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SYSTEMATIC REVIEW

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Stem cell–based therapies for temporomandibular joint disorders: A systematic review

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ABSTRACT

Temporomandibular joint disorders (TMDs), particularly those involving degenerative cartilage changes and osteoarthritis, represent a significant clinical challenge due to the limited intrinsic regenerative capacity of fibrocartilaginous tissues. Stem cell–based therapies have emerged as a promising regenerative strategy aimed at modulating inflammation and promoting structural joint repair. This systematic review evaluated the current evidence regarding the therapeutic potential of mesenchymal stem/stromal cells (MSCs) and related cell-derived products for the treatment of temporomandibular joint (TMJ) disorders. A structured literature search was conducted in PubMed/MEDLINE and Google Scholar for studies published between January 2000 and December 2025, following PRISMA 2020 guidelines. Eligible studies included clinical trials, observational studies, case series, animal studies, and systematic reviews investigating stem cell–based interventions in TMJ pathology. A total of 26 studies met the inclusion criteria and were analyzed qualitatively. Preclinical studies consistently demonstrated anti-inflammatory, chondroprotective, and regenerative effects following intra-articular administration of MSCs or MSC-derived products. Clinical studies reported reductions in pain intensity and improvements in mandibular function, although methodological heterogeneity and limited sample sizes restricted the strength of conclusions. Emerging approaches involving extracellular vesicles and secretome-based therapies showed promising translational potential. Overall, stem cell–based therapies represent a biologically plausible and potentially effective treatment modality for TMJ disorders; however, high-quality randomized controlled trials with standardized outcome measures are required to confirm their long-term efficacy and safety.

KEY WORDS

Temporomandibular joint; Conventional therapeutic approaches; Stromal cells; Stem cell; Extracellular vesicles

ARTICLE HISTORY

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Introduction

The temporomandibular joint (TMJ) is a complex synovial articulation responsible for essential functions such as mastication, speech, and swallowing. Its unique anatomical configuration, characterized by fibrocartilaginous surfaces and a load-bearing articular disc, makes the TMJ particularly susceptible to biomechanical overload, microtrauma, and inflammatory insults [1,2]. Degenerative conditions affecting the TMJ, including osteoarthritis (TMJOA) and cartilage defects of the mandibular condyle, are frequently associated with pain, joint dysfunction, restricted mandibular movement, and progressive structural deterioration [3–5].

Articular cartilage damage in the TMJ represents a major clinical challenge due to the limited intrinsic regenerative capacity of cartilaginous tissue. This limitation is primarily attributed to the low proliferative activity of chondrocytes, the absence of vascularization, and reduced cellular turnover within the extracellular matrix [6]. When left untreated, cartilage lesions may progress toward degenerative joint disease, characterized by irreversible degradation of cartilage and subchondral bone remodelling, often accompanied by chronic inflammation and fibrosis [3–7].

Conventional therapeutic approaches for TMJ degenerative disorders include conservative management with analgesics, anti-inflammatory drugs, occlusal splints, physiotherapy, and minimally invasive procedures such as arthrocentesis and intra-articular injections of corticosteroids or hyaluronic acid [8–10]. Although these modalities may provide symptomatic relief, they do not address the underlying biological mechanisms responsible for cartilage degeneration and frequently fail to halt disease progression in advanced cases [11]. Surgical interventions, including arthroplasty, arthroscopy, and total joint replacement, are therefore required in severe conditions, but are associated with significant morbidity and economic burden [12].

In this context, regenerative medicine has emerged as a promising alternative aimed at restoring joint homeostasis by modulating inflammation and promoting tissue repair. Mesenchymal stem/stromal cells (MSCs) have gained considerable attention due to their multipotent differentiation capacity, immunomodulatory properties, and paracrine secretion of bioactive factors that regulate inflammation and extracellular matrix remodeling [13–15]. Experimental studies have demonstrated that MSCs may differentiate toward chondrogenic lineages and enhance cartilage repair through the secretion of growth factors, anti-inflammatory cytokines, and extracellular matrix components [16–18].

Preclinical investigations using different animal models have provided robust evidence supporting the therapeutic potential of MSCs in TMJ cartilage regeneration. Transplantation of bone marrow-derived MSCs embedded in platelet-rich plasma has been shown to induce regeneration of large, full-thickness cartilage defects in the mandibular condyle, resulting in restoration of the articular surface and subchondral bone without evidence of sclerosis [19].

