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A review of exosomes derived from mesenchymal stem cells as a treatment approach for temporomandibular disorders

Temporomandibular eklem bozukluklarında tedavi yaklaşımı olarak kullanılan mezenkimal kök hücre kaynaklı eksozomlar üzerine bir derleme

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ABSTRACT

Stem cell-based therapies are contemporary approaches that particularly involve the use of mesenchymal stem cells. Mesenchymal stem cells are multipotent precursors capable of differentiating from various cell sources, including adipocytes, myocytes, osteoblasts, and chondrocytes. They have self-renewal capabilities and possess properties that support hemostasis, reduce inflammation, modulate the immune response, and promote tissue regeneration. The paracrine activity of mesenchymal stem cells serves as a significant mechanism for their therapeutic efficacy. Recently, there has been a growing interest in the secretomes of mesenchymal stem cells which consist of growth factors, cytokines, chemokines, and extracellular vesicles. Extracellular vesicles are classified into two subtypes: ectosomes and exosomes. These secretions hold potential as innovative tools in regenerative medicine and dentistry for diagnosing, managing, and monitoring various diseases. This review focused on mesenchymal stem cells-derived exosomes and their potential as an alternative strategy for the therapeutic management of temporomandibular disorders. It also summarized the benefits and drawbacks associated with this treatment.

Keywords: Stem cell, exosome, temporomandibular joint, regeneration, inflammation

ÖZ

Kök hücre temelli uygulamalar, mezenkimal kök hücrelerin yaygın olarak kullanıldığı güncel tedavi yaklaşımlarıdır. Mezenkimal kök hücreler, yağ hücreleri, miyosit, osteoblast ve kondrositler dâhil olmak üzere çeşitli hücre kaynaklarından farklılaşabilen çok potansiyelli öncülerdir. Kendi kendilerini yenileyebilirler ve hemostaz, inflamasyon süreçleri, bağışıklık mekanizması, doku tamiri gibi birçok hücresel yanıtta rol oynarlar. Mezenkimal kök hücrelerin parakrin etkisi, terapötik etkinlikleri için önemli bir mekanizma görevi görür. Son dönemde, büyüme faktörleri, sitokinler, kemokinler ve hücre dışı veziküller gibi mezenkimal kök hücre kaynaklı sekretomlara artan bir ilgi mevcuttur. Bu sekretomlardan olan hücre dışı veziküller iki alt tipe ayrılır: ektozomlar ve ekzosomlar. Eksozomlar, rejeneratif tıp ve diş hekimliğinde çeşitli hastalıkların teşhisi, yönetimi ve takibi için yenilikçi araçlar olarak potansiyel taşımaktadır. Bu derlemede, mezenkimal kök hücre kökenli eksozomlar ve eksozomların, temporomandibular eklem bozukluklarının terapötik tedavisinde alternatif bir uygulama olarak potansiyelleri incelenmiştir. Ayrıca, bu tedavinin sunduğu faydalar ve olası dezavantajları da özetlenmiştir.

Anahtar Sözcükler: *Kök hücre, eksozom, temporomandibular eklem, yenilenme, inflamasyon*

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INTRODUCTION

The temporomandibular joint (TMJ) is a synovial joint formed by a diarthroidal connection between the mandibular fossa of the temporal bone and the head of the mandibular condyle (1, 2). It plays a crucial role in mastication through rotational and translational movements (2). The main components of the TMJ include the articular disc, articular capsule, innervating and vascular structures, ligaments, and the muscles involved in mastication (3).

The temporomandibular joint issues can arise from excessive mechanical loading on healthy articular cartilage or normal loading on damaged cartilage, leading to disc displacement and osteoarthritis. Additionally, age, gender and psychological stress are defined as contributions to temporomandibular disorders (TMDs) (4). Today, the exact etiology of the disease is clearly unknown.

Temporomandibular disorders encompasses a variety of conditions that affect the masticatory muscles, TMJ, and their related anatomical structures, each with distinct causes and clinical presentations. Common symptoms include clicking or popping sounds from the joint, often in the early stages, a limited range of motion and functionality, and orofacial pain (5).

Recent approaches to treating TMDs have increasingly focused on reducing inflammation, remodeling subchondral bone and cartilage, alleviating pain, and improving TMJ function (6). Various treatment methods have been developed over the years to achieve these goals. Current treatment options for temporomandibular disorders (TMD) vary widely. They include non-invasive techniques such as physical therapy and the use of occlusal splints (7,8). There are also minimally invasive procedures, like trigger point injections and arthrocentesis (9,10). In more severe cases, invasive therapies may be necessary (11), which can include total joint replacement. Additionally, stem cell-based therapies now offer a promising alternative for managing TMD conditions.

This review emphasizes the role of (MSCs)-derived exosomes and their effectiveness in structurally restoring damaged tissue, discussing their potential based on current literature.

