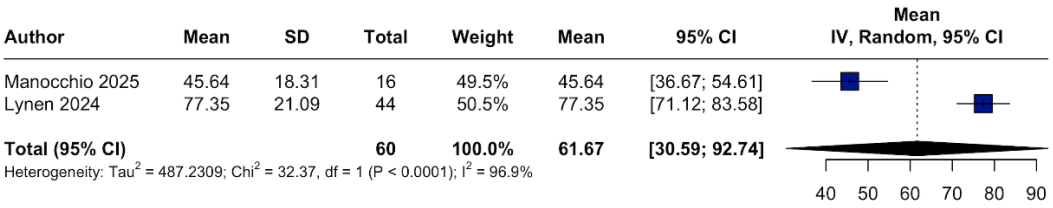
Supplementary Figure 8B. Mean KOOS activities of daily living (ADL) subscale score at 3 months after CM-Chitosan injection.
CI, Confidence interval; IV, Inverse variance; SD, Standard deviation



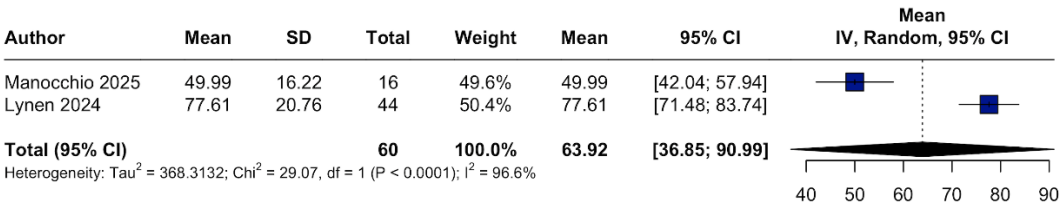
Supplementary Figure 8C. Mean KOOS sport and recreation subscale score at 3 months after CM-Chitosan injection.
CI, Confidence interval; IV, Inverse variance; SD, Standard deviation



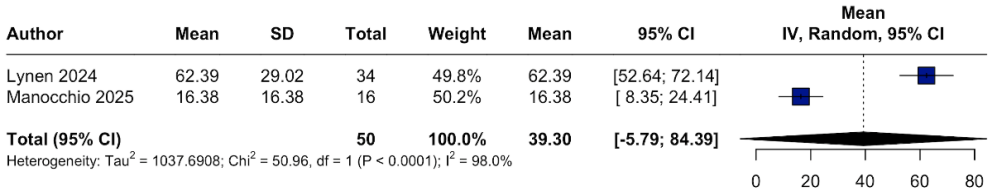
Supplementary Figure 8D. Mean KOOS quality of life subscale score at 3 months after CM-Chitosan injection.
CI, Confidence interval; IV, Inverse variance; SD, Standard deviation



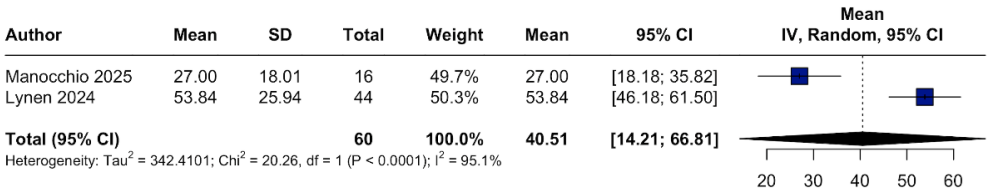
Supplementary Figure 9A. Mean KOOS symptoms subscale score at 6 months after CM-Chitosan injection.
CI, Confidence interval; IV, Inverse variance; SD, Standard deviation



Supplementary Figure 9B. Mean KOOS activities of daily living (ADL) subscale score at 6 months after CM-Chitosan injection.
CI, Confidence interval; IV, Inverse variance; SD, Standard deviation



Supplementary Figure 9C. Mean KOOS sport and recreation subscale score at 6 months after CM-Chitosan injection.
CI, Confidence interval; IV, Inverse variance; SD, Standard deviation



Supplementary Figure 9D. Mean KOOS quality of life subscale score at 6 months after CM-Chitosan injection.
CI, Confidence interval; IV, Inverse variance; SD, Standard deviation

