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REVIEW

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Hyaluronic acid injections for pain relief and functional improvement in patients with temporomandibular disorders: An umbrella review of systematic reviews

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Abstract

Background: Temporomandibular disorders (TMD) are the main cause of chronic facial pain, and intra-articular (IA) injections of hyaluronic acid (HA) are commonly performed.

Objectives: This umbrella review of systematic reviews aimed at analysing the effectiveness of HA injections on pain and functional outcomes in patients affected by TMD.

Methods: PubMed, Cochrane Library and PEDro were systematically searched from inception until 17 January 2023 to identify systematic reviews evaluating the effects on pain and functional outcomes of HA IA injections. PROSPERO registration number: CRD42022382586.

Results: Out of 316 papers suitable for title/abstract screening, 18 articles were included in the umbrella review. Thirteen studies included only randomized controlled clinical trials (RCTs). The included systematic reviews reported no statistically significant differences between HA and corticosteroids, whereas platelet derivates seem to have good results in pain relief. The literature did not show severe adverse events, except for mild pain in the site of injection. Concerning the quality assessment of the 18 systematic reviews, 2 (11.11%) had a high quality, 3 (16.67%) a moderate quality, 7 (38.89%) a low quality and 6 (33.33%) a critically low quality.

Conclusions: Taken together, findings of this umbrella review showed intriguing effects of IA HA injections in terms of reduction of pain intensity and improvement of functioning in patients affected by TMD. Furthermore, there is no agreement on the effectiveness of a combination of arthrocentesis or arthroscopy with IA HA injections. Although the literature showed these positive results after IA HA injections, the overlapping of primary studies in the systematic reviews included might have affect our results, such as the very low quality of the papers. Thus, further RCTs are needed to confirm the efficacy of IA injections of HA on pain relief in patients with TMD.

KEYWORDS
hyaluronic acid, injections, osteoarthritis, pain, sodium hyaluronate, temporomandibular joint disorders

1 | INTRODUCTION

Temporomandibular disorders (TMD) are a broad group of pathological conditions involving the temporomandibular joint (TMJ), the masticatory musculature and the surrounding anatomical structures.[1] They have the potential to produce chronic pain conditions and are a main cause of disability.[2,3]

According to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) guidelines, TMD could be divided into extra-capsular disorders, including myogenous conditions and intra-capsular disorders, including arthrogenous conditions, as disc displacement, arthralgia and degenerative conditions.[1] Specifically, TMJ osteoarthritis and osteoarthrosis are forms of degenerative joint disease, depending on the inflammatory or non-inflammatory nature of the disease, respectively.[1]

The reported prevalence of arthrogenous TMD in general population was of 31.1% in adults and elderlies and of 11.3% in children and adolescents,[4] and studies on TMD patients reported a prevalence of about 40% for disc displacements and about 30% for arthralgia and degenerative conditions.[5,6]

Etiopathogenesis has been accepted as multifactorial with several predisposing or perpetuating risk factors, including muscle overuse, parafunctions, genetic predisposition, pregnancy and bruxism[5–7]; moreover, the TMD commonly showed overlapping features with other chronic systemic conditions, as fibromyalgia and primary headache.[8–10]

In addition to the most common clinical manifestations, which include pain, joint noises, tenderness, dysfunction and functional limitation in the articular movement, other non-specific symptoms like headaches, earaches, tinnitus, dizziness, posture impairment, and neck and shoulder pain were reported.[5]

The non-invasive approaches, including behavioural therapy, physical therapy drugs, occlusal splints and laser therapy are considered as the first-line treatments to improve articular range of motion, reduce pain and prevent further degenerative damage.[11–13]

Among the minimally invasive techniques, intra-articular (IA) injections of sodium hyaluronate, including hyaluronic acid (HA), have gained attention as a potentially effective approach, also in combination with joint arthrocentesis and lavage.[14–16] HA is a linear polysaccharide physiologically found in synovium, vitrous humour and connective tissue.[17,18] The rationale for HA viscosupplementation lies in HA action as chondroprotective drug for anti-inflammatory and lubrication purposes, able to decrease mechanical wear, promote the tissue repair process in the cartilage and to induce an endogenous synthesis of acid by the synovial cells.[17,18]

Injections of HA were found to significantly decrease pain after 12 months,[19] and better results in terms of pain relief were reported with the use of 5 weekly injections compared to a single injection.[20] Moreover, injections with sodium hyaluronate seem to be more effective in reducing pain than corticosteroids (CS) and less effective than plasma-rich platelets (PRP).[19,21–23] However, other authors[24] showed no statistically significant difference between HA and PRP in terms of pain and functional outcomes. Bergstrand et al.[25] analysed the long-term efficacy of IA arthrocentesis comparing lavage alone to arthrocentesis *plus* and IA injection of HA, concluding that both approaches could decrease pain. On the contrary, in patients with disc displacement, arthrocentesis plus HA injection seemed to be more effective, mainly in chewing efficiency and quality of life.[26]

Also, the results of recent systematic reviews were not in agreement, and authors concluded that IA pharmacological injections of CS, HA and PRP had no effect on TMJ pain and functional outcomes compared with placebo injection,[27,28] whereas other recent meta-analysis reported the efficacy of HA injections in TMJ.[29,30]

Therefore, the objective of this umbrella review was to evaluate the available scientific evidence on the effects of IA injections of HA on pain relief and improvement of jaw function in patients affected by TMD.

2 | MATERIALS AND METHODS

2.1 | Registration and search strategy

Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were followed to conduct this review.[31] An a priori protocol was established and registered on the prospective register of systematic reviews PROSPERO, with number: CRD42022382586.

A thorough search of the literature was firstly performed on three databases: MEDLINE Central via PubMed, Cochrane Database of Systematic Reviews (CDSR) of the Cochrane Library and Physiotherapy Evidence Database (PEDro), and 'Epistemonikos' database from their inception up to 17 January 2023. Our search was restricted for systematic reviews published in English language.

2.2 | Selection criteria

We evaluated for inclusion systematic reviews, including randomized trials, quasi-randomized trials, prospective or retrospective studies answering the question: 'Are Hyaluronic Acid injections effective on relieving pain and improving functional outcomes in patients with TMD?'

Specifically, all systematic reviews were assessed for eligibility according to the following participants, intervention, comparison and outcomes (PICOs) model:

P—Participants: consisting of patients affected by TMD.

I—Intervention: consisting of IA injections of HA, regardless of the protocol and the number of injections administered. We also included studies that analysed IA injections of HA combined with arthrocentesis or arthroscopy.

C—Comparison: consisting of placebo/sham therapy and any other non-invasive, minimally invasive or invasive therapeutic interventions, including IA injections of HA.

O—Outcome measures: consisting of pain intensity and functional outcomes evaluating jaw-movement limitation. More in detail, Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) or other measurable pain scales were considered as primary outcomes for the pain assessment. Concerning the functional outcomes, every measurable jaw-movement limitation was considered, with a focus on Maximum Mouth Opening (MMO). When available, adverse events (AEs) were collected.