Understanding Exosomes: Their Origins and Isolations

Over the past decade, researchers have rapidly advanced their understanding of the exosomes, as well as their physiological and pathological functions (12). Exosomes represent the most significant subcategory of extracellular vesicles (EVs) as an endosomal origin, which are membrane-derived vesicles released into the extracellular environment. These EVs were first identified in two studies published in 1983, where the authors described vesicles released from animal-origin reticulocytes into the extracellular space (13, 14). Initially, exosomes were considered cellular debris or garbage disposal, which were signs of cell death. However, extensive research conducted since their discovery has revealed important insights into exosome biology, function, and potential clinical applications (15-18).

These membrane vesicles are derived from specific cell types and exhibit similar therapeutic effects to those of their parent cells, including immunogenicity, inflammatory response, and regenerative capability (19). Mesenchymal stem cells-derived exosomes, as one of the parent cells, are particularly interesting for tissue engineering and regenerative medicine (20).

Mesenchymal stem cells produce multiple small EVs including apoptotic bodies, microvesicles, and exosomes (16). Exosomes are nanosized, measuring between 30 and 120 nanometers, sypherical, and have a lipid bi-layered membrane (21).

For isolating exosomes, several techniques can be utilized, including ultracentrifugation, ultrafiltration, immunoisolation, polymer-based precipitation, size exclusion chromatography, ion exchange chromatography, microfluidics-based technologies, and membrane-based isolation (21-24). Each method leverages specific characteristics, including size, shape, density, surface/membrane components, and ionic charges. Below are the details of the most commonly used methods:

- Ultracentrifugation, including differential ultracentrifugation and density-gradient ultracentrifugation, separates particles based on their density and size by using gradually increasing centrifugal force (25-26).
- Ultrafiltration separates molecules of specific sizes using a porous filter. Like ultracentrifugation, it relies on differences in particle size or molecular weight (27-28).
- Immunoisolation uses antibodies that target surface biomarkers on exosomes, thereby

isolating specific molecules in the loaded samples (29).

- Polymer-based precipitation refers to the ability of exosomes to accumulate at the base by decreasing their solubility in a salt or glycol solution (26).
- Size exclusion chromatography separates exosomes based on their size. Molecular separation occurs in a structure with pores of various sizes, while biofluids act as the mobile phase (27, 30).
- Microfluidic-based technologies integrate various methods to isolate exosomes from small-scale cell layers. This newly developed approach utilizes microfluidic chips with affinity, filtration, or electromagnetic waves (31-33).

These methods introduce the capability to extract exosomes from various sample matrices (24). Additionally, the combined use of these isolation methods has been documented in scientific research and technological advancements (32, 34) (*see 'What are the cons and pros?' for limitations of isolation methods*).

Therapeutic Potential of MSCs-Derived Exosomes

Before discussing the therapeutic effects of exosomes derived from MSCs, it is important to outline the pathogenesis of TMDs. These disorders impact the complex structures of cartilage, bone, and synovial tissue, particularly in cases of osteoarthritis. Inflammation plays a critical role in their pathogenesis, leading to elevated levels of inflammatory cytokines, such as interleukin-6 (IL-6), IL-8, and IL-1β. The increased expression of these cytokines contributes to cartilage degradation and inhibits the synthesis of the cartilage matrix, resulting in the upregulation of catabolic enzymes within the cartilage (35, 36). Tumour necrosis factor-alpha (TNF-α) (37) and several other proinflammatory cytokines, including IL-1, IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) are produced by dissociated synovial mononuclear cells. These cytokines can mutually regulate each other's effects during the inflammatory process, illustrating the complexity of their interactions in inflammation (37). Additionally, the disruption of metabolic homeostasis leads to an increased expression of matrix metalloproteinases (MMPs), which causes pathological changes in the structures of the TMJ (38, 39). Given this context, MSC-derived exosomes are anticipated to promote regeneration and prevent the degradation of the joint complex through their cellular content.

A diagram was included to schematically illustrate the local injection of exosomes into the articular cartilage (Figure-1).

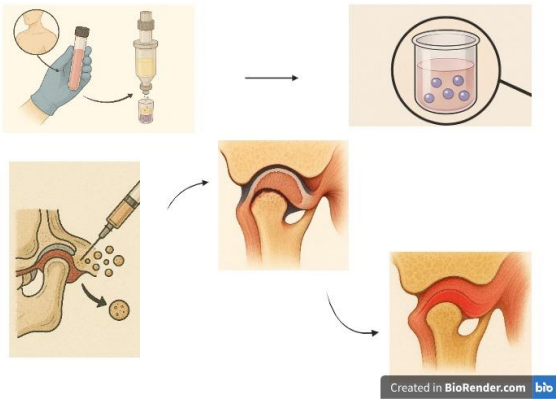

Figure-1. A diagram illustrates the preparation of exosomes and their intra-articular injection into the TMJ.

Despite variations in their surface marker profiles, contents, and sizes, exosomes share common properties, functions, and applications based on their specific origins. The regulatory mechanisms of MSC-derived exosomes, which underlie their paracrine activity, involve lipids, proteins, DNA, mRNA, and microRNA (miRNA) (40, 41). The expression of various non-coding RNAs in exosomes and their protein compositions enhances their functional roles and therapeutic effects (42). Among these RNA molecules, miRNAs are essential regulators of gene expression and play crucial roles in modulating inflammation, apoptosis, and tissue regeneration (43-45).

