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REVIEW

Efficacy of intra-articular injections of hyaluronic acid in patients with glenohumeral joint osteoarthritis: A systematic review and meta-analysis

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Abstract

Symptomatic primary glenohumeral (GH) joint osteoarthritis (OA) can be challenging to treat. Hyaluronic acid (HA) has emerged as a promising treatment for the nonsurgical management of GH-OA. In this systematic review with meta-analysis, we aimed to evaluate the current evidence regarding the efficacy of intra-articular HA on pain relief in patients suffering from GH-OA. A total of 15 studies (only randomized controlled trials providing data at the end of the intervention) were included. The relevant studies were selected based on the following PICO model: P: patients with diagnosis of shoulder OA; I: HA infiltrations as therapeutic intervention administered; C: no restriction for comparators assessed; O: pain, in terms of visual analog scale (VAS) or numeric rating scale. The risk of bias among the included studies was estimated using the PEDro scale. A total of 1023 subjects were analyzed. Comparing HA injections combined with physical therapy (PT) compared to PT alone resulted in superior scores, showing an overall effect size (ES) of 4.43 ($p = 0.00006$). Moreover, pooled analysis of VAS pain scores demonstrated a significant improvement in the ES of the HA in comparison with corticosteroid injections ($p = 0.002$). On average, we reported a PEDro score of 7.2. A total of 46.7% of studies showed probable signs of a randomization bias. The findings of this systematic review and meta-analysis showed that IA injections of

HA might be effective on pain relief with significant improvements compared to baseline and compared to corticosteroid injections in patients affected by GH-OA.

KEYWORDS
hyaluronic acid, meta-analysis, shoulder, systematic review, viscosupplementation

1 | INTRODUCTION

Symptomatic primary glenohumeral (GH) joint osteoarthritis (OA) is a condition resulting in pain, reduction of range of motion (ROM), and a progressive loss of shoulder function.[1] Patients suffering from GH-OA typically complain of pain at night, especially when lying on the affected shoulder. Primary GH-OA might occur over a broad age range; it is estimated that shoulder pain affects 5%–21% of the adult population in the United States, and GH-OA affects nearly a third of the world's population older than 60 years.[2] Chronic shoulder pain can result in significant dysfunction, disability, and consequently, increased healthcare costs.

Painful GH-OA is difficult to treat and highly disabling. Shoulder arthroplasty is effective at reducing pain and improving ROM[3,4] but is associated with significant cost and morbidity.[5] Current forms of nonoperative management of GH-OA include a combination of conservative treatment therapies. Physical therapy (PT) can be advised to keep ROM and muscle strength. Pharmacological treatments, including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotic/nonnarcotic analgesics, and intra-articular (IA) injections of corticosteroids (CS) have been the mainstay of nonsurgical treatment. Evidence supporting these treatments has been inconclusive and may be associated with a significant adverse effect profile.[6] Analgesics can be insufficient and can be associated with well-known adverse effects, especially in elderly patients. NSAIDs have the potential to cause gastrointestinal, renal, and cardiac effects.[7,8]

Thus, hyaluronic acid (HA) has emerged as an alternative treatment for the nonsurgical management of GH-OA. HA has both analgesic and chondroprotective properties.[5] The use of IA HA in patients with OA is well documented.[9] HA therapies can be broadly classified as low-molecular-weight (LMW) preparations (500–730 kDa)[10] and high-molecular-weight (HMW) preparations (620–3200 kDa), whereas natural human HA is a single-chain product with a molecular weight of 5000 kDa.[11] Several papers have recently investigated the efficacy of different IA HA preparations for OA.[9,12,13] Concerning shoulder joint, Strauss et al. reported that HA injections are well tolerated to treat shoulder pain of various pathologies and may be an alternative to PT and CS injections.[12] In 2014, Colen et al. published a systematic review of 8 studies on the effect of IA HA injections for GH-OA.[13] Zhang et al. performed a systematic review and meta-analysis to evaluate the efficacy of HA to reduce pain in patients with GH-OA.[9] The authors reported (1) that intra-articular HA injection was safe and improved pain for patients with GH-OA and (2) that a significant placebo effect may have been present.

In this systematic review with meta-analysis, we aimed to evaluate the current evidence regarding the efficacy of IA HA on pain relief in patients suffering from GH-OA.

2 | METHODS

2.1 | Search strategy and selection criteria

This systematic review has been conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[14] and the Cochrane Handbook for Systematic Reviews of Interventions.[15] The protocol of this systematic review has been registered on the International Prospective Register of Systematic Reviews (PROSPERO) with number CRD42022385161.

On January 25, 2023, two authors (MM and NM) systematically searched three different databases (PubMed, Scopus, and Web of Science). The search strategy is reported in Table 1.

After removing the duplicates, two reviewers (RR and MM) independently screened all the documents for title and abstract and then, for full-text. Then, a third author (AdS) was asked to solve any disagreement by collegial discussion.

TABLE 1 Keyword search strategy for each Database.

PubMed
("hyaluronic acid"[MeSH Terms] OR ("hyaluronic"[All Fields] AND "acid"[All Fields]) OR "hyaluronic acid"[All Fields]) AND ((("shoulder"[MeSH Terms] OR "shoulder"[All Fields] OR "shoulders"[All Fields] OR "shoulder s"[All Fields] OR "glenohumeral"[All Fields]) AND ("osteoarthritis"[MeSH Terms] OR "osteoarthritis"[All Fields] OR "osteoarthrosis"[All Fields])) OR ("osteoarthritis"[MeSH Terms] OR "osteoarthritis"[All Fields] OR "osteoarthritides"[All Fields]))
Scopus
TITLE-ABS-KEY(("hyaluronic acid" AND "acid OR "hyaluronic acid") AND ((("shoulder" OR "shoulder" OR "shoulders" OR "shoulder s" OR "glenohumeral") AND ("osteoarthritis" OR "osteoarthritis" OR "osteoarthrosis")) OR ("osteoarthritis" OR "osteoarthritis" OR "osteoarthritides")))
Web of Science
(("hyaluronic acid" AND "acid OR "hyaluronic acid") AND ((("shoulder" OR "shoulder" OR "shoulders" OR "shoulder s" OR "glenohumeral") AND ("osteoarthritis" OR "osteoarthritis" OR "osteoarthrosis")) OR ("osteoarthritis" OR "osteoarthritis" OR "osteoarthritides")))

The relevant studies were selected based on the following PICO model:

(P) Participants: patients with diagnosis of shoulder OA;

(I) Intervention: hyaluronic acid infiltrations as therapeutic intervention administered;

(C) Comparator: no restriction for comparators assessed;

(O) Outcome: pain, in terms of visual analog scale (VAS) or numeric rating scale.