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Similarly, human umbilical cord matrix-derived MSCs demonstrated significant anti-inflammatory and chondroprotective effects in rabbit models of TMJOA, with upregulation of cartilage-specific extracellular matrix markers and suppression of pro-inflammatory cytokines [20,21].

More recently, advances in cell priming strategies and biomaterial-based delivery systems have further enhanced the regenerative potential of MSCs. IFN-γ-primed MSCs exhibited superior immunomodulatory activity and cartilage regeneration capacity in TMJOA models, highlighting the importance of controlling the inflammatory microenvironment for successful joint repair [22]. In parallel, the development of injectable biomaterials, such as GelMA-based microspheres combined with MSCs and sustained-release growth factors, has demonstrated improved cartilage healing by facilitating cell retention, infiltration, and localized chondrogenic differentiation within TMJ defects [23].

Despite these encouraging findings, clinical evidence remains limited. A recent systematic review and meta-analysis of clinical trials involving intra-articular administration of autologous MSCs in TMJ disorders reported significant reductions in articular pain and improvements in maximum mouth opening; however, the overall quality of evidence was considered low, emphasizing the need for further well-designed studies [24]. Nonetheless, the cumulative preclinical and early clinical data strongly support the rationale for exploring MSC-based regenerative strategies as a biological alternative for the treatment of TMJ cartilage degeneration [25].

Materials and Methods

Study design

This study was conducted as a systematic review integrating clinical and preclinical evidence on stem cell–based therapies for temporomandibular joint disorders. In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The methodological protocol was developed a priori and predefined the research questions, search strategy, eligibility criteria, study selection process, data extraction procedures, and methods for quality assessment and evidence synthesis. The PRISMA 2020 checklist and flow diagram were used to ensure transparency and methodological rigor.

Research questions

The review was guided by structured research questions formulated according to the PICO framework:

Population (P)

Human patients diagnosed with temporomandibular joint disorders (TMDs) and/or experimental animal models of temporomandibular joint pathology.

Intervention (I)

Stem cell–based therapies, including mesenchymal stem cells (MSCs) derived from bone marrow, adipose tissue, umbilical cord, synovial fluid, or related cell-derived products (e.g., stromal vascular fraction, conditioned medium, exosomes).

Comparison (C)

Placebo, saline injection, conventional therapies, active comparators (e.g., hyaluronic acid, corticosteroids), or no treatment.

Outcomes (O)

- Primary outcomes: pain reduction (visual analog scale or equivalent) and functional improvement (maximum mouth opening, mandibular range of motion).
- Secondary outcomes: tissue regeneration, imaging or histological findings, biomarker modulation, and adverse events.

Literature search strategy

A comprehensive literature search was conducted using two electronic databases:

- PubMed/MEDLINE
- Google Scholar

The final search was performed on January 5, 2026, covering publications from January 2000 to December 2025. The selection of these databases was justified by the extensive biomedical indexing of PubMed/MEDLINE and the complementary coverage of grey literature provided by Google Scholar.

Search terms and Boolean strategy

The search strategy combined Medical Subject Headings (MeSH) and free-text terms using Boolean operators. The PubMed search strategy was as follows:

(temporomandibular joint OR TMJ OR TMD)

AND

(mesenchymal stem cells OR stem cell therapy OR MSC

OR adipose-derived stem cells OR bone marrow stem cells

OR umbilical cord stem cells)

AND

(pain OR VAS OR visual analog scale)

AND

(mouth opening OR range of motion OR mandibular movement)

A similar strategy was applied in Google Scholar, most relevant publications sorted by relevance.

Eligibility criteria

Inclusion criteria

Inclusion Criteria Studies were eligible if they met the following criteria:

- Investigated temporomandibular joint disorders in humans or animal models.
- Evaluated any form of stem cell–based therapy.
- Reported at least one clinical, functional, biological, or regenerative outcome.
- Included clinical trials, observational studies, case series (≥3 cases), animal studies, or systematic reviews.