S—Study design: systematic review.

In vitro studies, animal studies and every study on human not following our inclusion criteria were excluded. Moreover, articles aggregating the outcomes of HA injections with those of other therapies were excluded.

The primary outcome was the pain intensity (VAS and NRS) and the secondary outcomes were the evaluation of jaw-movement limitation, including MMO, and the occurrence of adverse events.

2.3 | Study selection

Two reviewers independently screened the articles evaluating their eligibility. Discrepancies and inconsistencies were resolved through discussion and consulting a third reviewer. When the article was considered eligible, full text article was obtained and independently evaluated from the two reviewers for inclusion. Duplicates were excluded.

2.4 | Data extraction

The same reviewers independently performed the data extraction completing a specific preformed form. For each included article, details were extracted on citation, authors, publication year, journal, study design, date of the search, number of databases sourced and searched, number of primary studies included in the systematic review/meta-analysis, number of total participants, types of interventions, comparisons, outcomes on study and length of follow-up. When one of these data was not available, the primary studies included were manually screened for data collection.

2.5 | Study quality assessment

The methodological quality of the studies included in the umbrella review was assessed following the AMSTAR2 checklist,[32] a 16-point tool for critical appraisal of systematic reviews.

The AMSTAR2 is the 'A MeaSurement Tool to Assess systematic Reviews' and it is made up by 16 items, with each of them judged with 'Yes', 'Partial Yes' and 'No'. Seven items are considered critical. The domains considered as critical are the 2 (*registration of the protocol before starting the review*), 4 (*adequate search of the literature through the databases*), 7 (*description of the excluded studies and the justification for exclusion*), 9 (*satisfactory assessment of risk of bias in the included studies*), 11 (*correct use of statistical methods in performing a meta-analysis*), 13 (*evaluation of the impact of different risk of bias when analysing the results*) and 15 (*evaluation of publication bias*). Overall quality of the included studies was judged by adhering to the tool guidance with the following criteria: high (none or one non-critical weakness), moderate (more than one non-critical weakness), low (one critical weakness) and critically low (more than one critical weakness). Two authors independently assessed the quality of the single studies and discrepancies between the two authors were solved by discussion.

3 | RESULTS

3.1 | Study characteristics

The initial search in the electronic databases yielded a total of 316 articles. After the removal of the duplicates, 228 were screened for titles and abstracts, according to the PICOs model. Out of the 42 articles selected for full text assessment, 24 papers were excluded due to the following reasons: study design not respecting the inclusion criteria ($n=4$), different topic ($n=13$), not in English language ($n=6$) and withdrawn by the authors ($n=1$).

Therefore, 18 systematic reviews, evaluating the effects of IA injections of HA in patients with TMD, were included in the umbrella review. Figure 1 illustrates the PRISMA 2020 flow diagram with the entire selection process of systematic reviews for inclusion in the umbrella review.

Publication date of the included studies ranged between 2010 and 2022, and interesting to note, 13 systematic reviews or meta-analyses were published in the last 5 years. Thirteen studies[28–30,33–42] included only randomized controlled clinical trials (RCTs) and eight systematic reviews[28,34,36,38,39,43–45] also performed a meta-analysis on the data of the included studies. All articles but one[44] performed a systematic search on at least two databases. Six articles[30,35,38,44–46] put restrictions on publication date, with three articles[30,35,44] restricting the search to an approximately 10-year period. The number of the studies included in the systematic reviews ranged between 3 and 36, with a median of 8.

The main data on the included studies have been synthesized in Table 1. Quantitative synthesis of the results was not available in all the studies, and the data reported were mostly retrieved by the meta-analyses included.

All the included articles considered the IA injections of HA as intervention or comparison. Four articles[30,40,44,47] analysed IA injections of HA intervention, according to the PICO model of the study included. Five articles[34–36,41,43] evaluated PRP or other platelet

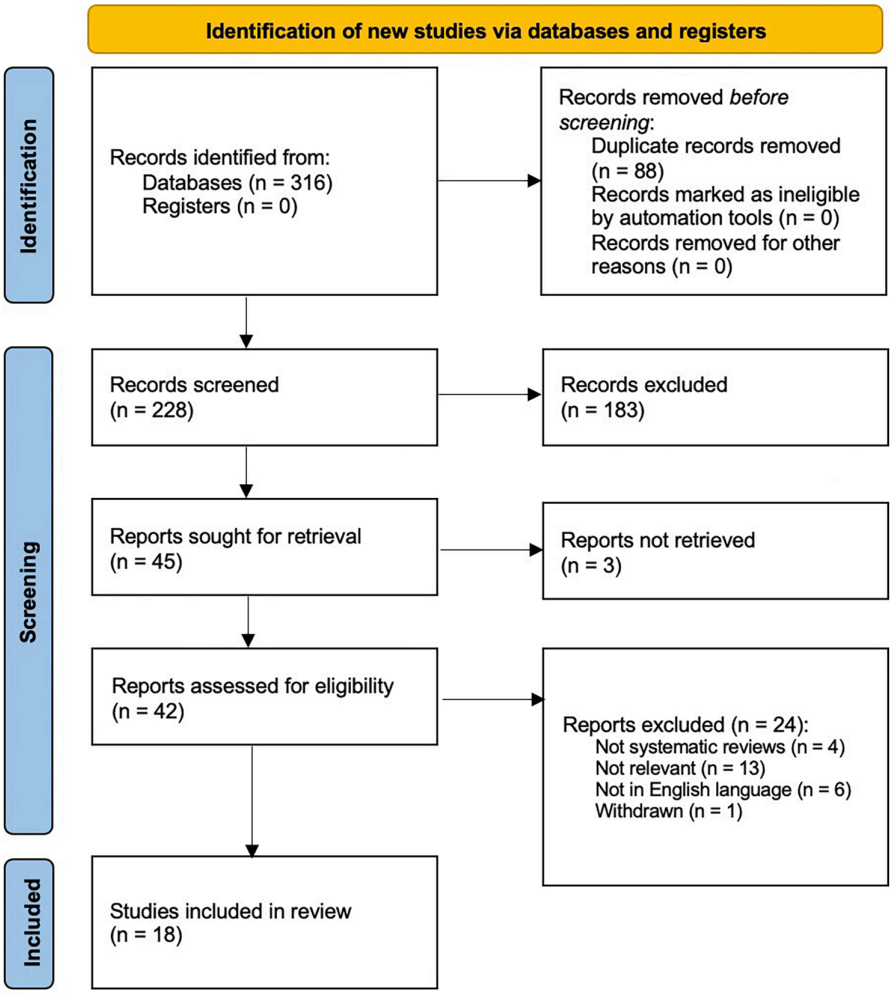

FIGURE 1 PRISMA 2020 flow diagram.

concentrate injections and one study[45] IA injections of CS; in both cases, IA injections of HA were analysed as a comparison. Two studies[42,47] focused both on IA injections of CS and HA. Five studies[28,29,33,38,39] considered multiple comparisons between different therapies (IA injections of HA included). One study[37] mainly focused on arthroscopy *plus* interventions, and HA injections were considered as combined with this surgical technique.