Only randomized controlled trials (RCTs) providing data at the end of the intervention were included. Exclusion criteria were: (1) patients suffering from any inflammatory disorders or rheumatic diseases (e.g., rheumatoid arthritis, psoriatic arthritis); (2) patients with fibromyalgia; (3) studies including arthrocentesis as treatment; (4) studies including local pressure pain assessment; (5) studies with a cross-over design; (6) studies written in a language different from English; (7) full-text unavailability (i.e., posters and conference abstracts); and (8) studies involving animals.

2.2 | Data extraction and synthesis

Two different authors (RR and MM) evaluated the records resulting from selection process. All relevant data were subsequently extracted independently. Then, a third author (FF) was asked to solve any disagreement by collegial discussion. The relevant data extracted were: (I) title, authors, and publication year; (II) nationality; (III) population characteristics; (IV) interventions' characteristics; (V) control characteristics; (VI) outcome measures; (VII) main findings; (VIII) follow-up evaluations; and (IX) assessment of secondary outcomes.

All data were extracted and synthesized in a table with a qualitative synthesis performed by two authors independently from full-text documents.

2.3 | Quality assessment

We adopted the risk-of-bias checklist in the Physiotherapy Evidence Database (PEDro) scale to estimate the included studies' methodological quality.[16] Two authors (RR and NM) separately evaluated each article and presented the results, and any disagreements were resolved involving a third author (AdS) The PEDRO tool consists of nine domains through which it is possible to find any bias in a study. Each judgment consists of the following possibilities: low risk of bias, moderate risk of bias/some concerns, serious risk of bias, critical risk of bias, and no information on a 10-point scale. Domain-level reports provide the basis for an overall risk-of-bias judgment.

2.4 | Statistical analysis

A systematic summary of patient characteristics and results of the included studies were reported in an Excel spreadsheet. Summaries of intervention effects for each study were provided. The results of the included studies were reported in a qualitative manner (e.g., statistically significant results, consistency of results, or a combination thereof). Statistical analysis was performed on R 3.5.0 (R Foundation) and RevMan version 5.3. A p-value < 0.05 was considered as statistical significance. The heterogeneity between the comparisons was estimated by means of the chi-squared and I^2 statistical tests. An I^2 > 50% results in significant heterogeneity across articles, legitimizing an effect size (ES) measure via a random effects model was used to determine pooled estimates with 95% CIs.

3 | RESULTS

3.1 | Main characteristics of the included studies

A total of 1819 records were identified from the search process. After the title and abstract screening step, 1752 of them were excluded. Next, out of the 67 full-text studies screened, 15 articles that satisfied the eligibility criteria were included. Further details on the identification and inclusion/exclusion of the screened studies are reported in the PRISMA 2020 flow diagram (see Figure 1 for further details).

The main characteristics of these studies are provided in detail in Table 2. The included studies have been published in the last 15 years (from 2007 to 2022). Nine v[6,17–24] (60.0%) were conducted in Europe (six studies[6,17–19,21,24] from Italy, one study[23] from England, one study[22] from France, and one study[20] from the Netherlands) and six studies[25–30] (40.0%) were conducted in the Americas (five studies[25–28,30] from the United States and one study[29] from Brazil). A total of 1023 subjects were analyzed, whereas 397 subjects were included in the comparator group (undergoing no intervention, PT, corticosteroid injection, and PRP injection). The size of the study cohorts included ranged from 27[28] to 300[30] patients. Concerning the follow-up evaluations, only one study performed a follow-up at 52 weeks from baseline.[26]

3.2 | HA injections without comparison/control groups

Brander et al. reported that two injections of HA (2 mL of 8 mg/mL Hylan G-F 20; Synvisc, Genzyme Corporation), applied under a fluoroscopic guidance, did reduce pain from glenohumeral OA, for up to 6 months after treatment, irrespective of the presence of concomitant rotator cuff pathology.[25] Moreover, the intervention was associated with improvement in shoulder-related quality of life and function. There were no significant adverse effects (AEs) observed throughout the study.

McKee et al. demonstrated that a single injection of Durolane® (nonanimal hyaluronic acid; NASHA) could be efficacious in patients with symptomatic GH-OA. Improvements in pain were clinically and statistically significant.[20]