Exclusion criteria

Studies were excluded if they:

- Did not involve temporomandibular joint pathology.
- Did not include stem cell–based interventions.
- Were exclusively in vitro.
- Were editorials, commentaries, or conference abstracts without full text.
- Provided insufficient data for outcome extraction.

Study selection followed a four-stage PRISMA workflow:

- Identification: Database searches and removal of duplicates.

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- Screening: Title and abstract screening by two independent reviewers.
- Eligibility: Full-text assessment against inclusion and exclusion criteria.
- Inclusion: Final selection by consensus.

Disagreements were resolved through discussion, with consultation of a third reviewer when necessary. The complete selection process is illustrated in the PRISMA 2020 flow diagram (Figure 1).

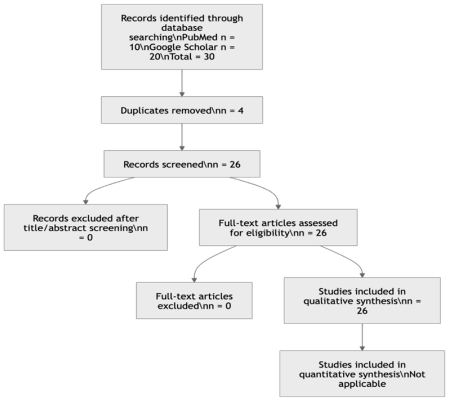

Figure 1. PRISMA 2020 flow diagram of study selection.

A standardized data extraction form was developed and pilot-tested. Extracted data included:

- Study characteristics (author, year, country, design).
- Population characteristics (species, diagnosis, severity).
- Stem cell source, processing method, and administration protocol.
- Comparator characteristics.
- Clinical, functional, histological, imaging, and biomarker outcomes.
- Adverse events and follow-up duration.

Data extraction was independently performed by two reviewers, with discrepancies resolved by consensus.

Quality assessment and risk of bias

Risk of bias was assessed using tools appropriate to the study design:

- Cochrane RoB 2 for randomized clinical trials.
- SYRCLE risk of bias tool for animal studies.
- AMSTAR 2 for systematic reviews.
- Newcastle–Ottawa Scale (adapted) for non-randomized studies and case series.

Quality assessments were conducted independently by two reviewers.

Data synthesis

Due to heterogeneity across study designs, interventions, and outcome measures, a narrative qualitative synthesis was primarily performed. Studies were grouped according to stem cell source, administration method, and outcome domain.

Where sufficient homogeneity existed, quantitative synthesis was considered using random-effects models to evaluate changes in pain scores and functional outcomes.

After application of the eligibility criteria and full-text screening, 26 studies met the inclusion criteria and were included in the qualitative synthesis. Narrative reviews and systematic reviews were retained when they contributed mechanistic insights or contextual interpretation supporting translational integration between experimental and clinical findings.

Certainty of evidence

The overall certainty of evidence for each outcome was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Ethical considerations

This study analyzed previously published data and did not involve direct experimentation in humans or animals. Therefore, ethical approval was not required.

Reporting standards

This systematic review adheres fully to PRISMA 2020 reporting standards, including the provision of a PRISMA checklist and flow diagram.

Methodological limitations

Potential limitations include restriction to two databases, heterogeneity of included studies, variable methodological quality, and possible publication bias.

Result

Overview of included studies

A total of 26 studies were included in the final qualitative synthesis. The general characteristics of the studies, including study design, population, stem cell source, intervention, comparator, follow-up, and primary outcomes, are summarized in Table 1.

A total of 26 studies were included in this review. Most were preclinical animal studies (38.5%), followed by clinical studies (23.1%) and narrative reviews (23.1%), while systematic reviews accounted for 11.5% and in vitro studies for 3.8%.

Regarding stem cell sources, bone marrow-derived mesenchymal stem cells were the most frequently investigated (26.9%), followed by adipose-derived stem cells (19.2%). Studies evaluating multiple MSC sources represented 23.1%, while secretome or extracellular vesicle-based approaches accounted for 11.5%.

Geographically, China contributed the largest number of studies (23.1%), followed by Egypt (11.5%), whereas several countries, including Italy, Brazil, and South Korea, each contributed 7.7% of the included publications (Figure 1).

Table 1. Summary of the included studies evaluating stem cell-based therapies for temporomandibular joint disorders, including study design, stem cell source, intervention characteristics, and primary outcomes.