Interventions including arthrocentesis have been considered by 14 articles.[28–30,35,36,38–41,43–47] Only one study[42] considered specifically only IA injections without arthrocentesis/arthroscopy, and one study[37] focused on arthroscopy *plus* interventions, and HA injections were considered as combined with this surgical technique. The other articles evaluated the effects of IA injections of HA alone and in combination with arthrocentesis/arthroscopy.

The main characteristics of the interventions recorded in the included studies have been summarized in Table 2.

3.2 | Main findings of the included systematic reviews

The primary outcome was the pain intensity (VAS and NRS), and the secondary outcomes were the evaluation of jaw-movement limitation, including MMO, and the occurrence of adverse events. The number of patients with improved symptoms, treatment success, articular noises and masticatory efficacy has also been studied in singular studies, and the main findings have been synthesized in Table 3.

3.2.1 | Effects on pain

As the pain intensity was considered as primary outcome, all the included studies performed an evaluation of pain improvement after treatments and the scale most frequently used to assess the level of pain was the VAS.

All articles but one[28] reported that IA injections of HA with or without arthrocentesis/arthroscopy improved pain. According to Al-Moraissi et al.,[39] all the treatments including HA reported an overall reduction of VAS score when compared to placebo: IA injections of HA reported a standardized mean difference (SMD) of 2.05 with a 95% confidence interval (CI) of 2.83–1.27; arthrocentesis *plus* HA (SMD = 1.20; 95% CI [2.08; 0.32]); arthroscopy *plus* HA (SMD = 1.35; 95% CI [2.87; −0.18]). Xie et al.[28] reported no effects on improving pain and functional outcomes by injecting CS, HA and PRP.

TABLE 1 Main characteristics of the systematic reviews included in the umbrella review.

References	Number of searched databases	Study type included	No of studies included	Date recent search	No of participants (participants assigned to HA therapy)	Interventions including therapies with HA (number of included studies)	Meta-analysis	AMSTAR2
Xie et al.[28]	4	RCT	9	January 2022	316 (136)	Arthrocentesis + HA (5) IA injections of HA (2)	Yes	High
Gutiérrez et al.[35]	3	RCT	8	15 May 2021	404 (114)	Arthrocentesis + HA (4) Arthroscopy + HA (1)	No	Low
Liapaki et al.[29]	4	RCT	9	25 September 2019	434 (158)	Arthrocentesis + HA (3) Arthroscopy + HA (1) IA injections of HA (2)	No	Low
Sàbado-Bundó et al.[30]	3	RCT	6	From 1 January 2009 to 28 December 2019	197 (98)	Arthrocentesis + HA (5) Arthroscopy + HA (1)	No	Moderate
Al-Hamed et al.[36]	3	RCT	9	6 March 2020	407 (112)	Arthrocentesis + HA (3) Arthroscopy + HA (1) IA injections of SH (1)	Yes	Low
Sakalys et al.[37]	4	RCT	3	From 2009 to 2019	232	Arthroscopy + HA (2)	No (M-A only on pain level)	Moderate
Liu et al.[38]	7	RCT	11	From 1 January 1985 to 30 September 2018	549	Arthrocentesis + HA (6) Arthrocentesis + HA + CS (1)	Yes	Low
Li et al.[34]	3	RCT	6	July 2018	323	Arthroscopy + HA (1) IA injections of HA (2)	Yes	Critically Low
Al-Moraissi et al.[39]	5	RCT	36	March 2019	1476 (No sample size from four studies)	Arthrocentesis + HA (10) Arthroscopy + HA (1) IA injections of HA (4)	Yes	Low
Haigler et al.[43]	5	RCT (3) and prospective controlled trials (2)	5	4 May 2018	285	Arthrocentesis + HA (2) Arthroscopy + HA (1)	Yes	Critically Low
Ferreira et al.[50]	10	RCT	18	April 2017	882 (303)	Arthrocentesis + HA (11) IA injections of HA (7)	No	Low
Liu et al.[45]	6	Randomized/Quasi-Randomized Controlled Trials and cohort studies	8	Between 1 January 1980 and 30 June 2016	387	Arthrocentesis + HA (1) IA injections of HA (4)	Yes	Critically Low
Bousnaki et al.[41]	2	RCT	6	May 2017	323 (88)	Arthrocentesis + HA (2) Arthroscopy + HA (1)	No	Moderate
Moldez et al.[42]	3	RCT	7 (4 for MA)	7 June 2016	372 (200)	IA injections of HA (7)	Yes	Low
Goiato et al.[47]	2	RCT (7) and prospective or retrospective studies (1)	8	March 2016	350 (154)	Arthrocentesis + HA (2) IA injections of HA (6)	No	Critically Low
Machado et al.[46]	6	Randomized/quasi-randomized controlled clinical trials	9	Between 1966 and October 2010	472 (203)	Arthrocentesis + HA (1) Arthroscopy + HA (1) IA injections of HA (7)	No	Critically Low
de Souza et al.[33]	5	RCT	3		114	IA injections of HA (1)	No	High
Manfredini et al.[44]	1	Peer-reviewed papers	19	From 1 January 1999 to 9 November 2009	604	Arthrocentesis + HA (7) IA injections of HA (13)	No	Critically Low

TABLE 2 Interventions and comparisons in the systematic reviews included in the umbrella review.

