

General

Effectiveness of hydrogel-based therapies in the treatment of talus osteoarthritis: a systematic review

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Background

Talus osteoarthritis (OA) is a disabling condition that negatively affects the lives of individuals in terms of pain, functional limitation. Hydrogels, due to their viscoelastic, bioactive, and biocompatible properties, have emerged as a promising therapeutic option in cartilage repair and OA management. Currently hydrogel applications in other joint OA such as knee are extensively studied, while their use in talocrural joint degeneration remains underexplored. This systematic review aims to analyze the uncertainty in the effectiveness and safety of hydrogel-based therapies in the treatment of talus OA.

Methods

Following PRISMA guidelines, a systematic search was conducted across PubMed, Embase, Scopus, Web of Science, and the Cochrane Library from 2015 up to 2025. Eligible studies included case series, cohort and randomized clinical trials investigating hydrogel implementation for talus OA. Data extraction and risk of bias assessments were independently performed by two reviewers. Thematic synthesis was applied due to heterogeneity in study designs.

Results

Preliminary screening identified 5 relevant studies. Hydrogel types included hyaluronic acid derivatives. Outcomes assessed included pain scores, joint function and imaging-based structural changes.

Conclusion

Hydrogel-based therapies represent a promising joint-preserving option for talus osteoarthritis, offering potential cartilage support and symptom relief. However, current evidence remains limited. Larger, well-designed clinical trials with standardized outcome measures are essential to validate efficacy and refine formulations tailored to the unique biomechanics of the ankle joint.

INTRODUCTION

Osteoarthritis (OA) is a common degenerative joint disease, causing pain and functional limitation of elderly population. The primary osteoarthritis of the ankle is a very rare condition, while secondary OA of this joint is frequently posttraumatic or caused by inflammatory conditions. The rarity of primary form can be explained by anatomical difference: the surface area is small and the cartilage is thin.¹ As etiology of ankle OA is mainly posttraumatic, it tends to affect the younger population of 18-44 years old.² Treatment includes conservative therapy and surgical proce-

dures, including joint-preserving and joint-sacrificing one. Conservative treatment is aimed on delaying the need in surgical intervention and includes non-pharmacological therapy as physical exercises, lifestyle change orthotics and pharmacological therapy being Nonsteroidal antiinflammatory drugs, intra-articular corticosteroid injections, visco-supplementation, platelet-rich plasma and mesenchymal stem cells. Although there are a variety of options, there is no consensus on the approach to treatment of patients with OA of the ankle joint.³

In recent years, hydrogels have gained attention as new biomaterials with therapeutic potential in cartilage repair

and OA management. Hydrogels are hydrophilic, three-dimensional polymer networks that can mimic the viscoelastic properties of native articular cartilage. It can also serve as scaffolds, drug carriers, or stem cell delivery vehicles.⁴ The material used to prepare the hydrogels can be natural, including hyaluronic acid, chitosan, alginate, fibrin, collagen, elastin and synthetic including polyethylene glycol, polyglutamic acid based polymers.⁵ Their injectable nature allows for minimally invasive implementation, which is especially advantageous in joints with limited anatomical access such as the talus. There are numerous studies investigating the therapeutic features of hydrogel injection in knee OA, however its application in the ankle joint remains underexplored. The unique biomechanics of the ankle, which can be characterized by high congruence and load transmission through a relatively thin cartilage layer, makes the response to treatment different. Potentially it might affect the retention of hyaluronic acid within the joint. These biomechanical differences highlight the importance of ankle-specific research despite the rarity than adapting findings from the knee. Therefore it is necessary to analyze the response of the ankle to hydrogel-based treatment and evaluate long-term outcomes.

Given the potential of hydrogels to function as a joint-preserving treatment option, this systematic review considers its use in talus OA. This review aims to evaluate the effectiveness, safety, and clinical utility of hydrogel-based therapies for talocrural joint osteoarthritis, with a focus on identifying knowledge gaps and informing future research directions.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) checklist and the Cochrane Handbook for Systematic Reviews of Interventions.^{6,7}

LITERATURE SEARCH STRATEGY

A comprehensive literature search was conducted in the first half of February 2025 up to the end of March 2025 across the electronic databases such as: PubMed, Scopus, Embase, and Google Scholar. The search was limited to publications in the English language. Following search phrases were used (“hydrogel” OR “injectable scaffold*” OR “biomaterial*” OR “viscosupplementation” OR “tissue engineering”) AND (talus OR ankle OR talocrural OR “ankle joint”) AND (osteoarthritis OR “cartilage degeneration” OR “joint disease” OR “articular cartilage”. The search was limited to studies from 2015 to ensure that latest outcome assessments were done, delivery techniques were up-to-date and there were advances in the formulation of HA.