Author / Year	Country	Study design	N	TMJ disorder	Stem cell type	Method	Follow-up	Main findings
De Riu et al. 2019	Italy	Randomized controlled clinical trial	30 patients (15 BMNc, 15 HA)	Degenerative TMJ disorders with internal derangement	Bone marrow cell concentrate	Arthrocentesis followed by intra-articular BMNc injection after lavage	12 m	BMNc superior: significantly greater pain relief at 6 months (p=0.028) and 12 months (p=0.000) and greater MMO at 6 months (p=0.001) and 12 months (p=0.000) compared with HA

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Khairy et al. 2019	Egypt	Prospective comparative clinical trial	30 patients (15 per group)	TMJ-OA	Adipose-derived stem cells (ADSCs)	Arthrocentesis followed by intra-articular injection of HA (Group I) or ADSC (Group II) [2]	18 m	ADSC group sustained improvement: Group II showed significant and sustained improvement across clinical parameters and CT-evidence of remodeling at 18 months; Group I had transient improvement not sustained; synovial TGF-B1 decreased significantly in Group II
Other clinical reports M Khalifah	Egypt	Clinical study	11 Pacients	TMJ disorders	Synovial fluid-derived MSCs	Combined with low level laser therapy in protocol	Insufficient evidence	Study reports improvement in pain and MMO with combined low level laser and synovial fluid-MSC therapy but numeric data and sample size not provided in abstract
Chęcinski et al. 2022	Poland	Systematic review and meta-analysis of clinical trials	Not applicable	TMJ articular pain and restricted MMO	Autologous MSCs	Intra-articular administration reported across included trials [4]	6 m	Pooled clinical signal: average articular pain decreased by =85% and MMO increased by >40% at 6 months; regression models reported AP relief = 5.8 - 0.8 In(x) (R2=0.90) and MMO increase = 33.5 + 2.4 In(x) (R2=0.89); included trials judged at high risk of bias
Köhnke et al. 2021	Germany	Randomized controlled animal trial (rabbit)	28 rabbits randomized to 4 groups (ABS, HA, MSCs, HA+MSCs)	Induced TMJ osteoarthritis model	GMP-compliant mesenchymal stromal	Single intra-articular injection (+ HA) four weeks after OA induction [5]	1 m / 2m	Chondroregenerative effect: STx and HA+STx groups had significantly increased cartilage thickness versus controls (HA+STx vs ABS p=0.028; HA+STx vs HA p=0.042; STx vs ABS p=0.036) indicating MSC-mediated cartilage regeneration in this rabbit OA model
Kim et al. 2019	South Korea	Animal / preclinical study	25 total (5 each gruop)	Monosodium iodoacetate-induced TMJ-AO	(hUCM-MSCs)	Intra-articular injection at different concentrations [6]	Follow-up not specified in abstract	Dose-dependent benefit: hUCM-MSCs showed anti-inflammatory and cartilage-regenerative effects at tested doses; median dose produced prominent cartilage protection and regeneration versus untreated controls and comparable anti-inflammatory effect to dexamethasone with unique chondrogenesis
Wang et al. 2021	China	Preclinical in vitro and in vivo study	Sample sizes not given in abstract (insufficient evidence)	TMJ-OA	Bone marrow MSC	Local injection of isolated BMSC-sEVs in animal OA models [7]	Follow-up not specified in abstract	Mechanistic regeneration: BMSC-sEVs promoted cartilage reconstruction, upregulated proliferative and chondrogenic markers, and acted via autotaxin-YAP signaling; effects lost after autotaxin knockdown/inhibition
Yang et al. 2024	China	Preclinical cell/EV study in rat TMD model	Sample size not provided in abstract	TMJ disc degeneration in TMD	Bone marrow MSC	Local intra-articular injection of BMSC-EVs [8]	Follow-up not specified in abstract	Protective effects: BMSC conditioned medium and BMSC-EVs reduced inflammation, promoted chondrogenesis, inhibited apoptosis and alleviated disc degeneration in vivo, suggesting translational potential