References

1. Langworthy M, Dasa V, Spitzer AI. Knee osteoarthritis: disease burden, available treatments, and emerging options. Ther Adv Musculoskelet Dis. 2024;16. doi:10.1177/1759720X241273009
2. Li HZ, Liang XZ, Sun YQ, Jia HF, Li JC, Li G. Global, regional, and national burdens of osteo-arthritis from 1990 to 2021: findings from the 2021 global burden of disease study. Front Med (Lau-sanne). 2024;11. doi:10.3389/fmed.2024.1476853
3. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. The Lancet. 2019;393(10182):1745-1759. doi:10.1016/S0140-6736(19)30417-9
4. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. EClinicalMedicine. 2020;29-30. doi:10.1016/j.eclinm.2020.100587
5. Di J, Bai J, Zhang J, et al. Regional disparities, age-related changes and sex-related differences in knee osteoarthritis. BMC Musculoskelet Disord. 2024;25(1). doi:10.1186/s12891-024-07191-w
6. Courties A, Kouki I, Soliman N, Mathieu S, Sellam J. Osteoarthritis year in review 2024: Epi-demiology and therapy. Osteoarthritis Cartilage. 2024;32(11):1397-1404. doi:10.1016/j.joca.2024.07.014
7. Uhlig T, Slatkowsky-Christensen B, Moe RH, Kvien TK. The burden of osteoarthritis:the soci-etal and the patient perspective. Therapy. 2010;7(6):605-619. doi:10.2217/thy.10.70
8. Moseng T, Vliet Vlieland TPM, Battista S, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis: 2023 update. Ann Rheum Dis. 2024;83(6):730-740. doi:10.1136/ard-2023-225041
9. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatolo-gy/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis and Rheumatology. 2020;72(2):220-233. doi:10.1002/art.41142
10. Peck J, Slovek A, Miro P, et al. A Comprehensive Review of Viscosupplementation in Osteo-arthritis of the Knee. Orthop Rev (Pavia).Open Medical Publishing. 2021;13(2). doi:10.52965/001C.25549
11. Sherman SL, Gudeman AS, Kelly JD, Dimeff RJ, Farr J. Mechanisms of Action of Intra-articular Hyaluronic Acid Injections for Knee Osteoarthritis: A Targeted Review of the Literature. American Journal of Sports Medicine.SAGE Publications Inc. Preprint posted online September 1, 2025. doi:10.1177/03635465241302820
12. Migliore A, Procopio S. Effectiveness and Utility of Hyaluronic Acid in Osteoarthritis. Vol 12.; 2015.
13. Emans PJ, Skaliczki G, Haverkamp D, et al. First-in-human Study to Evaluate a Single Injec-tion of KiOmedine®CM-Chitosan for Treating Symptomatic Knee Osteoarthritis. Open Rheumatol J. 2022;16(1). doi:10.2174/18743129-v16-e2206100
14. Lynen NA, Eichhorn C, Portelange N, Chausson M, Weyenberg W. Long-Term Efficacy Fol-lowing Intra-articular Injection of Carboxymethyl-chitosan, a New Product Class for Knee Osteoar-thritis: Results from an Observational Study in Germany. Rheumatol Ther. 2024;11(3):649-662. doi:10.1007/s40744-024-00661-6
15. Van Overschelde P, Vansintjan P, Portelange N, Chausson M, Weyenberg W. Twelve-month efficacy of carboxymethyl-chitosan in refractory knee osteoarthritis: A randomized controlled trial (PIONEER). Osteoarthr Cartil Open. 2025;7(2). doi:10.1016/j.ocarto.2025.100605
16. Douette P, Chausson M, Theatre E, et al. Biological Safety Evaluation of KiOmedine® CM-chitosan, an Innovative Non-animal Carboxymethyl-Chitosan Biomaterial Intended for Injectable Bi-omedical Applications. Journal of Biomaterials. 2020;4(2):39. doi:10.11648/j.jb.20200402.12