Exosomes derived from MSCs have the potential to significantly impact the development and progression of various diseases because they can transfer miRNAs to neighboring cells or circulate throughout the human body. By preconditioning MSCs in vitro before isolating the exosomes, these exosomes can be specifically designed to have immunosuppressive effects. This approach enables the treatment of inflammatory and autoimmune conditions in a cell-free manner (34, 40).

Liu et al. (2022) (46) reported that MSC-derived exosomes significantly promote the differentiation of M2 macrophages, a process that plays a crucial

role in the inflammatory response. These EVs exhibit high levels of miR-27b-3p expression, suggesting that MSC exosomes may regulate macrophages by targeting macrophage colony-stimulating factor-1 (CSF-1). Qui et al. (2020)(47) found that inhibiting cell apoptosis can be achieved by decreasing the DNA methylation of miR-143 and miR-124, providing evidence for the upregulation of these miRNA expressions by MSC-derived exosomes.

Some studies have shown that the miRNA profile of exosomes can be enhanced with various elements, which may yield positive results. Yuan et al. (2025) (48) investigated the effect of the strontium (Sr) element on exosomes and the selective loading of miRNA in synovial-based MSC exosomes. The results revealed that MSC-derived exosomes mitigated chondrocyte ferroptosis and reduced osteoclast-mediated joint pain in TMJ osteoarthritis, specifically by triggering the loading of miRNAs, including miR-143-3p.

Exosomes contain a higher concentration of functional enzymes and proteins than their parent cells including both large and small proteins, as well as signaling molecules, cytokines, interleukins, chemokines, and growth factors (49). The protein composition of exosomes reflects the physiological and pathological state of their host cells and can vary in response to stress and changes in the microenvironment (49). They can be modified genetic materials, at their surfaces and within their contents (15, 17). These factors contribute to reduce fibrosis, and to support tissue revascularization, and formation.

Mesenchymal stem cells -derived exosomes enhance the synthesis of the extracellular matrix, including type II collagen and sulfated glycosaminoglycans (s-GAG), thereby accelerating the filling of neoplastic tissue (50). Zhang et al. (2019) (51) reported that MSC exosomes improve s-GAG synthesis, which is inhibited by IL-1β, and suppress the production of nitric oxide and MMP13 induced by IL-1β. These effects can be partially reversed by inhibitors that target adenosine receptor activation, as well as those that inhibit AKT, ERK, and AMPK phosphorylation. In a comparative animal study (52), found that the group treated with MSC-derived exosomes exhibited a decrease in the levels of IL-1β, tumor necrosis factor-alpha (TNF-α), nuclear factor kappa B (NF-κB), MMP-13, and MMP-3, alongside an increase in collagen II gene expression.

Exposing MSCs to an inflammatory environment can enhance the functions of small EVs. To reduce TMD-mediated inflammation, Wang et al. (2021) (37) conducted in vivo and in vitro studies analyzing the cartilage reconstruction effect of MSC-derived exosomes. The results showed a downregulation in the expression of inflammatory cytokines, with researchers observing higher rates of cell proliferation and migratory activity in cartilage tissue. Additionally, autotaxin was detected in the BMSC-sEVs, and key proteins in the Hippo pathway, such as Yes-associated protein (YAP) and phosphorylated YAP (p-YAP), were found to be upregulated, indicating their importance in cartilage formation and regeneration.

Luo et al. presented findings on MSC-derived exosomes from human exfoliated deciduous teeth (SHED) concerning TMJ inflammation. They reported that treatment with SHED exosomes suppressed the expression of IL-6, IL-8, MMP-1, MMP-3, MMP-9, MMP-13, and disintegrin. Similarly, Yang et al. (2024) (53) observed that local injections of MSC-derived exosomes promoted the chondrogenic differentiation of TMJ disc fibroblasts while inhibiting apoptosis and inflammatory responses.

Conversely, some studies suggest that there may be differences in the inflammatory effects of these exosomes despite their regenerative properties (53-55). Bousnaki et al. (2023) (54) investigated dental pulp stem cell (SECR)-based exosomes for TMD treatment. They found that SECR application in vitro resulted in a significant downregulation of MMP-13, MMP-9, and MMP-3, while still maintaining higher levels of the inflammatory cytokines IL-6 and IL-10.

Moreover, MSC-derived exosomes promote tissue repair after mechanical injury. Zhou et al. (2024) (55) utilized urine-derived stem cell (USC)-based exosomes in a rat model, which indicated that these exosomes enhanced the structural integrity and smoothness of compromised condylar cartilage surfaces. They also exhibited inhibitory effects on osteoclastogenesis within the subchondral bone layer of the condylar cartilage and reduced apoptosis in the joint structure following mechanical injury.

Studies related to TMD management using MSC-derived exosomes have been summarized in Table-1.