References	Intervention	Comparison	Arthrocentesis
Xie et al.[28]	Two or more IA injections between corticosteroids (CS), hyaluronic acid (HA), platelet-rich plasma (PRP) and placebo injections (Ringer's Lactated Solution)	Two or more IA injections between corticosteroids (CS), hyaluronic acid (HA), platelet-rich plasma (PRP) and placebo injections (Ringer's Lactated Solution)	Yes
Gutiérrez et al.[35]	Arthrocentesis or arthroscopy with an IA injection of PRP or PRGF	Patients with TMDs who did not receive an IA injection or were injected with another type of substance like HA, saline solution, Ringer's Lactate solution after arthrocentesis/arthroscopy	Yes
Liapaki et al.[29]	IA injections of HA, CS or blood products, with/without arthrocentesis or arthroscopy	Different injectables or injectable versus normal saline or Ringer's lactate	Yes
Sàbado-Bundó et al.[30]	Minimally invasive surgery of the TMJ (arthrocentesis or arthroscopy) with IA injections of HA	Patients who underwent the same minimally invasive surgery of the TMJ (same number of sessions) without HA IAI (or with placebo injections of saline solution [ss] or Ringer's lactate [RL])	Yes
Al-Hamed et al.[36]	Platelet concentrate (PC) injection with/without arthrocentesis or arthroscopy	HA or saline/Ringer's solution injections, with/without arthrocentesis or arthroscopy.	Yes
Sakalys et al.[37]	IA injection following arthroscopy	Comparison between efficiency of different substances for IA injections	No
Liu et al.[38]	Different IA injection of drugs after arthrocentesis or just arthrocentesis alone without additional injection of any drug		Yes
Li et al.[34]	PRP or similar products (i.e. PRGF)	Control treatment: i.e. placebo or HA	No
Al-Moraissi et al.[39]	Two or more of the treatment modalities for arthrogenous TMD included in the 'Treatment Administered' section	Patients who did not receive any treatments and/or placebo (which includes IA injection of normal saline, application of inactive laser)	Yes
Haigler et al.[43]	Arthrocentesis or arthroscopy with normal saline or lactated Ringer solution plus PRP or PRGF IA injections	Arthrocentesis or arthroscopy with saline or lactated Ringer solution only, arthrocentesis or arthroscopy followed by saline injection, or arthrocentesis or arthroscopy followed by HA injections	Yes
Ferreira et al.[50]	IA administration of HA or its derivatives. The use of HA in surgical interventions, such as arthroscopy, was not considered	Placebo, active agents, or another form of therapy	Yes
Liu et al.[45]	IA injection with CS alone with/without arthrocentesis	Hyaluronate or placebo IA injections, with/without arthrocentesis	Yes
Bousnaki et al.[41]	Patients treated with PRP injections	Patients treated with other types of IA drug therapy or placebo	Yes
Moldez et al.[42]	CS or SH IA injections without arthrocentesis	Placebo, CS or SH IA injections	No
Goiato et al.[47]	IA injections of HA	Other types of IA drug therapies	Yes
Machado et al.[46]	IA injections of CS or SH with/without arthrocentesis or arthroscopy	Placebo or other therapies with/without arthrocentesis or arthroscopy	Yes
de Souza et al.[33]	IA injections of SH	IA injections of CS	No
Manfredini et al.[44]	IA injections of HA (with or without arthrocentesis/arthroscopy)	Placebo, conservative treatments or other therapies with/without arthrocentesis or arthroscopy	Yes

Abbreviations: CS, corticosteroid; HA, hyaluronic acid; IA, intra-articular; NSAIDs, non-steroidal anti-inflammatory drugs; PDGF, platelet-derived growth factor; PRGF, plasma rich in grow factors; TMD, temporomandibular disorders.

Arthroscopy	Treatments administered	Follow-up
No	IA injection of HA, IA injections of CS, Arthrocentesis, Arthrocentesis+PRP, Arthrocentesis+HA, Arthrocentesis+CS, Arthrocentesis+Ringer's solution	Short-term (3–6 months) Long-term (>12 months)
Yes	Arthrocentesis, Arthrocentesis + HA, Arthrocentesis + PRP, Arthroscopy + PRGF, Arthroscopy + saline solution, Arthroscopy + HA	From 6 to 24 months
Yes	Arthrocentesis, Arthrocentesis + CS, Arthrocentesis + HA, Arthrocentesis + PRP, Arthroscopy + PRGF, Arthroscopy + HA, IA injections of HA, IA injections of CS	≥6 months
Yes	Arthrocentesis, Arthrocentesis + HA, Arthroscopy, Arthroscopy + HA	6–12 months
Yes	IA injections of PRP, IA injections of PRGF, IA injections of HA, Arthrocentesis + saline solution, Arthrocentesis + Ringer's Solution, arthrocentesis + HA, arthroscopy + saline solution	3–24 months
Yes	Arthroscopy alone, Arthroscopy + HA, Arthroscopy + PRGF	3–6 months
No	Arthrocentesis alone, Arthrocentesis + HA, Arthrocentesis + dexamethasone, Arthrocentesis + prednisolone, Arthrocentesis + betamethasone, Arthrocentesis + betamenthasone + HA, Arthrocentesis + morphine, Arthrocentesis + tramadol, Arthrocentesis + PDGF, Placebo	1–3 months
Yes	IA injections of HA, IA injections of PRP, Arthroscopy + HA, Arthroscopy + PRP, Arthroscopy	3–6–12–18–24 months
Yes	Conservative treatments, Physical Therapy, IA injections of HA, IA injections of CS, Arthrocentesis alone, Arthrocentesis + HA, Arthrocentesis + PRP, Arthrocentesis + CS, Arthroscopy alone, Arthroscopy + PRP, Arthroscopy + HA, Open joint surgery	Short-term (≤5 months) Long-term (≥6 months, up to 4 years)
Yes	Arthrocentesis + Ringer's Solution, Arthrocentesis + PRP, Arthrocentesis + HA, Arthroscopy + HA, Arthroscopy, Arthroscopy + PRGF, Arthroscopy + saline solution	12 months
No	Arthrocentesis, Arhtrocentesis + HA, Arthrocetesis + CS, Arthrocentesis + Ringer's Solution, Arthrocentesis + PRP, IA injections of HA, IA injections of CS, IA injections of NSAIDs, Placebo	From 1 week to 1 year
No	Arthrocentesis, Arthrocentesis + CS, Arthrocentesis + HA, Arthrocentesis + Ringer's solution, IA injections of HA, IA injections of CS	Short-term (3–4 weeks) Long-term (>6 months)
No	Arthrocentesis + PRP, Arthrocentesis + HA, Arthrocentesis + Ringer's solution, Arthroscopy + PRP, Arthroscopy + saline solution, Arthroscopy + HA	From 1 to 24 months
No	IA of saline solution, IA injections of HA, IA injections of CS, IA injections of tenoxicam	From 4 weeks to 2 years
No	IA injections of HA, IA injections of CS, IA injections of NSAIDs, IA injections of saline solution, Arthrocentesis, Arthrocentesis + CS, Arthrocentesis + HA	From 1 month to 24 months
Yes	Arthrocentesis + HA, Arthrocentesis + Saline solution, Arthroscopy + HA, Arthroscopy + Ringer's solution, IA injections of CS, IA injections of HA	From 4 weeks to 6 months
No	Any form of non-surgical or surgical therapy for TMJ OA	14 days, 1 month, 6 months
No	Arthrocentesis, Arthrocentesis + HA, IA injections of CS, IA injections of HA, Oral drugs, Orthotic treatment	From 3 months to 1 year

TABLE 3 PICO model and main findings of the systematic reviews included in the umbrella review.