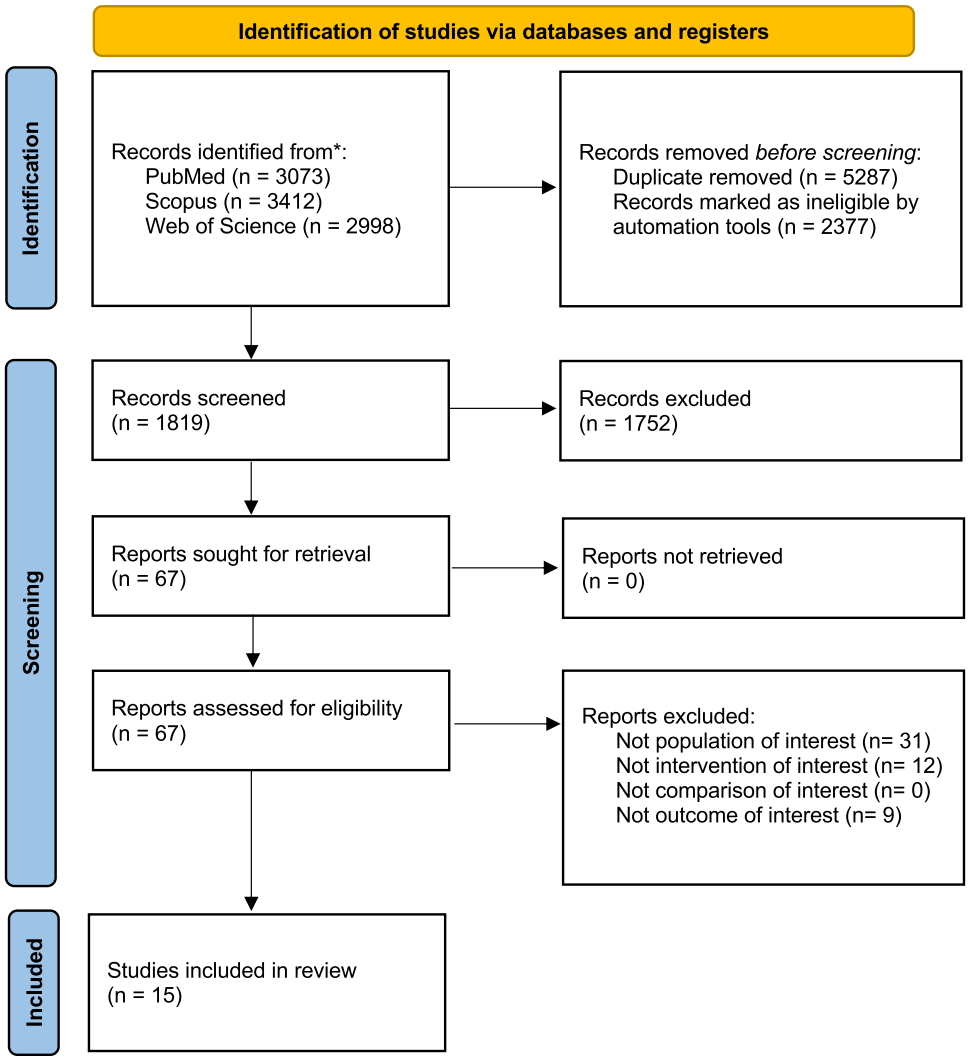

FIGURE 1 Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram.

Noël et al. utilized a single injection of 2 mL of Hylan G-F 20 and reported a significant decrease in the VAS pain score ($p < 0.001$).[22] In turn, they reported a decline in patient-reported function, with the mean Western Ontario Osteoarthritis of the Shoulder score increasing from 45.7% at baseline to 62.4% ($p = 0.008$) after 6 months. Finally, the mean SF36 score increased from 38.6 points at baseline to 43.3 points after 6 months ($p = 0.007$).

Oduoza et al. highlighted that a single injection of sodium hyaluronate (OstenilPlus, prefilled syringe 40 mg/2 mL) provides a statistically significant improvement in the OSS at 6 and 12 weeks ($p < 0.05$) but not at 6 months. In patients with mild OA, there were no statistically significant changes.[23]

Porcellini et al. administrated two injections, applied in an interval of 1 week, of HYADD®4-G (Hymovis®-, Fidia Farmaceutici SpA). A significant decrease in pain and an improved shoulder function were documented for up to 6 months. The VAS score decreased, and CS and ROM values improved.[6]

Silverstein et al. reported a statistically significant reduction of VAS ($p < 0.001$), and significant improvements of the UCLA score ($p < 0.001$), and SST ($p < 0.001$) at the 6-month follow-up following a protocol of three injections of Hylan G-F 20, with an interval of 1 week between injections.[28]

Weil et al. reported the outcomes following three injections of high molecular weight hyaluronate (2.5 mL each) Euflexxa® (1% sodium hyaluronate), at an interval of 1 week, showing improvements in pain (VAS, WOMAC), ROM, stiffness, and clinical outcome scores.[30]

3.3 | HA injections combined with PT versus PT alone

In 2015, in their study, Di Giacomo et al. compared the application of five intra-articular injections with Hyalgan 20 mg/2 mL (molecular weight 500–730 kDa) at an interval of 15 days between injection combined with a specific physiotherapy (PT) program to a treatment with PT alone.[19] The adjunct of HA injection showed a greater and long-lasting efficacy in terms of reduction of shoulder pain ($p < 0.05$) and improvement in daily activities.

TABLE 2 Main characteristics of the randomized controlled trials included in the present systematic review.