STUDY SELECTION

There was a manual screening of titles and abstracts of publications by two independent reviewers. The articles which were unrelated to the focus were excluded. After

the initial filter, all eligible studies were sorted alphabetically by first author and publication year. Disagreements between reviewers were resolved through discussion and, if necessary, arbitration by a third reviewer (YR).

ELIGIBILITY CRITERIA

INCLUSION CRITERIA

Clinical studies such as randomized controlled studies, case series, cohort studies evaluating intra-articular injections of hydrogel-based therapies for ankle OA were eligible for inclusion to this review. Studies should have included quantitative outcomes on pain, joint functionality, imaging-based assessment. The article must be published in peer-reviewed journals.

EXCLUSION CRITERIA

Case reports were excluded. The studies investigating non-hydrogel-based therapies were excluded. The reports of in vitro, computational or cadaveric studies were excluded. The articles which are not focused on osteoarthritis (congenital defects) were excluded. Studies including stem cells without the hydrogel were excluded. Studies which did not include relevant quantitative outcomes were excluded.

DATA EXTRACTION

Two authors (DS and MM) independently extracted data from the included studies. Extracted variables included:

- Study characteristics: author, year, journal, country, study design.
- Population and intervention details: sample size, patient demographics, gender distribution, history of trauma, hydrogel composition, delivery method, follow-up duration.
- Outcomes of interest:
 - Pain scales (e.g., Visual Analogue Scale (VAS)),
 - Functional scores (e.g., American Orthopaedic Foot & Ankle Society scale (AOFAS)),
 - Quality of life (if present)
 - Adverse events, complications, patient satisfaction and need for revision procedures.

All extracted data were cross-verified, and disagreements were discussed for consensus. The quality of randomized control trials (RCT) was evaluated by reviewing the adequacy of the randomization, completeness of the data presented.

RESULTS

Primary search of the literature revealed 24 articles using PubMed and 0 articles using Embase according to the search of mentioned keywords. The abstracts were screened to exclude the papers published before 2014 (n= 14), non-hydrogel treatment (n=1), different joint (n=1) and different focus being surgical procedure (n=1). The search on Scopus revealed 1 duplication, which was excluded. The search on

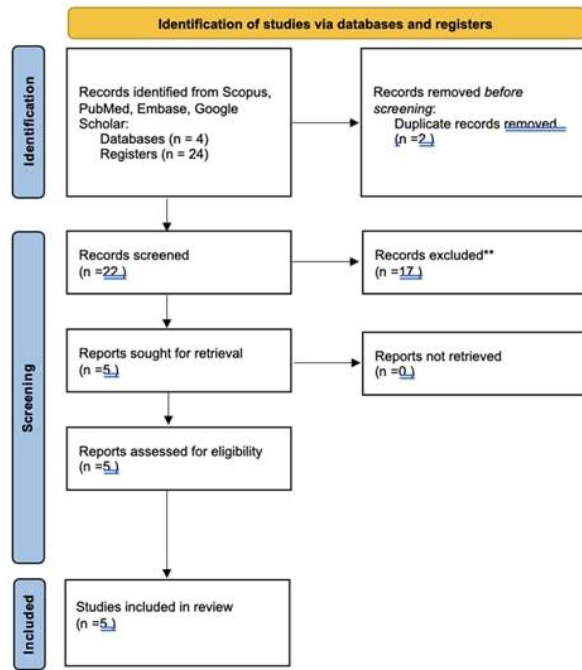


Figure 1. PRISMA flow diagram.⁸

Google Scholar revealed 1 duplication. As reported in figure 1, a total of 5 studies were included in this review. The process of selection is reflected in Fig. 1.

As reported in Table 1, four out of five studies reported the effectiveness of Hyaluronic acid hydrogel. Interestingly, both single form and conjugated to another treatment modality revealed the effectiveness in terms of pain symptom reduction.