References	Participants	Interventions and Comparisons	Outcome
Xie et al.[28]	TMJ OA based on RDC/TMD, DC/TMD and imaging	IA injection of HA, IA injections of CS, Arthrocentesis, Arthrocentesis + PRP, Arthrocentesis + HA, Arthrocentesis + CS, Arthrocentesis + Ringer's solution	VAS, MMO, lateral movement
Gutiérrez et al.[35]	Arthrogenous TMD based on RDC/TMD, DC/TMD, and Wilkes' classification	Arthrocentesis, Arthrocentesis + HA, Arthrocentesis + PRP, Arthroscopy + PRGF, Arthroscopy + saline solution, Arthroscopy + HA	VAS MMO
Liapaki et al.[29]	TMJ OA defined by the DC/TMD or RDC/TMD criteria	Arthrocentesis, Arthrocentesis + CS, Arthrocentesis + HA, Arthrocentesis + PRP, Arthroscopy + PRGF, Arthroscopy + HA, IA injections of HA, IA injections of CS	Joint pain MMO AEs
Sàbado-Bundó et al.[30]	Arthrogenous TMD based on RDC/TMD, Wilkes' classification, clinical examination and/or imaging	Arthrocentesis, Arthrocentesis + HA, Arthroscopy, Arthroscopy + HA	VAS MMO
Al-Hamed et al.[36]	TMJ OA or disc displacement. Not specified how diagnosis was performed	IA injections of PRP, IA injections of PRGF, IA injections of HA, Arthrocentesis + saline solution, Arthrocentesis + Ringer's Solution, Arthrocentesis + HA, Arthroscopy + saline solution	VAS MMO Jaw Movements Joint Sounds Masticatory Efficacy
Sakalys et al.[37]	Arthrogenous TMD based on MRI	Arthroscopy alone, Arthroscopy + HA, Arthroscopy + PRGF	VAS MMO
Liu et al.[38]	TMJ OA according to the criteria of RDC/TMD	Arthrocentesis alone, Arthrocentesis + HA, Arthrocentesis + dexamethasone, Arthrocentesis + prednisolone, Arthrocentesis + betamethasone, Arthrocentesis + betamenthasone + HA, Arthrocentesis + morphine, Arthrocentesis + tramadol, Arthrocentesis + PDGF, Placebo	VAS MMO
Li et al.[34]	TMJ OA, with disc displacement with or without reduction and degenerative changes in the condyle surface. Not specified how diagnosis was performed	IA injections of HA, IA injections of PRP, Arthroscopy + HA, Arthroscopy + PRP, Arthroscopy	VAS AEs
Al-Moraissi et al.[39]	Arthrogenous TMD based on the RDC/TMD or DC/TMD (osteoarthritis and/or disc displacement of the TMJ)	Conservative treatments, physical therapy, IA injections of HA, IA injections of CS, Arthrocentesis alone, Arthrocentesis + HA, Arthrocentesis + PRP, Arthrocentesis + CS, Arthroscopy alone, Arthroscopy + PRP, Arthroscopy + HA, Open joint surgery	VAS MMO

Main findings
Pain: • None of the drugs injected significantly improved pain at short- or long-term follow-up. At short-term, CS had poorer results than placebo; PRP showed better results than HA. At long-term follow-up, PRP had the best results • PRP had the largest probability to be the best injectable option at both short- and long-term follow-up MMO and lateral movements: None of the drugs injected significantly improved functional outcomes at short- or long-term follow-up
Pain: • All the treatments (both interventions and comparisons) improved pain. Seven out of eight reported better results for the adjunct of PRP/PRGF to arthrocentesis/arthroscopy. PRP + arthrocentesis/arthroscopy had better results than HA + arthrocentesis/arthroscopy, with statistical significant results in three studies MMO: All the studies showed an increased MMO
Pain: • Arthrocentesis + HA improved pain after 12/24 months; HA without arthrocentesis improved pain at 12 months and results were superior to CS at 6 months • HA + arthroscopy had lower improvements than PRP/PRGF + arthroscopy MMO: • HA + arthrocentesis improved MMO at 6, 12 and 24 months • HA alone improved MMO at 6 months, independently from the molecular weight Authors reported limited AEs
Pain: • VAS decreased in all studies. Four studies reported better results in the group adding IA injections of HA to arthrocentesis/arthroscopy. Results were statistically significant in three studies MMO: All studies reported improvements in MMO, statistically significant in two studies out of six
Pain: All interventions reduced pain compared to baseline. PC was more effective than HA injection at 3 months, but not at 12 months MMO: Non-significant difference between PC and HA injections at 3 and 12 months Jaw movements/Joint sounds: No differences between the interventions.
Pain and MMO: • PRGF and HA improve both outcomes • HA results were better that no-injection in both outcomes, but only pain improvement showed a statistically significant difference • PRGF had better results than HA at 18 months. Quantitative data analysis showed that IA injections were more effective than arthroscopy alone at 6 months
• Tramadol and morphine were effective on both outcomes • PDGF had excellent results on both outcomes Pain: • Arthrocentesis + sodium hyaluronate injections had better results than arthrocentesis alone • Arthrocentesis + PDGF had better results than arthrocentesis alone • HA + CS had better results than CS alone but not better than HA alone SUCRA values for pain improvement (probabilities to be the best treatment, reported up to HA position): • Morphine (89.95%), >tramadol (78.77%) > PDGF (74.48%), dexamethasone (67.01%), placebo (53.13%) > hyaluronic acid (40%) MMO: • Arthrocentesis + sodium hyaluronate had better results than arthrocentesis alone • Arthrocentesis + PDGF had better results than arthrocentesis + placebo • HA had good effects for improving MMO in the short term SUCRA values for MMO improvements (reported up to HA position): PDGF (83.84%), Hyaluronic acid (57.07%)
Pain: • PRP improved VAS at 6 and 12 months (statistically significant results) • PRP had better results than HA at 12 months AEs: Two studies reported complications (one study reported pain during injections, the other momentary swelling and pain on the day after injection)
Minimally invasive procedures improve pain and MMO on a short/intermediate term and are more effective than conservative treatments Pain: a. short-term follow-up: IA injections of HA had the best results b. intermediate follow-up: No differences between IA injections of HA, arthroscopy and arthrocentesis MMO: • Arthroscopy had the best results (with or without drug instillation) • PRP followed by HA may improve the effects of arthroscopy

(Continues)

TABLE 3 (Continued)