Table-1. Studies on the use of exosomes derived from mesenchymal stem cells (MSCs) in the treatment of temporomandibular joint disorders (TMD)

Authors	Variables						
	Study Type	Study Design	Treatment Model	Source	Data	Future Perspective	Limitation
Liu et al. (2022)	in vitro/in vivo	Rabbit model: TMJ condylar osteochondral defect	Two independent group: Group 1 inflammation-stimulated ADSCs Group 2 ADSCs group	ADSCs MSC-derived exosomes	The number of cells migrating in the sEV-treated groups was significantly higher than in the control and scaffold groups, indicating that IAE has a stronger capacity to promote cell migration compared to AE.	Exposing MSCs to an inflammatory environment can effectively enhance the functions of sEVs. Additionally, modified sEVs yield improved therapeutic effects.	Preclinical study Lack of long-term treatment outcomes Utilized only one type of exosome cargo
Qui et al.(2020)	in vivo	Mouse model: OA	Four groups, Group1 SHAM group, Group 2 OA group, Group 3 OA + EXO group Group 4 aOA + EXO-CUR group	Exosomes derived from MSCs incubated with CUR	Exosomes derived from curcumin-treated mesenchymal stem cells (MSCs) were found to increase the expression of both miR-143 and miR-124. Exosomes obtained from curcumin-treated MSCs were shown to decrease the expression levels of ROCK1, TLR9, and NF-kB	The exosomes derived from curcumin-treated MSCs demonstrated a significant therapeutic effect on OA. TUNEL assays indicated that the apoptosis of OA cells was inhibited when these cells were treated with exosomes from curcumin-treated MSCs.	Preclinical study Lack of long-term treatment outcomes
Yuan et al. (2025)	in vivo	Rat model: creating unilateral anterior crossbite with metal tube to induce OA	Five group : Group 1 Sham, Group 2 TMJOA, Group 3 TMJOA+SMSC-EXOs Group 4 TMJOA+Sr-SMSC-EXOs Group 5 TMJOA+SiAlix-Sr-SMSC-EXOs.	Sr-enhanced SMSC-EXOs	The Sr-SMSC-EXOs group exhibited a smoother articular bone surface and a higher density of subchondral bone compared to the SMSC-EXOs group. The subchondral bone in the SiAlix-Sr-SMSC-EXOs group showed uneven morphology and had a lower density than that of the Sr-SMSC-EXOs group.	Treating SMSCs with Sr optimized the miRNA profile within exosomes. Sr-SMSC-EXOs were more effective in reducing chondrocyte ferroptosis and alleviating osteoclast-mediated joint pain compared to untreated SMSC-EXOs.	Preclinical study Utilized only one type of exosome cargo, Lack of long-term outcome data, A small sample size, Insufficient knowledge regarding subcondylar healing.

Zhang et al. (2019)	in vitro/ in vivo	in vitro model: Interleukin (IL)-1β-stimulation of chondrocytes to induce OA inflammation Rat model: MIA to induce OA	Forty six rats (92 TMJs) were randomly allo cated to three groups– Goup1 OA+PBS (16 rats), Group2 OA+Exosome (16 rats) Group 3 Sham (14 rats)	HESC-derived MSCs	Rats treated with OA+Exosomes exhibited significantly lower levels of genes associated with pro-inflammation (IL-1β), apoptosis (BAX), fibrosis (α-SMA), and pain (Substance P, CGRP, NGF, P75NTR, and TrkA) compared to those treated with OA+PBS. OA+Exosome rats experienced less pain, as indicated by higher HWT than the OA+PBS group, starting as early as two weeks after treatment. The pain was reduced to baseline and was similar to that of the sham group from week 5. The OA+PBS group showed minimal improvement in HWT scores across the duration of the experiment.	MSC exosomes can alleviate pain and promote repair in osteoarthritic TMJs by effectively reducing inflammation, enhancing proliferation, and facilitating matrix synthesis.	Preclinic al study Exosome source* Lack of long-term outcome data Insufficie nt knowled ge regardin g the healing of the soft tissue compone nt in TMJ
Wang et al. (2021)	in vivo/ in vitro	Rabbit model: chemical modelling with collagenase injection to induce OA	Four groups: Goup 1 control group (rabbits in the former control group treated with PBS), Group 2 OA group (rabbits in the former OA group treated with PBS), Group 3 sEV group (rabbits in the former control group treated with sEVs), Group 4 OAsEV group (rabbits in the former OA group treated with sEVs).	BMSC-sEVs	The migratory ability of the MSCs in the OA group was reduced compared to the control group. The migration of the MSCs in the sEV group was enhanced. The migratory ability of MSCs in the OAsEV group was greater than that observed in the OA group. The duration of treatment (12, 24, and 48 hours) did not affect these results.	BMSC-derived sEVs have the potential to promote cartilage reconstruction in osteoarthritis via the autotaxin-YAP signaling axis.	Preclinic al study Lack of long-term outcome data Additiona l analysis (mass spectrom etry, protein sequenci ng etc.) is needed for the Hippo pathway and its interactio ns with other pathways involved in the YAP mechani sm.