Article	Nationality	Study group	Control group	Intervention	Comparison	Outcome measure and time-point assessments	Main findings
Brander et al. American Academy of Physical Medicine and Rehabilitation 2010	USA	*n* = 33; 13 M/20 F Age: 67 years (range 36–88) Diagnosis: advanced symptomatic glenohumeral OA of at least 3 months duration, confirmed using the KL Grades on radiographs obtained within 12 weeks of screening.	NA	2 injections of HA (2 mL of 8 mg/mL Hylan G-F 20) 14 days apart at visits 1 and 3. An anteroposterior fluoroscopic image was taken with posterior approach.	NA	VAS and WORC at baseline and 6 months.	Reduces pain from glenohumeral OA, whether or not rotator cuff pathology is present, for up to 6 months after treatment. Treatment was associated with improvement in shoulder-related quality of life and function. There were no significant AEs observed throughout the study.
Di Giacomo et al. Journal of Biological Regulators & Homeostatic Agents 2021	Italy	*n* = 30; 21 M/9 F Age: 67.1 (range 55–83) years Diagnosis: Glenohumeral OA with KL degree II or III confirmed with radiographs.	*n* = 30; 189 M/12 F Age: 64.2 (range 52–81) years Diagnosis: Glenohumeral OA with KL degree II or III confirmed with radiographs.	Single injection with HMW HA (HyalOne® 60 mg/4 mL 1.500–2.000.000 Da) in combination with PEP.	Only PEP	CS, ROM at baseline, 1, 3, and 6 months from the beginning of the therapy.	Significantly higher decrease of shoulder pain and improvement in daily activities compared to patients treated with physical therapy alone ($p < 0.05$). significant long-term improvement in ROM between the two groups ($p < 0.05$).
Di Giacomo et al. Joints 2017	Italy	*n* = 31 17 M/22 F Age: 71.3 ± 6.7 years Diagnosis: Glenohumeral OA with KL degree II, III, and IV with contraindications to surgical treatment.	*n* = 30; 15 M/24 F Age: 69.8 ± 6.4 years Diagnosis: Grade II, III, and IV of OA with contraindications to surgical treatment.	3 injections with Hyalubrix (30 mg/2 mL) (>1500 kDa), one injection every 15 days combined with a specific physiotherapy program. Posterior approach.	Only PEP	CS, ROM at baseline and at 6 months from the beginning of the therapy.	Greater positive effect in terms of pain reduction compared with patients who received only physical therapy treatment. It is a safe and effective treatment option for the management of shoulder pain due to moderate to severe glenohumeral OA in terms of pain relief ($p < 0.05$) and function improvement.
Di Giacomo et al. Journal of Biological Regulators & Homeostatic Agents 2015	Italy	*n* = 31; 15 M/16 F Age: 62.5 (range 49–82) years Diagnosis: Glenohumeral OA with KL degree I, II, or III confirmed with radiographs.	*n* = 30; 11 M/19 F Age: 65.5 (range 49–83) years Diagnosis: Glenohumeral OA with KL degree I, II, or III confirmed with radiographs.	5 intra-articular injections with Hyalgan 20 mg/2 mL (molecular weight 500–730 kDa), 1 injection every 15 days, and a specific physiotherapy program.	Only PEP	CS, ROM at baseline and at 5.2 months from the beginning of the therapy.	The greater and long-lasting efficacy in terms of reduction of shoulder pain ($p < 0.05$) and improvement in daily activities.

(Continues)

TABLE 2 (Continued)

Article	Nationality	Study group	Control group	Intervention	Comparison	Outcome measure and time-point assessments	Main findings
Kirschner et al. Clinical Journal of Sports Medicine Online 2022	USA	*n* = 36; 18 M/18 F Age: 68.4 ± 11.9 years Diagnosis: Glenohumeral OA.	*n* = 34; 14 M/20 F Age: 69.1 ± 11.5 years Diagnosis: Glenohumeral OA.	Single injection of 6 mL of HA of lower molecular weight (500,000–730,000 Dalton) (Hyalgan Fidia Pharma).	Single injection of 6 mL Leukocyte-PRP.	SPADI, ASES, and NRS at baseline, 1, 2, 3, 6, and 12 months.	Improvements in pain, disability, and functional impairments with no differences between treatments.
Know et al. Journal of Shoulder and Elbow Surgery 2013	USA	*n* = 150; 89 M/61 F Age: 66.1 ± 10.7 years Diagnosis: Glenohumeral OA.	*n* = 150; 75 M/75 F Age: 66.1 ± 11.7 years Diagnosis: Glenohumeral OA.	3 weekly injections of HA.	3 weekly injections of the phosphate-buffered saline (PBS).	VAS, OMERACT-OARSI, ASES, SGA score, PGA score, and the Medical Outcomes Study 12-item Short-Form Survey, PCS, and MCS scores at baseline, 2, 3, 5, and 6 months.	Numeric advantage, but no statistically significant differences, in efficacy were found between HA- and PBS-treated patients with Glenohumeral-OA.
McKee et al. Medical Devices: Evidence and Research 2019	The Nether-lands	*n* = 41; 29 M/12 F Age: 65.4 ± 9.5 years Diagnosis: Glenohumeral OA with KL degree II or III with radiographic reference.	NA	Single injection of Durolane® (NASHA nonanimal hyaluronic acid).	NA	SPOM, VAS, SPAN, ASES, SSI, and rescue medication at baseline, 1.5, 2.5, and 6 months.	Single injection of NASHA may be efficacious in patients with symptomatic GH-OA. Improvements in pain were clinically and statistically significant.
Merolla et al. Musculoskelet Surgery 2011	Italy	*n* = 51; 13 M/38 F Age: 61 ± 4.9 years Diagnosis: arthritic painful shoulder confirmed with radiographs.	*n* = 33; 10 M/23 F Age: 63 ± 5.6 years Diagnosis: arthritic painful shoulder confirmed with radiographs.	3 injections, 1 week apart, of Hylan G-F 20 (Synvisc, Genzyme Corporation), molecular weight 6×10^6 Da.	3 injections, 1 week apart, of methylpredni-solone acetate (Depo-Medrol®, Pfizer) 40 mg/mL.	VAS, SPADI, CS, SSI, and Subjective satisfaction at baseline, 1, 3, and 6 months.	Intra-articular injection with Hylan G-F 20 is effective in reducing pain and improving function in shoulder osteoarthritis.
Noël et al. Joint Bone Spine 2009	France	*n* = 33; 18 M/15 F Age: 56.7 ± 9.3 years Diagnosis: Glenohumeral OA with an osteophyte at the lower part of the humeral head	NA	Single injection of 2 mL of Hylan G-F 20.	NA	VAS, WOOS score, SF36 quality-of-life score at baseline, 7 days, 1, 2, 3, and 6 months.	VAS score decreased significantly ($p < 0.001$). The mean WOOS score was 45.7% at baseline, and 62.4% ($p = 0.008$) after 6 months. The mean SF36 score was 38.6

TABLE 2 (Continued)