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Yang et al. 2022	China	Preclinical cartilage defect model (likely rodent)	Sample size not provided in abstract	TMJ cartilage defect/arthritis model	Bone marrow MSC	Injectable superwettable GelMA microspheres with BMSCs and sustained TGF-B release applied to defect site [9]	Experimental endpoint not specified in abstract	Accelerated cartilage repair: BMSC-coated GelMA microspheres exhibited rapid defect adhesion and sustained TGF-B delivery, promoting TMJ cartilage healing in defect model
Gomez et al. 2020	Country not specified in abstract	Preclinical transplantation study (large/full-thickness defect)	Sample size not provided in abstract (insufficient evidence)	Large/full-thickness TMJ cartilage defect model	Human MSC	Transplantation of MSC construct into defect site [10]	Follow-up not specified in abstract	Regeneration observed: MSC transplantation induced regeneration of large/full-thickness TMJ cartilage defects in the reported model
Ogasawara et al. 2020	Japan	Animal / preclinical study	Animal numbers not specified in abstract	TMJ-OA	Dental pulp stem cell	Local application of secretome in vivo; in vitro macrophage assays [11]	1 m / 2m	Multifaceted benefits: Dental pulp stem cell factors reduced inflammation, improved cartilage parameters and attenuated pain-related behaviors in experimental TMJOA models
Bousnaki et al. 2023	Greece	Preclinical rat chemically-induced TMJOA study	Group sizes unspecified in abstract	TMJ-OA	Dental pulp stem cell	Intra-articular application of secretome / cell lysate	1 m / 2m	Improved clinical and structural metrics: SECR reduced pro-inflammatory gene expression in vitro and improved pain behavior, food intake, weight, bone density, and histological repair in vivo at 4 and 8 weeks
AbuBakr et al., 2023	Egypt	Animal study (MIA-induced TMJ-OA)	Sample size not provided in abstract	Monoiodoacetate (MIA) induced TMJ osteoarthritis model	MSC	Intra-articular injections	Experimental follow-up not specified	Comparative therapeutic effect: Study compares microvesicle therapy with PRP in MIA model; reported differential effects on OA pathology though numeric details not provided in abstract
Pagotto et al., 2021	Brazil	Systematic review (narrative) of MSCs in TMJ-associated structures	Not applicable	TMJ disc and cartilage/osteochondral defects and OA	Mesenchymal stem cells	Various delivery methods across included studies	Not applicable	Consistent preclinical benefit, limited human data: MSC presence improved clinical, histological and morphological TMJ parameters in included studies but heterogeneity and small human sample sizes limit conclusions
Zhao & Xie, 2021	China / International	Narrative review on MSC-centered therapies for TMJOA	Not applicable	TMJ-OA	Multiple MSC sources	Reviews intra-articular injections, tissue engineering approaches and secretome /exosome strategies	Not applicable	Comprehensive overview:MSCs have chondrogenic, trophic and immunomodulatory actions and show potential but clinical evidence is limited and heterogeneous