Yang et al.(2024)	In vivo	Rat model: disc degeneration	Three groups: Group1 control (n = 4), Group 2 perforation (n = 4), Group 3 EVs (n = 4) groups.	BMSC-EVs	Both the perforation and EV-treated perforation groups had significantly fewer cells around the perforation sites compared to the control group. EVs helped reduce apoptosis and significantly preserved TMJFBs.	BMSCs reduced inflammation and promoted chondrogenesis in TMJ disc fibroblasts. BMSC-derived EVs promoted the proliferation, migration, and chondrogenic differentiation of TMJ disc fibroblasts while inhibiting apoptosis and inflammatory responses. Local injection of BMSC-EVs into the TMJ model mitigated disc degeneration.	Preclinical study Lack of long-term outcome data Insufficient knowledge regarding the healing of the bony structures in TMJ
Zhou et al.(2024)	In vivo	Rat model: mechanical force to induce OA	Three groups: a sham experimental group (n = 7),a mouth-opening (MO) model group (n = 7), and a USC-EXO treatment group (n = 7)	urine-derived stemcell exosomes	A reduction in cartilage thickness in the MO group compared to the SHAM group. The USC-EXOs-treated group exhibited significantly greater cartilage thickness than the MO group.	USC-EXOs promote the recovery of cartilage thickness in the TMJ. USC-EXOs result in substantial reductions in TMJOA. USC-EXOs enhance the structural integrity and smoothness of the damaged condylar cartilage surface. USC-EXOs have inhibitory effects on osteoclast activity within the subchondral bone layer of the condylar cartilage and also reduce apoptosis in the TMJ.	Preclinical study Lack of long-term outcome data Insufficient knowledge about this exosome source

* The use of embryonic stem cells is restricted or prohibited in numerous countries. This limitation affects the reproducibility of studies.

Abbreviations: ADSC, adipose derived stem cell; IAE ,inflammation-stimulated adipose-derived MSC (ADSC)-derived sEV; HESC human embryonic stem cell-derived MSCs; HWT, head withdrawal threshold; BMSC-sEVs, Bone marrow mesenchymal stem cell (BMSC)-derived small extracellular vesicles; phosphate buffer saline (PBS); OA, osteoarthritis; EXO, exosome; CUR, curcumin; Sr, stronrium; SMSC, sinovial mesenchymal stem cell; PBS, phosphate-buffered saline; MIA, monosodium iodoacetate.

What are the Cons and Pros?

MSC-derived exosomes provide specific advantages for stem cell-based therapy, avoiding the drawbacks associated with their cellular counterparts. These advantages include improved targeting efficiency due to specific proteins, stability during freezing and thawing, and a relative lack of ethical concerns (50). There is considerable preclinical evidence supporting the ability of MSC-derived exosomes to repair joint damage and treat degenerative cartilage and bone structures through their dual secretory functions. Among the anti-inflammatory factors they help downregulate inflammatory markers such as TNF-α, MMP and IL. By reducing inflammation in the early stages, MSC-derived exosomes offer a promising approach for alleviating chronic pain caused by TMD (48). Additionally, the trophic factors, including various growth factors, promote cell proliferation, reduce scar tissue formation, and trigger the repair of

endogenous cartilage for TMDs. Furthermore, numerous studies have highlighted important aspects of MSC-derived exosomes that are relevant for practical applications and enhance their regenerative potential. One of these aspects is the method used to isolate these EVs. Currently, there is no universally accepted 'gold standard' method for exosome separation. All these methods used in literature share similar limitations when discerning particles with overlapping size ranges, such as microvesicles and exosomes (34). Particle size heterogeneity, low purity, and time-consuming applications requiring expensive equipment are among its main limitations. (21, 22) Notably, microfluidics-based techniques, which rely on the specific surface markers of EVs and utilize capture particles attached to different carriers, can effectively differentiate various good-quality exosomes. However, these methods may result in lower yields (15, 32) and are not suitable for large-scale applications (22). Additionally, the reproducibility of the method, the purity of the isolated material, and the size and concentration of the included particles contribute to exosome heterogeneity, which must be standardized to ensure their clinical applications (21, 22).

Exosomes are stable for long-term storage and transport (15) however; they have a short half-life, which can pose a challenge in reaching their target area to exert their effects (56). Although this disadvantage is less significant for local applications than for systemic ones, it is still essential to ensure that a sufficiently effective concentration of exosomes is maintained. This is important for the targeted delivery to the affected joint and adjacent tissues. For intraarticular injections, additional doses may be administered to boost the concentration; however, this approach can increase costs and the need for repeated injections (57), which may make the treatment less acceptable to patients. Additionally, the distribution and retention of exosomes can be affected by the surrounding microenvironment, which is typically marked by inflammation and changes in permeability. The properties of cell membranes and the components of the extracellular matrix may also hinder the internalization process in degenerative tissues, such as cartilage or bony structures of TMJ (58).

While exosomes have negligible risk of tumorigenesis and immune response (15), injection of these small EVs may lead to certain side effects. Some researchers reported erythamatous papule or nodules (59), skin necrosis (60), and granulomas (61) at the injection sites. There is a risk of allergic reactions to MSC-exosomes derived from individuals other than the recipient themselves. In synovial fluid, exosomes can negatively impact the expression of anabolic genes while promoting the expression of catabolic and pro-inflammatory genes in chondrocytes (62). Furthermore, these EVs have the potential to induce the formation and proliferation of osteoclasts, even in the absence of specific receptors on macrophages or monocytes (63). These findings suggest that the processes of osteogenesis and the initiation of the anti-inflammatory response by exosomes are influenced by the microenvironment at the injection site and the cell-to-cell communication associated with exosomes.