Article	Nationality	Study group	Control group	Intervention	Comparison	Outcome measure and time-point assessments	Main findings
		measuring at least 2 mm along the long axis on plain AP radiographs in neutral rotation.					points at baseline, and 43.3 points after 6 months ($p = 0.007$).
Oduza et al. Journal of Arthroscopy and Joint Surgery 2022	England	$n = 55$; 22 M/33 F Age: 44.5 years Diagnosis: clinical and radiological diagnosis of glenohumeral OA. Cases were classified as being mild in 11 (20%), moderate in 21 (38%), and severe in 23 (42%) using Samilson–Prieto classification.	NA	Single injection of sodium hyaluronate (OstenilPlus prefilled syringe 40 mg/2 mL).	NA	OSS, SANE score, pain scores with NRP, and the WOOS at baseline, 1,5, 3, and 6 months.	In the severe group, there was a statistically significant improvement in the OSS at all time points ($p < 0.05$). In the moderate group, there were statistically significant improvements at 6 weeks and 12 weeks ($p < 0.05$) but not at 6 months. In the mild group, there were no statistically significant changes.
Porcellini et al. Joints 2016	Italy	n = 41; 30 M/11 F Age: 65 years Diagnosis: chronic shoulder pain due to OA	NA	2 injections, 1 week apart, of HYADD®4-G (Hymovis®-, Fidia Farmaceutici SpA)	NA	VAS, EQ-5D questionnaire and CM score at baseline, 1 week, 3, 4 and 6 months	Significant decrease in pain and improved shoulder function for up to 6 months. The VAS score decreased and CS and ROM values improve.
Silverstein et al. American Journal of Sports Medicine 2007	USA	$n = 27$; 17 M/10 F Age: 62 (47–79 range) years Diagnosis: Glenohumeral OA.	NA	3 injections, 1 week apart, of Hylan GF-20.	NA	VAS, UCLA, and SST score at baseline, 1, 3, and 6 months.	At 6-month follow-up VAS ($p < 0.001$), UCLA ($p < 0.001$), and SST ($p < 0.001$) scores decreaased. More patients slept comfortably after treatment (56%).
Tafgliafico et al. European Radiology 2010	Italy	$n = 33$; 10 M/23 F Age: 72 ± 6 years Diagnosis: cuff tear arthropathy with 3 or major by Hamada grade.	$n = 60$; 26 M/30 F Age: 71 ± 6.1 years Diagnosis: cuff tear arthropathy with 3 or major by Hamada grade.	2 injections, 1 week apart, of high weight (500–730 kDa) sodium hyaluronate under ultrasound (US) guidance.	No treatment	VAS and CS at baseline, 1, 2, 3, 4, 5, and 6 months.	Treated patients reported a significant decrease in symptoms at 1, 2, 3, and 4 (mean CS 62 ± 3.0 vs. 34 ± 6.5; mean VAS 3.3 ± 1.4 vs. 7.8 ± 3.1) months, $p < 0.001$. After this period the differences between treated and nontreated were no longer significant.

(Continues)

TABLE 2 (Continued)

Article	Nationality	Study group	Control group	Intervention	Comparison	Outcome measure and time-point assessments	Main findings
Tortato et al. Acta Ortopedica Braliseira 2022	Brazil	$n = 38$; 2 M/36 F Age: 72.7 (range 57–87) years Diagnosis: Glenohumeral OA.	$n = 32$; 1 M/31 F Age: 72.2 (range 53–88) years Diagnosis: Glenohumeral OA.	Single injection of Hylan G-F 20 (48 mg/6 mL; Synvisc One®).	Single injection of triamcinolone hexacetonide (Triancil®; 20 mg/1 mL diluted in 5 ml saline).	VAS, CS, modified UCLA, SPADI, and ROM at baseline, 1 week, 1, 3, and 6 months.	Improvements in ROM were significant ($p > 0.05$). A decrease in the general VAS for pain was observed in both groups, especially in the cases of mild and moderate arthritis that received HA (mean values from 8.1 initially to 4.9 after 6 months; $p = 0$).
Weil et al. Medical Devices: Evidence and Research 2011	USA	$n = 27$; 14 M/13 F Age: 59.1 (10.3) years Diagnosis: Glenohumeral OA.	NA	3 injections of platelet-rich plasma 2 mL into the affected shoulder every 2 weeks + conventional rehabilitation 5 days/week, one session of 45 min a day.	3 injections, 1 week apart, of high molecular weight hyaluronate (2.5 mL each) Euflexxa® (1% sodium hyaluronate).	VAS, ROM, WOMAC, OMERACT-OARSI Proposition D, ASES at baseline, 1, 2, 3, 6 weeks, 3, and 6 months.	Improvement in pain (VAS, WOMAC), ROM, stiffness, and physical functioning scores; 77.8% of subjects were rated as having an OMERACT-OARSI Proposition D high response.

Note: Values are presented as mean (standard deviation).

Abbreviations: ASES, American Shoulder and Elbow Surgeon Shoulder Score; CS, Constant Score; F, female; HA, hyaluronic acid; KL, Kellgren and Lawrance; M, male; MCS, Mental Component Summary; NRP, numeric rating Pain Scale; NRS, numeric rating scale; OA, osteoarthritis; OMERACT-OARSI, Outcome Measures in Rheumatoid Clinical Trials in Osteoarthritis Research Society International; OSS, Oxford Shoulder Score; PEP, physical exercise program; PGA, Physician Global Assessment; ROM, range of motion; SANE, Single Assessment Numeric Evaluation; SGA, Subject Global Assessment; SPADI, Shoulder Pain and Disability index; SPAN, shoulder pain at night; SPOM, shoulder pain on movement; SSI, Shoulder Strenght Index; UCLA, University of California at Los Angeles Shoulder Score; VAS, visual analog scale; WOOS, Wester Ontario OA of the Shoulder; WORC, Western Ontario Rotator Cuff Index.

In 2017, Di Giacomo et al. reported a comparison of an application of a three-injection program with Hyalubrix (30 mg/2 mL, MW > 1500 kDa), with one injection every 15 days, combined with a specific physiotherapy program, to a control group who received PT only.[18] They reported greater positive effect in terms of pain reduction compared with patients who received PT only. This approach was demonstrated to be a safe and effective treatment option for the management of shoulder pain due to moderate to severe glenohumeral OA in terms of pain relief ($p < 0.05$) and function improvement.