References	Participants	Interventions and Comparisons	Outcome
Haigler et al.[43]	TMJ OA based on RDC/TMD, DC/TMD, and/or imaging	Arthrocentesis + Ringer's Solution, Arthrocentesis + PRP, Arthrocentesis + HA, Arthroscopy + HA, Arthroscopy, Arthroscopy + PRGF, Arthroscopy + Saline Solution	VAS MMO Masticatory Efficacy AEs
Ferreira et al.[40]	TMJ OA and/or anterior disc displacement (with or without reduction) according to RDC/TMD	Arthrocentesis, Arhtrocentesis + HA, Arthrocetesis + CS, Arthrocentesis + Ringer's Solution, Arthrocentesis + PRP, IA injections of HA, IA injections of CS, IA injections of NSAIDs, Placebo	Pain measures AEs MMO Articular noises Tolerance to treatment
Liu et al.[45]	TMJ OA, TMJ arthritis (not rheumatic arthritis) or TMJ degenerative diseases, according to RDC/TMD	Arthrocentesis, Arthrocentesis + CS, Arthrocentesis + HA, Arthrocentesis + Ringer's solution, IA injections of HA, IA injections of CS	VAS MMO Treatment Success rate AEs
Bousnaki et al.[41]	Patients with TMJ OA or disc displacement with or without reduction. Not specified how diagnosis was performed	Arthrocentesis + PRP, Arthrocentesis + HA, Arthrocentesis + Ringer's solution, Arthroscopy + PRP, Arthroscopy + saline solution, Arthroscopy + HA	VAS MMO
Moldez et al.[42]	TMD based on RDC/TMD, Wilkes' classification, Helkimo Index, modified Helkimo Index, clinical examination and/or imaging	IA of saline solution, IA injections of HA, IA injections of CS, IA injections of tenoxicam	VAS Number of patients with improved symptoms AEs
Goiato et al.[47]	TMD based on RDC/TMD, clinical examination and/or imaging	IA injections of HA, IA injections of CS, IA injections of NSAIDs, IA injections of saline solution, Arthrocentesis, Arthrocentesis + CS, Arthrocentesis + HA	Pain measures Functional measures
Machado et al.[46]	TMD based on RDC/TMD, Helkimo Index, modified Helkimo Index, clinical examination and/or imaging	Arthrocentesis + HA, Arthrocentesis + saline solution, Arthroscopy + HA, Arthroscopy + Ringer's solution, IA injections of CS, IA injections of HA	Not specific pain and functional outcomes
de Souza et al.[33]	TMJOA according to the RDC/TMD	Any form of non-surgical or surgical therapy for TMJ OA	Primary outcomes: Pain, tenderness, discomfort, jaw movement, subjective TMJ sounds
Manfrediniet al.[44]	TMJOA according to the RDC/TMD or confirmed radiologically	Arthrocentesis, Arthrocentesis + HA, IA injections of CS, IA injections of HA, Oral drugs, Orthotic treatment	VAS Jaw Range of Motion

Abbreviations: CS, corticosteroid; CT, computed tomography; DC/TMD, diagnostic criteria for temporomandibular disorders; E, adverse events; HA, hyaluronic acid; IA, intra-articular; MMO, maximum mouth opening; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; PDGF, platelet-derived growth factor; PRGF, plasma rich in grow factors; RDC/TMD, research and diagnostic criteria for temporomandibular disorders; SH, sodium hyaluronate; SUCRA, surface under the cumulative ranking curve; TMJOA, temporomandibular joint osteoarthritis; VAS, Visual Analogue Scale.

IA injections without arthrocentesis/arthroscopy

The effectiveness of IA injections of HA alone (without arthrocentesis/arthroscopy) on relieving pain has been suggested by five articles[29,39,40,42,45] with one article[29] suggesting their effectiveness on pain at 12 months follow-up. Al-Moraissi et al.[39] concluded that IA injections of HA have the best results in the short-term follow-up (≤5 months) and, interesting to note, no differences were found with the association of injections with arthrocentesis and/or arthroscopy.

When compared to CS injections, Moldez et al.[42] reported no differences in the short-term follow-up (SMD = −0.40; 95%CI [−0.395; 0.315]). Liu et al.[45] reported a better success rate for HA injections compared to CS in the short term, whereas they reported no statistically significant differences (SMD = −0.058; 95% CI [−1.055; 0.939]) in long-term follow-up (6 months to 2 years). Studies included in one systematic review[29] reported HA injections having better results than CS at 6 months.

Main findings
Pain: Both PRP and HA injections after arthrocentesis or arthroscopy improve pain. The improvement was superior in PRP group, compared to HA group MMO: No statistically significant difference in MMO between groups AEs: Most common AE was pain during injection and postoperative discomfort
• It is not possible to determine the efficacy of HA injections in TMJ disorders. Authors suggest the effectiveness of HA injections in relieving pain • HA + arthrocentesis is not superior to arthrocentesis alone AEs: were mostly mild and self-limiting
Pain and MMO: • Both HA and CS were effective. In the short term, no significant difference between the two treatments • HA had a higher success rate • CS had better results than placebo on improving pain but poorer result on improving MMO AEs: Pain after injection, ear pressure, open bite, generalized rush and chewing disfunction
Pain: • PRP had better results than Ringer's lactate injections • PRP had better results than HA in two studies (one reported similar effects on pain at 12 months) MMO: Similar results as 'Pain' section
Pain: No statistically significant difference between CS and SH in long-term post-treatment (6 months to 2 years). SH showed better results than placebo. Number of patients with improved symptoms: SH had better results than placebo at 1- and 6-months follow-up Helkimo dysfunction score: SH and CS were both effective. SH had better results than placebo. AEs: One study reported mild and short-term discomfort; another study reported severe pain
IA injections of HA improve pain and function in patients with TMJ disorders
• Sodium hyaluronate is effective on treating TMJ derangements at short and medium terms • Despite similar results to CS at short-term follow-up, IA injections of sodium hyaluronate had better result at long-term follow-up
One study compared sodium hyaluronate vs corticosteroids. Authors reported that both therapies were effective at 6 months, with lower pain in the group treated with sodium hyaluronate. SH group had lower frequency of TMJ sounds after 14 days, but no differences at 1 and 6 months. No other statistically significant differences were found
A single HA injection was superior to oral administration of methocarbamol plus paracetamol Despite the effectiveness shown, HA injections did not prove superior to other active treatments, such as CS injections or occlusal appliances

When compared to PRP, HA was reported to have poorer outcomes.[34,36,43] Only one study did not give solid conclusion, even reporting evidence favouring PRP role.[41]

Arthrocentesis plus HA injections

The adjunct of HA administration after arthrocentesis has been debated in the included articles and yielded conflicting results: two articles[35,43] report pain improvements, with one[29] specifying pain improvements at 12 and 24 months; another article[30] suggested its use with a B degree of recommendation.

However, there is no agreement in the included systematic reviews: one[40] concluded that the association is not superior to arthrocentesis alone, with another study[39] reporting no outcome differences by adding HA injections to arthrocentesis/arthroscopy at an intermediate follow-up. On the contrary, another systematic review[38] reported that arthrocentesis alone had the lowest probabilities to be the best treatment, and each association of arthrocentesis *plus* injections (also placebo injections) had better results, with arthrocentesis *plus* HA having better results than arthrocentesis alone (mean difference [MD] of −1.30; 95% CI [−2.58; −0.02]).

Arthroscopy plus HA injections

The adjunct of HA injections to arthroscopy has been judged effective by two studies.[29,37] One study[37] reported that the adjunct of IA injections was more effective than arthroscopy alone at 6 months and both studies[29,37] reported that HA had poorer results than platelet derivates in adjunct to arthroscopy on relieving pain.