MSC-derived exosomes can differ in their molecular composition, including variations in miRNAs and proteomic profiles. These differences may be associated with the various sources from which MSC-derived exosomes are obtained (64). As a result, some exosomes may lack these potent regulatory molecules or may contain miRNAs with different functional roles (65). Altered levels of microRNA expression are linked to a decreased regenerative capacity of the exosomes (42). Given that the source of MSCs affects the function and characteristics of exosomes, it is important to acknowledge the inherent differences among exosomes derived from MSCs isolated from various cellular sources. These differences could significantly influence the therapeutic outcomes for TMDs.

CONCLUSION

The use of MSC-derived exosomes offers a promising approach for treating TMDs. This innovative method addresses degenerative joint disorders by utilizing the regenerative potential of MSCs. It has been shown to reduce cartilage degradation, promote the formation of significant fibrocartilaginous tissue or matrix, cell migration and proliferation, improvements in anti-inflammatory properties which leading to reduce pain outcomes.

However, there are some drawbacks to consider. Challenges in achieving therapeutic benefits include difficulties with the lack of a standardized method for separating exosomes from MSCs, ensuring effective concentration and release into the affected joint, potential side effects at the

injection site, and variations in the source of exosomes that could compromise their regenerative capacity.

Currently, the evidence supporting this treatment is limited; therefore, it is essential that preclinical studies are followed by clinical trials. Careful interpretation of existing data is essential, particularly regarding potential side effects, challenges, and limitations associated with this treatment. Future studies are anticipated to investigate various applications of MSC-derived exosomes in this area.

Conflicts of interest: Authors declared no conflict of interest.

References

1. Wang XD, Zhang JN, Gan YH, Zhou YH. Current understanding of pathogenesis and treatment of TMJ osteoarthritis. J Dent Res. 2015;94(5):666-73. https://doi.org/10.1177/0022034515574770
2. Almeida LE, Doetzer A, Beck ML. Immunohistochemical Markers of Temporomandibular Disorders: A Review of the Literature. J Clin Med. 2023;18:12(3):789. https://doi: 10.3390/jcm12030789.
3. Hill CN, Coombs MC, Cisewski SE, Durham EL, Bonthius DJ, Gardner GM, et al. Structure-function relationships of TMJ lateral capsule-ligament complex. J Biomech. 2022;130:110889. . https://doi.org/10.1016/j.jbiomech.2021.110889
4. Nickel, J. C., Iwasaki, L. R., Gonzalez, Y. M., Gallo, L. M., & Yao, H. Mechanobehavior and Ontogenesis of the Temporomandibular Joint. Journal of dental research. 2018;97(11):1185–92. https://doi.org/10.1177/0022034518786469
5. Schiffman, E., Ohrbach, R., Truelove, E., Look, J., Anderson, G., Goulet, J. P., et al. Orofacial Pain Special Interest Group, International Association for the Study of Pain. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group†. Journal of oral & facial pain and headache, 2014;28(1):6–27. https://doi.org/10.11607/jop.1151
6. González-Sánchez B, García Monterey P, Ramírez-Durán MDV, Garrido-Ardila EM, Rodríguez-Mansilla J, Jiménez-Palomares M. Temporomandibular Joint Dysfunctions: A Systematic Review of Treatment Approaches. J Clin Med. 2023;12(12):4156. https://doi.org/10.3390/jcm12124156.
7. Al-Moraissi EA, Farea R, Qasem KA, Al-Wadeai MS, Al-Sabahi ME, Al-Iryani GM. Effectiveness of occlusal splint therapy in the management of temporomandibular disorders: network meta-analysis of randomized controlled trials. Int J Oral Maxillofac Surg. 2020;49(8):1042-56. . https://doi.org/10.1016/j.ijom.2020.01.004.
8. Asquini G, Pitance L, Michelotti A, Falla D. Effectiveness of manual therapy applied to craniomandibular structures in temporomandibular disorders: A systematic review. J Oral Rehabil. 2022;49(4):442-55. . https://doi.org/10.1111/joor.13299.
9. Xu J, Ren H, Zhao S, Li Q, Li C, Bao G, et al. Comparative effectiveness of hyaluronic acid, platelet-rich plasma, and platelet-rich fibrin in treating temporomandibular disorders: a systematic review and network meta-analysis. Head Face Med. 2023;19(1):39. https://doi.org/10.1186/s13005-023-00369.
10. Hu Y, Zhang X, Liu S, Xu F. Ultrasound-guided vs conventional arthrocentesis for management of temporomandibular joint disorders: A systematic review and meta-analysis. Cranio. 2023;41(3):264-73. . https://doi.org/10.1080/08869634.2020.1829870.
11. Peres Lima FGG, Rios LGC, Bianchi J, Gonçalves JR, Paranhos LR, Vieira WA, et al.Complications of total temporomandibular joint replacement: a systematic review and meta-analysis. Int J Oral Maxillofac Surg. 2023;52(5):584-94. https://doi.org/10.1016/j.ijom.2022.10.009
12. Badawy AA, El-Hofey SM, Shaban AM, Orif SE, Uyanıkgil Y, El-Magd MA. Camel milk extracellular vesicles/exosomes: a fascinating frontier in isolation and therapeutic potential. Food Funct. 2025;20;16(2):344-365. https://doi.org/10.1039/d4fo04331f.
13. Pan B.T., Teng K., Wu C., Adam M., Johnstone R.M.x. Electron microscopic evidence for externalization of the transferrin receptor in vesicular form in sheep reticulocytes. J. Cell Biol. 1985;101(3):942–48. https://doi.org/10.1083/jcb.101.3.942