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Jiang et al., 2024	International authors	Systematic review of preclinical MSC therapies for TMJ repair	23 preclinical studies encompassing 125 mice, 149 rats, 470 rabbits, 74 goats [16]	TMJ cartilage/osteochondral defects and OA models	MSCs, secretome	Varied delivery methods	Not applicable	Preclinical efficacy with reporting limitations: Majority of animal studies reported improved cartilage repair and pain-related behavior with MSC-based therapies, but risk of bias and reporting deficits were common
Kim et al., 2024	South Korea	Experimental in vitro and in vivo rat TMJOA study	Animal numbers not specified in abstract (insufficient evidence)	Rat TMJ osteoarthritis model	IFN-γ-primed human umbilical cord MSCs	Local injection of primed hUC-MSCs in vivo; in vitro macrophage polarization assays	Short-term post-treatment assessments including changes by 2 weeks reported in abstract snippets	Immunomodulatory benefit: IFN-γ priming enhanced MSC capacity to induce M2 macrophage polarization and reduced inflammation, with rapid pain improvement observed from 2 weeks post-treatment in the model
Zhang et al., 2025	China	Preclinical TMJOA study (mechanistic)	Sample size not reported in abstract (insufficient evidence)	TMJ osteoarthritis	ADSC-enriched adipose extract	Local application in TMJOA models reported	Experimental follow-up not specified	Antifibrotic effect: ADSC-enriched adipose extract attenuated cartilage fibrosis by inhibiting chondrocyte senescence in TMJOA models, indicating a potential therapeutic pathway
Cardoneanu et al. 2022	Romania	Narrative review on TMJ OA mechanisms and regenerative strategies	Not applicable	TMJ-OA	PRP, HA, MSCs and combinations	Reviews intra-articular and combinatory regenerative approaches	Not applicable	Contextual synthesis:PRP and MSCs are more often associated with cartilage/bone repair than HA; combinations may enhance restorative potential but findings are sometimes discrepant across studies
Bavaresco et al., 2020	Brazil	Narrative review of MSC interventions in TMJ	Not applicable	TMJ degenerative changes	Multiple MSC sources	Summarizes intra-articular and tissue engineering delivery strategies	Not applicable	Promising but sparse clinical evidence:MSC use improved TMJ parameters in the small number of studies identified, but heterogeneity and small sample sizes limit conclusions
Peng et al. 2023 [2]	Taiwan	Clinical trial (dish to human)	Insufficient evidence	TMJ-OA	hPRP/HA	Intra-articular injection	Insufficient evidence	hPRP/HA used in a translational clinical trial from dish to human for TMJ-OA treatment [2].
Gong et al. 2022 [14]	In vitro review	Review of in vitro human stem cell studies	Not applicable	TMJ-related structures (in vitro)	Multiple MSC sources	In vitro culture systems; scaffolds	In vitro indicators of tissue formation reported (qualitative)	In vitro evidence supports the regenerative potential of various human stem cells for TMJ structures, highlighting need for in vivo validation [14].
Lee et al. 2020 [13]	Review	Narrative review on exosomes	Not applicable	TMJ-OA	MSC-derived exosomes	Exosome delivery discussed	Exosomes reported to regenerate cartilage and bone in preclinical reports (qualitative)	MSC-derived exosomes are a promising cell-free approach for TMJ cartilage and bone regeneration [13].

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Lee et al. 2020 [13]	Review article	Narrative review	Not applicable	TMJ-OA	Multiple MSC sources + exosomes; adipose SVF	Various	Review summarizes structure and functional regeneration potential	MSC-centered therapies exert multiple mechanisms (chondrogenesis, immunomodulation) and are promising for TMJ-OA treatment, but limitations remain [11].
Sembronio et Al. 2021	Italy	Randomized controlled animal trial	pts (20 Control / 20 F	TMJ-AO	DSC-enriched adipose extrac	Arthocentesis + AH	Day; 30 Days; 6 mou	Preliminary results of this clinical trial show that the injection of microfragmented adipose tissue can significantly improve outcomes of pain and function compared with the standard treatment
Mahmmood & Shihab, 2019	Iraq	Clinical study	11 Pacients	TMJ disorders	AD-MSQ	Intra-articular injection	Insufficient evidence	Nanofat injection in TMJ showed therapeutic benefits, simplicity, safety, lack of significant side effects, and complication.

Distribution by study type

As shown in Figure 2, preclinical animal studies represented the predominant study design among the included articles, accounting for nearly half of the total evidence base. In contrast, randomized controlled trials and prospective clinical studies were comparatively limited, emphasizing the early-stage and predominantly translational nature of stem cell research in temporomandibular joint disorders (Table 2).

Table 2. Distribution of included studies by study type.

Study Type	n	%
Preclinical / animal studies	10	38.5%
Clinical studies / trials	6	23.1%
Narrative reviews	6	23.1%
Systematic reviews / meta-analysis	3	11.5%
In vitro studies	1	3.8%

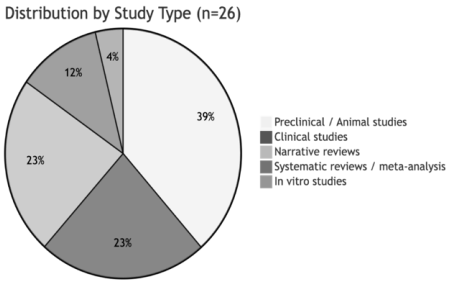

Figure 2. Distribution of included studies by study type: Pie chart showing relative proportions.