3.2.2 | Effects on function

All studies but two[34,42] performed a functional evaluation. Twelve systematic reviews[28–30,35,36–41,43,45] considered the changes in MMO for the evaluation of jaw-movement limitation, whereas three articles[44,46,47] reported effectiveness on improving non-specified functional outcomes.

Only Xie et al.[28] reported no effects of HA injections on functional outcomes; on the contrary, improvements in MMO have been reported by nine articles.[29,30,35–38,41,43,45]

When compared to placebo, treatments including HA showed better results: data obtained by Al-Moraissi et al.[39] reported that arthrocentesis *plus* HA had a SMD of 0.25 (95% CI [−0.42; 0.92]), IA injections of HA had a SMD of 0.66 (95% CI [−0.13; 1.45]), and arthroscopy *plus* HA had a SMD of 2.02 (95% CI [0.87; 3.17]).

When compared to CS, HA showed no significant difference (MD = −1.4; 95% CI [−6.28; 3.48]) at short-term follow-up.[45] PRP has been reported to have better results than HA,[34,36,43] whereas one study[41] does not give solid conclusion, even reporting more studies favouring PRP role.

The results of arthrocentesis *plus* HA showed to be better than the arthrocentesis alone (MD = 2.60; 95% CI [−0.82; −4.38]), according to Liu et al.[38]

3.2.3 | Adverse events

Six articles[29,34,40,42,43,45] reported the AEs following the treatment. More in detail, Li et al.[34] focused on PRP injections: the authors reported swelling, pain and post-injection discomfort in the group treated with PRP; when compared with HA, authors found less AEs or no significant complications. Liapaki et al.[29] reported limited AEs: pain during and after injection (more associated to PRP injections than HA), ear pressure, open bite and generalized rashes after CS injections. Haigler et al.[43] focused on PRP injections. Two articles of this systematic review reported AEs: one concerned PRP injections and reported serum extravasation and bleeding; the second one reported pain during injections more frequent in PRP than HA (in HA 15 out of 25 patients had pain, 2 of 25 had postoperative discomfort). Liu et al.[45] reported the AEs of three studies, including pain, ear pressure, open bite, rashes and chewing dysfunction with no significant differences between CS and hyaluronate. Ferreira et al.[40] reported AEs of five studies: two used high molecular weight hyaluronic acid (HMWHA) and the main adverse event was pain; in another study, the AEs were related to the surgical technique. In the systematic reviews performed by Moldez et al.,[42] two articles reported the AEs as pain of short duration.

3.3 | Quality assessment

The methodological quality of the included articles was assessed by the AMSTAR2 tool and was reported in Table 4. Out of 18 systematic reviews included in this umbrella review, we reported two (11.11%) high-quality studies, three (16.67) systematic reviews with a moderate quality, seven (38.89%) had a low-quality, and six (33.33%) were systematic reviews with a critically low quality.

The most common reason why they were judged to be low-quality studies was the absence of a list of the reasons for the exclusion of articles. The most common non-critical weakness was item number 10, which suggests reporting the financial funding obtained to conduct the study.

4 | DISCUSSION

The objective of this umbrella review was to evaluate the available scientific evidence on the effects of IA injections of HA on pain relief and improvement of jaw function in patients affected by TMD.

The most common clinical manifestations of TMD are pain, joint noises, tenderness, dysfunction and functional limitation in the articular movement; furthermore, TMD patients may also suffer from headaches, earaches, tinnitus, dizziness, posture impairment, and neck and shoulder pain.[3,5,6,48] Indeed, recent evidence showed that TMD could negatively influence quality of life, suggesting a prompt and adequate rehabilitation of TMD pain.[10,12,13,49]

Viscosupplementation with HA has been widely used in TMJ pathological changes considering that HA is a glycosaminoglycan naturally found in the synovial fluid.[50] It is formed by a high number of repeating units of disaccharide, forming chains, reaching high molecular weights, with a good solubility in water and a high level of viscosity even at low polymer concentrations. In healthy synovial fluid, HA has a molecular weight around 6000 kDa (high molecular weight, HMW).[50] Molecular weight of the HA injected may influence signalling response[51,52]; specifically, HA may act as a damage-associated molecular pattern, with HMW HA having anti-inflammatory and low molecular weight HA (LMW-HA) having pro-inflammatory properties.[50]

The number of injections administered varies in the systematic reviews included in the present umbrella: a series of two IA injections of HA spaced 7–14 days apart or five injections each 7 days apart are the most common viscosupplementation strategies.[53] Minimally invasive techniques have a limited effectiveness in the long term due to de degradation of the molecules, and this probably leads to repeated injections.[54] However, a greater number of injections are usually performed with HA compared to CS, because of its fewer potential complications as steroid administration might provoke oedema, hypoesthesia, skin hypopigmentation and skin atrophy.[55]

TABLE 4 AMSTAR2 quality assessment.

References	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall assessment
Xie et al.[28]	Y	Y	Y	Y	Y	Y	PY	Y	Y	N	Y	Y	Y	Y	Y	Y	High
Gutierrez et al.[35]	Y	PY	Y	PY	Y	Y	Y	Y	Y	N	NM	NM	Y	N	NM	Y	Low
Liapaki et al.[29]	Y	PY	Y	PY	Y	Y	N	Y	Y	N	NM	NM	Y	N	NM	Y	Low
Sàbado-Bundó et al.[30]	Y	PY	Y	PY	Y	Y	Y	Y	Y	N	NM	NM	Y	N	NM	Y	Moderate
Al-Hamed et al.[36]	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	T	Low
Sakalys et al.[37]	Y	PY	Y	PY	Y	N	Y	PY	Y	N	NM	NM	Y	Y	NM	Y	Moderate
Liu et al.[38]	Y	Y	Y	PY	Y	Y	N	PY	Y	N	Y	Y	Y	Y	Y	Y	Low
Li et al.[34]	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	Critically low
Al-Moraissi et al.[39]	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
Haigler et al.[43]	Y	PY	Y	PY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	Critically low
Ferreira et al.[40]	Y	PY	Y	Y	Y	Y	N	PY	Y	N	NM	NM	Y	Y	NM	Y	Low
Liu et al.[45]	Y	PY	N	PY	Y	Y	N	PY	PY	N	Y	N	Y	Y	N	Y	Critically low
Bousnaki et al.[41]	Y	PY	Y	PY	Y	Y	Y	Y	Y	N	NM	NM	Y	N	NM	Y	Moderate
Moldez et al.[42]	Y	PY	Y	PY	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Low
Goiato et al.[47]	Y	PY	Y	PY	Y	N	N	PY	N	N	NM	NM	Y	Y	NM	Y	Critically low
Machado et al.[46]	N	N	Y	PY	Y	N	N	PY	N	N	NM	NM	N	N	NM	Y	Critically low
de Souza et al.[33]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NM	NM	Y	Y	NM	Y	High
Manfredini et al.[44]	Y	PY	N	N	Y	N	N	PY	N	N	NM	NM	N	N	NM	N	Critically low

Note: Q1: Did the research questions and inclusion criteria for the review include the components of PICO? Q2: Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Q3: Did the review authors explain their selection of the study designs for inclusion in the review? Q4: Did the review authors use a comprehensive literature search strategy? Q5:. Did the review authors perform study selection in duplicate? Q6: Did the review authors perform data extraction in duplicate? Q7: Did the review authors provide a list of excluded studies and justify the exclusions? Q8: Did the review authors describe the included studies in adequate detail? Q9: Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? Q10: Did the review authors report on the sources of funding for the studies included in the review? Q11: If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Q13: Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review? Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? Q15: If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Abbreviations: N, no; NA, not applicable; NM, no meta-analysis performed; PY, partial yes; Y, yes.