In 2021, Di Giacomo et al. reported the outcomes following a single injection with HMW HA (HyalOne® 60 mg/4 mL 1.500–2.000.000 Da) in combination with PT in comparison to a PT control group.[17] They reported a significantly higher decrease of shoulder pain and improvement in daily activities compared to patients treated with PT alone ($p < 0.05$).

3.4 | HA versus corticosteroid injections

Merolla et al. reported the outcome following a three-injection program with Hylan G-F 20 with an interval of 1 week between injections, in comparison with a control group of three injections of methylprednisolone acetate (Depo-Medrol®, Pfizer) 40 mg/mL with an interval of 1 week between injections. The HA group demonstrated an effective pain relief and an improving functioning in shoulder OA.[21]

Tortato et al. reported the administration of a single injection of Hylan G-F 20 (48 mg/6 mL; Synvisc One®) compared to a single injection of triamcinolone hexacetonide (Triancil®, 20 mg/1 mL diluted in 5 mL saline).[29] A VAS reduction was observed in both groups, especially in the cases of mild and moderate arthritis that received HA, but with a mean value from 8.1 initially to 4.9 after 6 months in HA compared to the control group ($p < 0.05$).

3.5 | HA versus placebo control groups

Kwon et al. reported the results following 3 weekly injections of HA in their experimental group in comparison to 3 weekly injections of phosphate-buffered saline (PBS) in a placebo control group.[27] No statistically significant differences in efficacy were found between HA and PBS groups in patients with glenohumeral OA.

Tagliafico et al. reported administering two injections, of high weight (500–730 kDa) sodium hyaluronate under ultrasound (US) guidance at an interval of 1 week, in comparison to a control group that did not receive a treatment.[24] The HA intervention group reported a significant decrease in Constant score (62 ± 3.0 vs. 34 ± 6.5, $p < 0.05$), and an increase in VAS (3.3 ± 1.4 vs. 7.8 ± 3.1, $p < 0.05$).

3.6 | HA versus PRP

Kirschner et al. administered a single injection of 6 mL of HA of lower molecular weight (500,000–730,000 Da) in comparison with a single injection of 6 mL Leukocyte-PRP, showing similar improvements in pain, disability, and functional impairments with no differences between interventions.[26]

3.7 | Meta-analysis

A meta-analysis was performed to highlight the efficacy of HA injections in comparison to comparative interventions or control groups. Comparing HA injections combined with PT compared to PT alone resulted in superior scores in patients affected by shoulder OA, showing an overall ES of 4.43 (95% CI = 1.89–6.97, $p = 0.00006$), as shown by Figure 2. In this scenario, the HA injections seemed to improve the effect of PT regarding pain and function. Moreover, pooled analysis of VAS pain scores demonstrated a significant improvement in the ES of the HA in comparison with corticosteroid injections (−1.47; 95% CI = −2.39 to −0.55, $p = 0.002$). However, there was a nonsignificant ES of HA in terms of the VAS improvement in comparison with control groups receiving no treatment or placebo PBS injection (−2.30; 95% CI = −6.37 to 1.76, $p = 0.27$). While the comparison between groups receiving HA injections and groups not receiving an intervention showed a significant difference, HA injections alone compared to PBS injections, do not appear to provide an advantage; possibly due to the hydro-distensive nature of the approach. Given the low number of studies, a random-effects model was adopted.

3.8 | Quality assessment

The risk of bias among the included studies was estimated using the PEDro scale (see Table 3 for further details). All studies considered scored above 5 out of 10, on average we reported a score of 7.2. A total of 46.7% of studies showed probable signs of a randomization bias. In all the studies included the risk of missing outcome bias could be ruled out.

4 | DISCUSSION

The main finding of this investigation was that the intra-articular application of HA for GH-OA resulted in a significant improvement of pain and function compared to baseline at a short-term follow-up of up to 6 months. Moreover, based on the results of the meta-analysis, HA seems to be superior to alternative nonoperative treatment modalities such as corticoid injections and isolated PT for the treatment of glenohumeral OA. However, it should be noted that there could be a potential placebo effect related to the application of HA, as a superiority of intra-articular HA injection compared to placebo injections could not be demonstrated.

Although the precise cellular working mechanism of HA is not yet fully understood, it has been associated with analgesic and chondroprotective properties that are essential in comprehending