17. Manocchio N, Pirri C, Ljoka C, et al. Long-Term Efficacy of Carboxymethyl-Chitosan in Ad-vanced Knee Osteoarthritis: A Twelve-Month Follow-Up Study on Non-Responders to Hyaluronic Ac-id. Biomedicines. 2025;13(2). doi:10.3390/biomedicines13020270
18. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interven-tions.; 2019. doi:10.1002/9781119536604
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. The BMJ. 2021;372. doi:10.1136/bmj.n71
20. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. doi:10.1186/s13643-016-0384-4
21. Dougados M, Leclaire P, van der Heijde D, Bloch DA, Bellamy N, Altman RD. Response crite-ria for clinical trials on osteoarthritis of the knee and hip: a report of the Osteoarthritis Research Socie-ty International Standing Committee for Clinical Trials response criteria initiative. Osteoarthritis Carti-lage. 2000;8(6):395-403. doi:10.1053/joca.2000.0361
22. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tuto-rial. Evidence Based Mental Health. 2019;22(4):153-160. doi:10.1136/ebmental-2019-300117
23. Novy TCT, Joni IM, Lesmana R, Biben V, Setiawan. Chitosan Nanoparticles as an Alternative Therapeutic Approach for Knee Osteoarthritis Treatment: A Systematic Review. Int J Nanomedicine. 2025;20:6187-6203. doi:10.2147/IJN.S503829
24. Anil U, Markus DH, Hurley ET, et al. The efficacy of intra-articular injections in the treatment of knee osteoarthritis: A network meta-analysis of randomized controlled trials. Knee. 2021;32:173-182. doi:10.1016/j.knee.2021.08.008
25. Lee CL, Wang YC, Huang HT, Chen CH, Chang KL, Tien YC. Efficacy of Intra-Articular Injec-tion of Biofermentation-Derived High-Molecular Hyaluronic Acid in Knee Osteoarthritis: An Ultraso-nographic Study. Cartilage. 2022;13(1). doi:10.1177/19476035221077404
26. Altman RD, Åkermark C, Beaulieu AD, Schnitzer T. Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. Osteoarthritis Cartilage. 2004;12(8):642-649. doi:10.1016/j.joca.2004.04.010
27. Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P. A Double-Blind, Randomized, Saline-Controlled Study of the Efficacy and Safety of EUFLEXXA® for Treatment of Painful Osteoarthritis of the Knee, With an Open-Label Safety Extension (The FLEXX Trial). Semin Arthritis Rheum. 2009;39(1):1-9. doi:10.1016/j.semarthrit.2009.04.001
28. Iaconisi GN, Lunetti P, Gallo N, et al. Hyaluronic Acid: A Powerful Biomolecule with Wide-Ranging Applications—A Comprehensive Review. Int J Mol Sci. 2023;24(12):10296. doi:10.3390/ijms241210296
29. Migliorini F, Maffulli N, Simeone F, Jeyaraman N, Ramasubramanian S, Jeyaraman M. Intra-articular Hyaluronic Acid Injections May Be Beneficial in Patients with Less Advanced Knee Osteoar-thritis: A Systematic Review of Randomised Controlled Trials. Sports Medicine. 2025;55(8):1953-1969. doi:10.1007/s40279-025-02265-8
30. Ressler A. Chitosan-Based Biomaterials for Bone Tissue Engineering Applications: A Short Review. Polymers (Basel). 2022;14(16):3430. doi:10.3390/polym14163430
31. Mou D, Yu Q, Zhang J, et al. Intra-articular Injection of Chitosan-Based Supramolecular Hy-drogel for Osteoarthritis Treatment. Tissue Eng Regen Med. 2021;18(1):113-125. doi:10.1007/s13770-020-00322-z
32. Chevalier X, Sheehan B. Predictors of Clinical Benefit with Intra-articular Hyaluronic Acid in Patients with Knee Osteoarthritis - A Narrative Review. Curr Rheumatol Rev. 2024;20(4):379-387. doi:10.2174/0115733971274662240108074038
33. Rapp C, Boudif F, Bourgoin C, Lohse A, Conrozier T. A Cross-Sectional Study of Factors Pre-dicting the Duration of the Efficacy of Viscosupplementation in Knee Osteoarthritis. J Clin Med. 2024;13(7):1949. doi:10.3390/jcm13071949
34. Strand V, Lim S, Takamura J. Evidence for safety of retreatment with a single intra-articular injection of Gel-200 for treatment of osteoarthritis of the knee from the double-blind pivotal and open-label retreatment clinical trials. BMC Musculoskelet Disord. 2016;17:240. doi:10.1186/s12891-016-1101-0
35. Coimbra IB, Plapler PG, Campos GC de. Generating evidence and understanding the treat-ment of osteoarthritis in Brazil: a study through Delphi methodology. Clinics. 2019;74:e722. doi:10.6061/clinics/2019/e722
36. Barker TH, Migliavaca CB, Stein C, et al. Conducting proportional meta-analysis in different types of systematic reviews: a guide for synthesisers of evidence. BMC Med Res Methodol. 2021;21(1):189. doi:10.1186/s12874-021-01381-z
37. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in ran-domised trials. BMJ. 2019;366:l4898. doi:10.1136/bmj.l4898
38. Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. doi:10.1136/bmj.i4919
39. Pers YM, et al. Recommendations from the French Societies of Rheumatology and Physical Medicine and Rehabilitation on the non-pharmacological management of knee osteoarthritis. Ann Phys Rehabil Med. 2024;67(7):101883. doi:10.1016/j.rehab.2024.101883
40. Liao CD, Chen HC, Huang MH, Liou TH, Lin CL, Huang SW. Comparative Efficacy of Intra-Articular Injection, Physical Therapy, and Combined Treatments on Pain, Function, and Sarcopenia Indices in Knee Osteoarthritis: A Network Meta-Analysis of Randomized Controlled Trials. Int J Mol Sci. 2023;24(7):6078. doi:10.3390/ijms24076078