The aetiology of pain in TMD is often multifactorial and complex and patients with chronic TMD have frequently overlapping pain conditions of systematic diseases, and depression, anxiety, or other distressful conditions are often present, and these might be susceptible of oral pharmacological treatment.[56]

Focusing on arthrogenous TMD, excessive mechanical load may break the dynamic equilibrium between extracellular matrix synthesis and degradation, with cartilage damage and inflammation visible in synovial fluid composition. This reduces the lubrication capacity and may cause pain, also due to hypoxia.[57] So, a progressive destruction of the articular cartilage may occur, accompanied by reduction of both synovial fluid and joint space that can lead to bony erosion and sclerosis, and to the formation of subchondral cyst or osteophytes.[4]

In these cases, often the first approach consists of pharmacological agents, which include non-steroidal anti-inflammatory drugs, opioids, steroid or muscle relaxants.[58]

In our umbrella systematic review, two studies[39,44] considered comparisons with these oral drugs. One systematic review[44] reported that HA injections were more effective than oral drugs in pain relief; the other study[39] is the only one comparing minimally invasive techniques (including IA HA injections) with conservative treatments, concluding the minimally invasive techniques were more effective than oral drugs, defining these latter unable to modify the outcomes in the short or intermediate period.

When considering the effects of HA on pain, only one study[28] reports no benefits. Though it is a recent study with a strong methodology, this might be related to the restricted number of patients and to the heterogeneity in follow-up examination. Indeed, the effectiveness on pain up to 12 months has been reported in most of the systematic reviews included in the present study.[29] This might be related to the anti-inflammatory and analgesic activity of HA, promoting the synthesis of extracellular matrix (ECM) molecules, reducing the catabolic activity and promoting tissue repair.[49] This might suggest that HA has not only viscosupplementative properties, but it might have a modulatory activity on the processes generating osteoarthritis of the TMJ, as also reported by Iturriaga et al. in their systematic review.[59]

HA has been compared to several other drugs in the included studies, and no statistically significant differences were found when compared to CS.

On the contrary, the different effectiveness between PRP and HA has been studied in three of the included studies[34,36,43] and results showed that PRP demonstrated to be related to better outcomes. However, data from these articles have not been reported, as they did not undertake a separate analysis on IA injections of PRP and on arthrocentesis/arthroscopy *plus* IA injections of PRP; thus, the heterogeneous results might have underestimated the effectiveness of the arthrocentesis/arthroscopy technique on the outcomes.

Concerning the functional outcomes, the MMO has been the most frequently used measure for evaluating the functional improvement, and several of the included studies have assessed the effectiveness of HA injections (with or without arthrocentesis) on function.[29,30,35–41,43,45]

MMO was often measured as the maximum interincisal distance, and it was reported to range from 53 to 58 mm in healthy subjects. Although height, body size and age should be considered, a possible cut-off to define a reduced MMO was reported to be about 40 mm in adults.[60]

The effects on pain were in agreement with MMO improvement, which was about 5.41 mm in patients treated with HA.[43] However, as specified by Sàbado-Bundó et al.,[30] the MMO distance has been not taken twice (with and without pain). Furthermore, this measure is only one of the parameters assessing mandibular functionality: other tools have been developed and validated but are not commonly used.

The AEs have been reported by six articles[29,34,40,42,43,45] and mild pain has been the most frequently reported; however, the data derived from a small number of studies.

Taken together, safety of HA injections in TMJ have been suggested in literature[61] and the articles included in our umbrella review reported no infections or severe systemic AEs, supporting the safety of HA injections in TMD.[62] However, the systematic reviews included in this umbrella review often analysed the AEs, based on a small number of primary studies.

Another issue that should be taken into consideration is that different indexes, tools or criteria have been used to diagnose TMD in the included articles (as reported in Table 3). RDC/TMD[63] and DC/TMD[1] are the guidelines used to assess the presence of TMD in several of the included articles.[28,29,33,38–39,43] Three articles[28,43,46] considered the radiological aspect to assess the presence of TMD. Moreover, articular disorders are often classified according to Wilkes' Staging Classification for International Derangement of the TMJ.

This paper is not free from limitations: firstly, the data included in this article have been presented mostly narrative, and a quantitative synthesis has not been performed, due to the high heterogeneity of the included studies. Moreover, the data were often obtained by pooling the results of different combined treatment methods, not by one-to-one comparisons, so only the data obtained by single comparisons were reported. Another important limitation might be the overlap between the studies included in the systematic reviews and meta-analyses, with possible implications on the conclusions drawn by this umbrella review. Lastly, it should be noted that more than 70% of the included systematic reviews had a low quality or a critically low quality.

5 | CONCLUSION

Taken together, findings of the present umbrella review of systematic reviews showed positive results in terms of safety and effectiveness of IA injections of HA on pain intensity and functioning in TMD patients. The included systematic reviews reported no statistically significant differences between HA and CS, whereas platelet derivates seem to have good results in pain

relief. However, despite these intriguing results on the use of HA, it should be taken into consideration the low quality of the systematic reviews included in our umbrella review. Thus, more randomized clinical trials with methodological and diagnostic homogeneity are needed to confirm the efficacy of HA injections on pain relief in patients affected by TMD.

AUTHOR CONTRIBUTIONS

Francesco Agostini, Martina Ferrillo, Marco Paoloni, Alessandro de Sire: Conceptualisation; Francesco Agostini, Martina Ferrillo, Marco Paoloni, Alessandro de Sire: methodology; Andrea Bernetti, Nikolaos Finamore, Massimiliano Mangone: formal analysis; Francesco Agostini, Martina Ferrillo, Nikolaos Finamore: investigation; Andrea Bernetti, Amerigo Giudice, Alessandro de Sire: data curation; Francesco Agostini, Martina Ferrillo, Andrea Bernetti: writing—original draft preparation; Amerigo Giudice, Marco Paoloni, Alessandro de Sire: writing—review and editing; Nikolaos Finamore, Massimiliano Mangone: visualization; Amerigo Giudice, Marco Paoloni, Alessandro de Sire: supervision. All authors read and agreed to the published version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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