Distribution by stem cell source

Figure 3 demonstrates that bone marrow-derived mesenchymal stem cells were the most extensively investigated cell source, followed by adipose-derived stem cells and stromal vascular fraction preparations. These findings suggest a predominance of traditional mesenchymal stem cell sources, although newer regenerative approaches such as exosomes and scaffold-based therapies are gradually emerging in the literature (Table 3).

Table 3. Distribution of stem cell sources used in the included studies

Stem Cell Source	n	%
Bone marrow MSC / derivatives	7	26.9%
Adipose-derived MSC	5	19.2%
Dental pulp stem cells	2	7.7%
Umbilical cord MSC	2	7.7%
Synovial fluid MSC	1	3.8%
Secretome / extracellular vesicles	3	11.5%
Multiple / mixed sources	6	23.1%

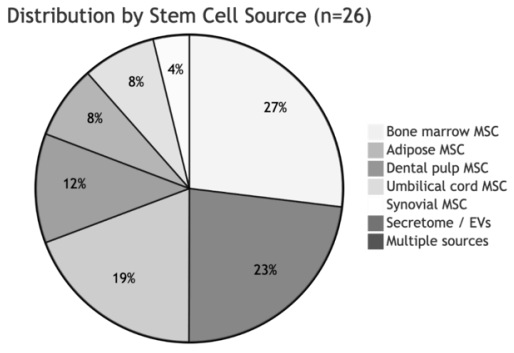

Figure 3. Distribution of included studies by stem cell source: Pie chart.

Geographical distribution of studies

Figure 4 highlights a marked geographical concentration of studies in Asia and Europe, which together accounted for more than 70% of the included literature. This regional predominance may reflect differences in regulatory frameworks, research funding, and institutional interest in regenerative therapies for temporomandibular joint disorders (Table 4).

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Table 4. Geographical distribution of included studies.

Country	n	%
China	6	23.1%
Egypt	3	11.5%
Italy	2	7.7%
Brazil	2	7.7%
South Korea	2	7.7%
Japan	1	3.8%
Poland	1	3.8%
Germany	1	3.8%
Greece	1	3.8%
Romania	1	3.8%
Iraq	1	3.8%
International / multi-country	5	19.2%

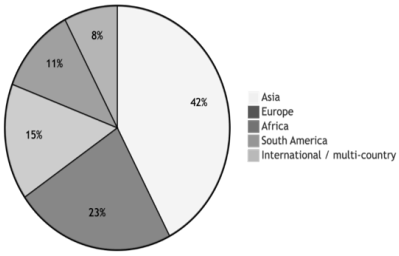

Figure 4. Geographical distribution of included studies: Pie chart.

Discussion

This systematic review synthesized evidence from 26 studies published between 2000 and 2026 investigating stem cell–based therapies for temporomandibular joint (TMJ) disorders [26]. The integrated analysis of clinical, preclinical, and translational studies demonstrated a consistent trend toward pain reduction, functional improvement, and structural or molecular indicators of joint repair following mesenchymal stem cell (MSC)–based interventions. However, the evidence base remains predominantly preclinical, with limited high-quality randomized clinical trials, underscoring the exploratory and evolving nature of this field [27–30].

Across study designs, intra-articular administration of MSCs or MSC-derived products emerged as the most common therapeutic approach, reflecting both anatomical accessibility of the TMJ and translational parallels with regenerative strategies used in other synovial joints [1–3].

The most robust quantitative clinical synthesis currently available is the systematic review and meta-analysis [4], which pooled data from five clinical studies involving 51 patients (69 TMJs). The authors reported an average reduction in articular pain of approximately 85% and an increase in maximum mouth opening exceeding 40% at six months following intra-articular administration of autologous MSCs. Regression modeling suggested a rapid initial response with gradual plateauing over time, indicating a characteristic temporal pattern of therapeutic effect [31,32].

Despite these encouraging findings, the certainty of evidence was limited by small sample sizes, inadequate randomization, lack of blinding, and short follow-up periods, resulting in a high overall risk of bias [4]. Consequently, while clinical outcomes appear promising, they must be interpreted cautiously until validated by adequately powered randomized controlled trials.