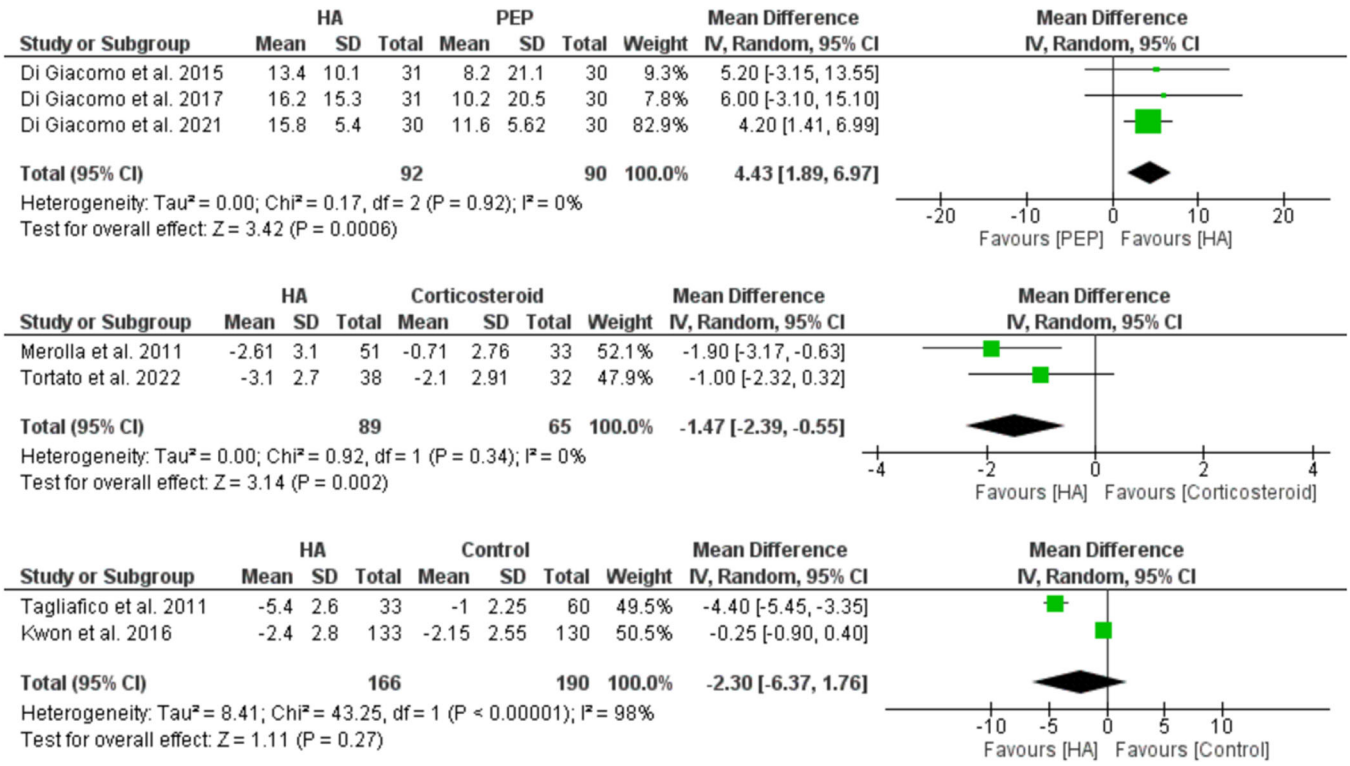

FIGURE 2 Forest plot comparing HA injections combined with PT compared to PT alone. CI, confidence interval; HA, hyaluronic acid; PT, physical therapy.

its clinical effects in a non-weight-bearing joint such as the shoulder.[31] As part of the physiologic synovial fluid, HA performs not only mechanical functions by maintaining the viscoelasticity of the synovial fluid, but also chondroprotective and anti-inflammatory functions.[31–34] As the concentration of native HA is reduced to approximately 50% of its physiologic concentration in OA,[35] an intra-articular injection of HA exhibits instant dual mechanical effects. As such, it functions as a lubricant during slow, low shear rate movements by increasing synovial viscosity and also provides shock absorption during rapid, high shear rate movements in its structure as an elastic solid.[31] Furthermore, and potentially more relevant in a non-weightbearing joint such as the shoulder, HA injections have been linked to chondroprotective capacities. In detail, HA injections have been demonstrated to reduce chondrocyte apoptosis and increased chondrocyte proliferation.[33,34] Through an immunomodulatory mechanism of action via suppression of IL-1β expression, HA has been further demonstrated to exhibit anti-inflammatory effects and thereby exhibits a beneficial impact on the osteoarthritic milieu of the affected joint.[32,36]

Taken together, the results of this systematic review underscored the promising role of HA injections as a valid nonoperative treatment option for glenohumeral OA.

In this scenario, a previous systematic review by Colen et al. investigated the early data regarding the effectiveness of intra-articular HA injection in joints other than the knee joint.[37] The six included studies specific to the shoulder provided early statistical evidence for improvement in pain and function, but were of low level of evidence and impeded a strong conclusion at that time.[37] Later systematic evaluations such as the systematic review by Zhang et al. confirmed these initial findings.[9] In their meta-analysis, they demonstrated a significant and substantial improvement in pain at 3 and 6 months after the injection as well as significant improvements in functional outcome scores.[9] The meta-analysis conducted in the current study, which incorporated five additional studies, confirms these results, emphasizing the potential of intra-articular HA injections as a promising nonoperative treatment option. Given that, an improvement of 1.4 points in the VAS pain score has been defined as the minimal clinically important difference (MCID) in shoulder OA,[38] the improvement following intra-articular glenohumeral HA injection seems to be both statistically significant and clinically relevant. These findings have been confirmed by the pooled results of previous quantitative syntheses that demonstrated a mean improvement of the VAS pain score of 2.6 points at 3 months and 2.9 points at 6 months.[9] Not only pain, but also the improvement in clinical function seems to be clinically relevant at short-term follow-up. As such, the mean improvement following glenohumeral HA injection at a cohort level exceeds the MCID values for the Constant Score (5.7 points)[39] and UCLA score (8.7 points)[39] in multiple studies.[18,21,24,28]

However, to date, the evidence available in the literature is still insufficient to quantitatively investigate the optimal HA injection regimen in terms of the total number of injections as well as the

TABLE 3 Quality assessment of the included studies according to the PEDro scale.

	Eligibility	Randomized allocation	Concealed allocation	Baseline comparability	Blinding of subjects	Blinding of therapists	Blinding of assessors	Key outcomes	Intention to treat	Between-group comparison	Measures of variability	PEDro scale
Brander et al. 2010[25]	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	6/10
Di Giacomo et al. 2021[17]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/10
Di Giacomo et al. 2017[18]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/10
Di Giacomo et al. 2015[19]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/10
Kirshner et al. 2022[26]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10/10
Know et al. 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10/10
McKee et al. 2019[20]	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	6/10
Merolla et al. 2011[21]	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	8/10
Noël et al. 2009[22]	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7/10
Oduza et al. 2022[23]	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	6/10
Porcelli et al. 2016	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	5/10
Silverstein et al. 2007[28]	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	5/10
Tagliafico et al. 2010	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7/10
Tortato et al. 2022[29]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	9/10
Weil et al. 2011[30]	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	5/10

optimal time interval between injections. While a weekly administration is the most common injection interval, the total number of injections ranges from 1[17,20,22,23,25,26,29] to 5.[19] A total number of injections as low as 1 demonstrated significant improvement of outcome parameters compared to baseline as well as in comparison to alternative interventions such as PT[17,20,22,23,25,26,29] or corticosteroid injections.[29] While there have been efforts to determine the optimal number of HA injections in knee OA, the data published are conflicting and do not clearly favor a certain range.[40,41] Also, currently there is insufficient evidence specific to shoulder OA to analyze the optimal formulation of HA and whether LMW or HMW preparations have a superior clinical effect.