STUDY CHARACTERISTICS AND INTERVENTIONS

A total of five studies met the inclusion criteria, studies conducted between 2019 and 2025. All studies evaluated intra-articular injection of hyaluronic acid (HA)-based hydrogels for talus OA. Of these, three studies included a placebo

or comparative control group while two were single-arm cohort or non comparative trials.⁹⁻¹³

HYDROGEL TYPES AND DOSAGE

The types of HA investigated included non-animal stabilized HA with single injection approach,⁹ HA-CS with total 3 injections – 1 injection every week,¹⁰ DC-HA conjugate with 3 injections every 4 weeks for 12 weeks DC-HA conjugate with injection every 4 weeks for 1 year and HA-CS injections – 1 injection every week.¹¹⁻¹³

OUTCOMES AND IMPROVEMENTS

Four studies reported significant improvement in pain and functional scores. For instance, Younger et al. found a significant reduction in VAS pain scores and improved function. Gomez et al. and Woo et al. demonstrated that HA combined with CS resulted in greater and longer-lasting improvements compared to corticosteroid alone, as measured by AOFAS and VAS scales. Kubo et al. found no significant difference between DC-HA and placebo, while Nishida et al. observed symptom improvement over one year in a small cohort.

SAFETY AND COMPLICATIONS

Younger et al. reported that most frequent adverse events reported by patients were arthralgia and headache (almost 25% each), nasopharyngitis (up to 20%) and pain in injection site (16%). Gomez et al. and Woo et al. reported no complications and adverse reactions. Kubo et al. reported common adverse events as common cold, injection site pain, nausea and palpitations in up to 7% cases. Nishida et al. reported common adverse events as nasopharyngitis, eczema, injection site pain in more than 5% cases.

Table 1. Summary of main results of selected studies.

Author, year	Study design	Control	Type of hydrogel	Number of patients	Main result
Younger et al, 2019 ⁹	Single arm cohort	None	Non-Animal HA	37	Effective reduction of pain and improvement of functionality (VAS score)
Gomez et al, 2023 ¹⁰	Randomized Comparative trial	Isolated CS	Hyaluronic Acid with corticosteroid	25	Combination of HA with CS provides longer and greater effect (AOFAS and VAS scores)
Kubo et al, 2022 ¹¹	Randomized Controlled Trial	Placebo	Diclofenac-Hyaluronate conjugate	29	Diary-based 11-point NRS score for pain no improvement, No improvement in comparison to placebo by SAFE-Q, equivocal results by SF-36 questionnaire and EQ-5D.
Nishida et al, 2021 ¹²	Randomized Controlled Trial	No control	Diclofenac-Hyaluronate conjugate	8	Improvement of symptoms compared to placebo for 1 year (NRS score, VAS, SF-36, EQ-5D)
Woo et al, 2025 ¹³	Randomized Comparative Trial	Isolated CS	Hyaluronic acid with Corticosteroid	74	Combination is more effective in relieving the pain (AOS scale). Significant improvement in VAS, score SF-36).

DISCUSSION

This systematic review analysed existing publications on the effectiveness and safety of hydrogel-based therapies in the treatment of talus OA. According to inclusion criteria, five clinical studies were included in the review. The majority of them investigated HA-based hydrogels, either alone or in combination with other agents such as corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs).

The findings of this review suggest that hyaluronic acid-based hydrogels are safe and provide symptomatic relief in patients with ankle OA. For example, study by Younger et al. and Woo et al. report improvement in pain score and joint function. Moreover, combination therapy with corticosteroid reported improved efficacy in comparison to corticosteroid alone and demonstrated prolonged symptom control.¹⁰ On the other hand, studies investigating HA combination with diclofenac revealed mixed results. According to Kubo et al., there is no superiority over the placebo, while Nishida et al. reported pain reduction within 1 year. This discrepancy can be explained by different regimen of the injections as in study by Kubo et al. there were 3 injections every 4 weeks for 12 weeks, while study by Nishida et al. reports injection every 4 weeks for 1 year. The longer administration might affect the reported outcomes. Moreover, study by Nishida is small, involving 8 patients only, therefore it is sensitive to variations such as age, joint condition, prior treatment history.

It was decided not to conduct the meta-analysis as there is a limited number of systematic reviews, heterogeneity in type of hydrogels, difference in control groups and protocols in term of number of injections. Moreover, there was a variety of the outcome measures reported across the studies. Therefore, authors decided to conduct the systematic review.