14. Harding C., Heuser J., Stahl P. Receptor-mediated endocytosis of transferrin and recycling of the transferrin receptor in rat reticulocytes. J. Cell Biol. 1983;97:329–39 https://doi.org/10.1083/jcb.97.2.329

15. Tan F, Li X, Wang Z, Li J, Shahzad K, Zheng J. Clinical applications of stem cell-derived exosomes. Signal Transduct Target Ther. 2024;9(1):17. https://doi.org/10.1038/s41392-023-01704-0.

16. Lotfy A, AboQuella NM, Wang H. Mesenchymal stromal/stem cell (MSC)-derived exosomes in clinical trials. Stem Cell Res Ther. 2023;14(1):66. https://doi.org/10.1186/s13287-023-03287-7.

17. Hade MD, Suire CN, Suo Z. Mesenchymal Stem Cell-Derived Exosomes: Applications in Regenerative Medicine. Cells. 2021;10(8):1959. https://doi.org/10.3390/cells10081959.

18. Ma CY, Zhai Y, Li CT, Liu J, Xu X, Chen H, et al. Translating mesenchymal stem cell and their exosome research into GMP compliant advanced therapy products: Promises, problems and prospects. Med Res Rev. 2024;44(3):919-38. https://doi.org/10.1002/med.22002.

19. Ren K. Exosomes in perspective: a potential surrogate for stem cell therapy. Odontology. 2019;107:271–84. https://doi.org/10.1007/s10266-018-0395-9.

20. Abid AI, Conzatti G, Toti F, Anton N, Vandamme T. Mesenchymal stem cell-derived exosomes as cell free nanotherapeutics and nanocarriers. Nanomedicine. 2024;61:102769. https://doi.org/10.1016/j.nano.2024.102769

21. Zhang Y, Bi J, Huang J, Tang Y, Du S, Li P. Exosome: A Review of Its Classification, Isolation Techniques, Storage, Diagnostic and Targeted Therapy Applications. Int J Nanomedicine. 2020;15:6917-34. https://doi.org/10.2147/IJN.S264498.

22. Kimiz-Gebologlu I, Oncel SS. Exosomes: Large-scale production, isolation, drug loading efficiency, and biodistribution and uptake. J Control Release. 2022;347:533-43. https://doi.org/10.1016/j.jconrel.2022.05.027

23. González-Cubero E, González-Fernández ML, Gutiérrez-Velasco L, Navarro-Ramírez E, Villar-Suárez V. Isolation and characterization of exosomes from adipose tissue-derived mesenchymal stem cells. J Anat. 2021;238(5):1203-17. https://doi.org/10.1111/joa.13365.

24. Ahmad P, Estrin N, Farshidfar N, Zhang Y, Miron RJ. Isolation methods of exosomes derived from dental stem cells. Int J Oral Sci. 2025;17(1):50. https://doi.org/10.1038/s41368-025-00370-y.

25. Coughlan C, Bruce KD, Burgy O, Boyd TD, Michel CR, Garcia-Perez JE, et al. Exosome Isolation by Ultracentrifugation and Precipitation and Techniques for Downstream Analyses. Curr Protoc Cell Biol. 2020;88(1):e110. https://doi.org/10.1002/cpcb.110.

26. Rahmatinejad F, Kharat Z, Jalili H, Renani MK, Mobasheri H. Comparison of morphology, protein concentration, and size distribution of bone marrow and Wharton's jelly-derived mesenchymal stem cells exosomes isolated by ultracentrifugation and polymer-based precipitation techniques. Tissue Cell. 2024;88:102427. https://doi.org/10.1016/j.tice.2024.102427.

27. Diaz G, Bridges C, Lucas M, Cheng Y, Schorey JS, Dobos KM, et al. Protein Digestion, Ultrafiltration, and Size Exclusion Chromatography to Optimize the Isolation of Exosomes from Human Blood Plasma and Serum. J Vis Exp. 2018;(134):57467. https://doi.org/10.3791/57467.

28. Altıntaş Ö, Saylan Y. Exploring the Versatility of Exosomes: A Review on Isolation, Characterization, Detection Methods, and Diverse Applications. Anal Chem. 2023;95(44):16029-48. https://doi.org/10.1021/acs.analchem.3c02224.

29. Yousif G, Qadri S, Parray A, Akhthar N, Shuaib A, Haik Y. Exosomes Derived Neuronal Markers: Immunoaffinity Isolation and Characterization. Neuromolecular Med. 2022;24(3):339-51. https://doi.org/10.1007/s12017-021-08696-6.