Notably, intra-articular HA injections appear to outperform typical nonoperative treatment options that are presently regarded as the gold standard of first-line therapy for glenohumeral OA, such as PT or corticosteroid injections. The quantitative synthesis in this systematic review, which included multiple reports comparing isolated PT to PT augmented with HA injections,[17–19] revealed significantly superior clinical outcomes for the combined approach with an ES of 4.4. This finding expands the evidence generated by previous pooled analyses.[9,37] Furthermore, in comparison to other agents such as corticosteroid formulations,[21,29] the meta-analysis conducted in this study revealed significantly greater improvements in pain following HA injections, with an ES of −1.4 on the VAS pain within the first 6 months. While both HA as well as corticosteroids exhibit analgesic and anti-inflammatory effects, these results after 6 months may reflect the sustained chondroprotective effect attributed to HA.[33,34]

The effectiveness of the HA injection treatments observed must be interpreted in the context of a potential placebo effect, which is a known phenomenon related to HA injections.[42] For example Kwon et al. reported in their study that the HA intervention group did not outperform a placebo group, which suggests a strong potential for a placebo effect involved in the treatment of glenohumeral OA with HA injection.[27] Alternatively, the similar effect of PBS in the placebo control group compared to HA may be attributable to the effect of the hydrodistension.[43] As a result—comparable to previous reviews[9]—the quantitative synthesis in this review could not demonstrate the superiority of HA compared to placebo injections.

To adequately interpret the findings of this systematic review, the results specific to HA must be benchmarked to alternative agents with differing biological mechanisms of action such as PRP or bone marrow aspirate concentrate (BMAC). While the evidence specific to the shoulder available is limited, PRP—with its demonstrated ability to reduce joint inflammation, decrease cartilage breakdown, promote tissue repair, and facilitate healing processes[44]—has been suggested as an alternative, clinically effective option for symptom alleviation in glenohumeral OA.[44,45] When comparing the efficacy of intra-articular HA to PRP injections for the management of glenohumeral OA, the study by Kirschner et al. included in this review did not show any significant differences between these two treatments.[26] However, in knee joint OA, PRP was found to have a higher probability for efficacy in both a recent network meta-analysis as well as a systematic review of level 1 studies.[46] As both substances may be subject to similar reimbursement categories and thus present as alternatives in nonoperative management, further evidence is needed to provide recommendations in the treatment of glenohumeral OA. Furthermore, the application of BMAC, which contains mesenchymal stromal cells, progenitor cells, growth factors, and other biologically potent agents, has been associated with analgesic, anti-inflammatory, and anabolic effects.[47] While preliminary evidence attests to superior clinical efficacy in the treatment of glenohumeral OA compared to cortisone application, a substantial increase in evidence is needed to evaluate this potential avenue.[48]

In summary, while in knee joint OA, there is substantial evidence that HA injections provide beneficial effects on symptom improvement,[49] the preliminary evidence for HA in shoulder OA is promising, but not yet conclusive.

It should be noted that the present is the first systematic review with meta-analysis including RCTs on this topic, evaluating the efficacy of intra-articular injections of HA to reduce pain in patients with GH-OA.

However, we are aware that our manuscript is not free from limitations. First, considering the limited number of studies reported, the authors were unable to perform any meaningful statistical analyses related to the optimal formulation of HA, the number of injections, and the injection interval. Second, confounding variables such as the products of HA utilized, the total number of injections, and the technique of injection (image-guided vs. blind) may influence the conclusions. The scarcity of available data in the current literature precluded direct group comparisons between those subgroups. Third, the follow-up times among studies included in this review varied and were largely limited to a short-term follow-up of 6 months, thus making it challenging to evaluate potential long-term benefits. However, it should be noted that most of the treatment protocols using HA for OA consist of multiple injections that need to be repeated over time (e.g., after 6–12 months). Fourth, this review is limited to studies with a low level of evidence with their inherent limitations, precluding the formulation of strong conclusions or recommendations. Finally, it is possible that relevant subgroups of patients or related studies were inadvertently excluded from our investigation due to the nature of systematic reviews and the search criteria and strategy employed.

5 | CONCLUSIONS

Taken together, the findings of this systematic review and meta-analysis showed that IA injections of HA might be effective on pain relief with significant improvements compared to baseline and compared to corticosteroid injections in patients affected by GH-OA. However, to date, there is still the need for further RCTs, considering the lack of clear data on the optimal formulation, the number of injections, and the injection interval of HA for GH-OA patients. On the other hand, we are aware that this meta-analysis might be useful for improving the knowledge of his topic and for

helping researchers and physicians involved in counteracting pain and disability due to GH-OA.

AUTHOR CONTRIBUTIONS

All authors have read and approved the final submitted manuscript. *Substantial conception/design of work*: Filippo Familiari, Raffaella Russo, and Alessandro de Sire. *Data collection*: Filippo Familiari, Raffaella Russo, Nicola Marotta, Michele Mercurio, and Alessandro de Sire. *Statistical analysis*: Nicola Marotta and Michele Mercurio. *Interpretation of data*: Filippo Familiari, Raffaella Russo, Marco-Christopher Rupp, Peter J. Millett, and Alessandro de Sire. *Drafting the work*: Filippo Familiari, Raffaella Russo, Marco-Christopher Rupp, and Alessandro de Sire. *Critically revising the work*: Antonio Ammendolia, Marco-Christopher Rupp, Arturo Pujia Tiziana Montalcini, Olimpio Galasso Peter J. Millett, and Giorgio Gasparini. *Manuscript preparation*: Filippo Familiari, Raffaella Russo, Marco-Christopher Rupp, and Alessandro de Sire. *Approving final version for publication*: all authors. *Agreement for accountability of all aspects of work*: all authors.

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