From previous studies, one large systematic review analyzed the effectiveness of hyaluronic acid by reviewing RCTs up to September 2014 and reported lack of data to claim efficacy or inefficacy as only 240 patients were included in the review. According to this study, the decrease in pain and physical function was reported by the participants. However, there was no evaluation in radiographic change and no data for the evaluation of the quality of life.¹⁴ Another systematic review evaluating the same period included 5 randomized controlled trials on use of hyaluronic acid intra-articular injections on 170 patients. The authors report improvement of functional scores and overall safety of the procedure, with no evidence of superiority of treatment option.¹⁵ The results of this review are in accordance with previous systematic reviews. However, the evidence remains preliminary, and current studies lack long-term follow-up and standardized outcome measures.

LIMITATIONS OF THE CURRENT LITERATURE

There are several limitations of this study that need to be taken into account when making final decisions. First is the relatively small sample size and short period of follow up (up to 12 months). It restricts from making generalisations

of the findings. Next, is variability of outcome measures. Analytical comparison was not conducted as the AOFAS, VAS scores were used inconsistently and there is no uniformity in the result report. Moreover, there are different compositions of hydrogels used, which complicates the evaluation of efficacy. Studies rely on clinical symptoms, which imaging was not done in all studies and histological assessment was not conducted.

Additionally, no studies evaluated cartilage regeneration or integration using magnetic resonance imaging (MRI) or second-look arthroscopy, making it difficult to assess structural efficacy. Patient-specific factors, such as age, joint alignment, and history of trauma, were inconsistently reported and not analyzed as covariates.

One of the major limitations encountered during the review process was the fact that there are relatively few studies focusing on treating talus osteoarthritis using hydrogels. It was expected, as generally there is a lower incidence of ankle osteoarthritis. It is a challenge for collecting the data, which in turn creates the research gap. From this perspective, it is possible to consider studying the hydrogel across different joints to review the potential to regenerate the cartilage. It might provide a wider understanding of the biological effect of the hydrogel on the repair process. On the other hand, the biomechanical and anatomical differences of the joints must be considered too as there is different contact surface, thickness of the cartilage and load on the joint. Anyway, it would be rational to conduct comparative analysis across different joints.

FUTURE RESEARCH DIRECTIONS

The suggestions for further research are focused on addressing the limitations of the studies. So, it would be advantageous to conduct RCT with larger cohorts and longer follow ups. Moreover, there should be more standardisation of outcome reports (AOFAS, VAS, MRI-based scoring). Different formulations of the hydrogels might be used to evaluate the effectiveness of this therapeutic approach. For example, binding to different anti-inflammatory and proliferation stimulating biochemicals such as TGF- β or IGF-1 might be beneficial.¹⁶ Next, use of scaffold technique with different natural materials such as collagen or cartilage matrix might be considered.¹⁷ Moreover, the comparative analysis of use of hydrogel in osteoarthritis of different bones would provide an informative view of regenerative potential of hydrogels.

CONCLUSIONS

Hydrogels show potential for treating talus OA through cartilage support and symptom relief. However, the evidence base is limited, with a need for standardized outcome measures, larger trials, and joint-specific formulation research. Overall, while early evidence suggests that hydrogel-based therapies may offer a promising, joint-preserving approach for talus osteoarthritis, robust, long-term clinical trials are necessary to confirm efficacy and optimize hydrogel formulations for ankle-specific biomechanics.

List of abbreviations

OA	Osteoarthritis
PRISMA	Preferred Reporting Items For Systematic Reviews And Meta-Analyses
VAS	Visual Analogue Scale
AOFAS	American Orthopaedic Foot & Ankle Society Scale
RCT	Randomized Control Trial
HA	Hyaluronic Acid
NSAID	Nonsteroidal Anti-Inflammatory Drugs
MRI	Magnetic Resonance Imaging

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AUTHORS' CONTRIBUTIONS

Conceptualization: D.S., Y.R., B.B., A.B.; Data curation: M.M., B.S.; Formal analysis: D.S., M.M., T.T., A.B.; Investigation: D.S., M.M., Y.R., B.B.; Methodology: D.S., A.B., T.T., B.S.; Project administration: D.S., Y.R., B.B.; Resources: M.M., T.T., B.S.; Software: A.B., T.T.; Supervision: D.S., Y.R., B.B., A.B.; Validation: M.M., B.S.; Visualization: D.S., M.M., T.T., B.S.; Writing – original draft: D.S., M.M., Y.R., B.B., A.B., T.T., B.S.; Writing – review & editing: D.S., M.M., T.T., B.S..

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DATA AVAILABILITY

All data analyzed in this systematic review were extracted from previously published studies, which are cited throughout the manuscript. No new data were generated.

CLINICAL TRIAL NUMBER

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare no competing interests.

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