In contrast to the limited clinical data, preclinical studies demonstrated remarkable consistency across species and experimental models. A comprehensive preclinical systematic review [5] analyzed 23 animal studies involving approximately 800 animals and reported reproducible findings, including:

- restoration of articular cartilage thickness and histological organization,
- increased expression of chondrogenic markers such as collagen type II and aggrecan,
- reduction of synovial inflammation and pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), and
- improvement in pain-related behavioral outcomes.

These convergent results strongly support the biological plausibility of MSC-based therapies for TMJ disorders and provide a mechanistic foundation for clinical translation [5–7].

Conventional treatments for temporomandibular disorders, including hyaluronic acid injections, platelet-rich plasma, and corticosteroids, are primarily symptomatic and often provide modest or short-term relief. Comparative clinical data suggest that MSC-based therapies may offer superior and more sustained benefits [33–35].
based therapies for TMJ disorders and provide a mechanistic foundation for clinical translation [5–7].

The randomized clinical trial by De Riu et al. [8] demonstrated that bone marrow–derived nucleated cell concentrates were superior to hyaluronic acid in reducing pain and improving mouth opening at both six and twelve months. These findings suggest that regenerative approaches may address underlying joint pathology rather than merely alleviating symptoms.

Bone marrow–derived MSCs and adipose-derived stem cells accounted for the majority of studies included in this review, reflecting their accessibility and established clinical workflows [8–10]. Umbilical cord–derived MSCs, although largely investigated in preclinical settings, demonstrated potent anti-inflammatory and chondrogenic effects, comparable to pharmacologic anti-inflammatory agents in some models [11,12].

An emerging and particularly promising area involves cell-free therapies, such as MSC-derived exosomes and secretome. These products reproduce many of the paracrine effects of MSCs while offering advantages in terms of immunogenicity, storage, standardization, and regulatory scalability [13–15]. Their increasing representation in recent publications reflects a broader paradigm shift in regenerative medicine.

The therapeutic effects of MSC-based interventions are mediated primarily through paracrine and immunomodulatory mechanisms, rather than direct engraftment. MSCs secrete a wide range of bioactive molecules, including growth factors (TGF-β, IGF-1, FGF), anti-inflammatory cytokines (IL-10), and extracellular vesicles containing regulatory microRNAs [6,7,13].

- These mechanisms contribute to:
- suppression of inflammatory cascades,
- inhibition of matrix-degrading enzymes such as MMP-13,
- promotion of extracellular matrix synthesis, and
- modulation of nociceptive signaling pathways involved in chronic TMJ pain [6,14–16].

Recent studies also demonstrated that priming strategies, such as interferon-γ preconditioning, can enhance the immunomodulatory potency of MSCs, leading to superior therapeutic outcomes in TMJ osteoarthritis models [12].

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In clinical and preclinical studies, MSC-based therapies demonstrated a favorable short-term safety profile, with adverse events typically limited to local pain or swelling [4,8,9]. Serious complications, including infection or neoplastic transformation, were exceedingly rare or absent. However, long-term safety data beyond two years remain scarce, highlighting the need for extended follow-up and post-market surveillance [36-39].

This review has several limitations, the current evidence base is limited by heterogeneity in cell sources, processing methods, dosing, administration techniques, and outcome measures, which precludes robust quantitative synthesis. Furthermore, the predominance of small, non-randomized clinical studies limits causal inference and generalizability. Publication bias and geographical concentration of studies may further influence reported outcomes.

Future research should focus on:

- Large, multicenter randomized controlled trials with standardized outcome measures.
- Head-to-head comparisons of different stem cell sources and delivery strategies.
- Dose–response studies to establish optimal therapeutic protocols.
- Development and clinical translation of cell-free regenerative products.

Such efforts are essential to transition stem cell–based therapies for TMJ disorders from promising experimental interventions to evidence-based clinical practice.

Conclusion

Mesenchymal stem cell–based therapies show promise as a regenerative approach for the treatment of temporomandibular joint disorders. Preclinical studies consistently demonstrate anti-inflammatory, chondroprotective, and functional benefits, and strategies such as inflammatory priming and biomaterial integration may further enhance their therapeutic effects. Early clinical findings suggest improvements in pain and mouth opening; however, the current evidence is limited by methodological heterogeneity and risk of bias. Therefore, well-designed and standardized randomized clinical trials are needed to confirm the efficacy and safety of MSC-based therapies in temporomandibular joint disorders.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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