30. Sidhom K, Obi PO, Saleem A. A Review of Exosomal Isolation Methods: Is Size Exclusion Chromatography the Best Option? Int J Mol Sci. 2020;21(18):6466. https://doi.org/10.3390/ijms21186466.

31. Zhao L, Wang H, Fu J, Wu X, Liang XY, Liu XY, et al. Microfluidic-based exosome isolation and highly sensitive aptamer exosome membrane protein detection for lung cancer diagnosis. Biosens Bioelectron. 2022;214:114487. https://doi.org/10.1016/j.bios.2022.114487.

32. Skuratovskaia D, Vulf M, Khaziakhmatova O, Malashchenko V, Komar A, Shunkin E, et al. Exosome Limitations in the Treatment of Inflammatory Diseases. Curr Pharm Des. 2021;27(28):3105-21. https://doi.org/10.2174/1381612826666201210120444.

33. Wu Y, Wang Y, Lu Y, Luo X, Huang Y, Xie T, et al. Microfluidic Technology for the Isolation and Analysis of Exosomes. Micromachines (Basel). 2022;13(10):1571. https://doi.org/10.3390/mi13101571.

34. Padinharayil H, Varghese J, Wilson C, George A. Mesenchymal stem cell-derived exosomes: Characteristics and applications in disease pathology and management. Life Sci. 2024;342:122542. https://doi.org/10.1016/j.lfs.2024.122542.

35. Chu WC, Zhang S, Sng TJ, Ong YJ, Tan WL, Ang VY, et al. Distribution of pericellular matrix molecules in the temporomandibular joint and their chondroprotective effects against inflammation. Int J Oral Sci. 2017;9(1):43-52. https://doi.org/10.1038/ijos.2016.57.

36. Qiao Y, Li J, Yuh C, Ko F, Mercuri LG, Alkhudari J,et al. Chemokine Regulation in Temporomandibular Joint Disease: A Comprehensive Review. Genes (Basel). 2023;14(2):408. https://doi.org/10.3390/genes14020408.

37. Wang Y, Zhao M, Li W, Yang Y, Zhang Z, Ma R, et al. BMSC-Derived Small Extracellular Vesicles Induce Cartilage Reconstruction of Temporomandibular Joint Osteoarthritis via Autotaxin-YAP Signaling Axis. Front Cell Dev Biol. 2021;9:656153. https://doi.org/10.3389/fcell.2021.656153.

38. Ferreira LM, Moura ÁF, Barbosa GA, Pereira HS, Dos Santos Calderon P. Do matrix metalloproteinases play a role in degenerative disease of temporomandibular joint? A systematic review. Cranio. 2016;34(2):112-7. https://doi.org/10.1179/2151090314Y.0000000034.

39. Nascimento GC, De Paula BB, Gerlach RF, Leite-Panissi CRA. Temporomandibular inflammation regulates the matrix metalloproteinases MMP-2 and MMP-9 in limbic structures. J Cell Physiol. 2021;236(9):6571-80. https://doi.org/10.1002/jcp.30341.

40. Asgarpour K, Shojaei Z, Amiri F, Ai J, Mahjoubin-Tehran M, Ghasemi F, et al. Exosomal microRNAs derived from mesenchymal stem cells: cell-to-cell messages. Cell Commun Signal. 2020;18(1):149. https://doi.org/10.1186/s12964-020-00650-6.

41. Luo P, Jiang C, Ji P, Wang M, Xu J. Exosomes of stem cells from human exfoliated deciduous teeth as an anti-inflammatory agent in temporomandibular joint chondrocytes via miR-100-5p/mTOR. Stem Cell Res Ther. 2019;10(1):216. https://doi.org/10.1186/s13287-019-1341-7.

42. Chamberlain CS, Prabahar A, Kink JA, Mueller E, Li Y, Yopp S, et al.Modulating the mesenchymal stromal cell microenvironment alters exosome RNA content and ligament healing capacity. Stem Cells. 2024;42(7):636-49. https://doi.org/10.1093/stmcls/sxae028.

43. Lei Z, Chen X, Chen K, Liu P, Ao M, Gan L, et al. Exosome-like vesicles encapsulated with specific microRNAs accelerate burn wound healing and ameliorate scarring. J Nanobiotechnology. 2025;23(1):264. https://doi.org/10.1186/s12951-025-03337-7.

44. Yang X, Zhang S, Lu J, Chen X, Zheng T, He R, et al. Therapeutic potential of mesenchymal stem cell-derived exosomes in skeletal diseases. Front Mol Biosci. 2024;11:1268019. https://doi.org/10.3389/fmolb.2024.1268019.

45. Xu Y, Wei C, Ma L, Zhao L, Li D, Lin Y, et al. 3D mesenchymal stem cell exosome-functionalized hydrogels for corneal wound healing. J Control Release. 2025;380:630-46. https://doi.org/10.1016/j.jconrel.2025.02.030.

46. Liu Y, Zhang Z, Wang B, Dong Y, Zhao C, Zhao Y, et al. Inflammation-Stimulated MSC-Derived Small Extracellular Vesicle miR-27b-3p Regulates Macrophages by Targeting CSF-1 to Promote Temporomandibular Joint Condylar Regeneration. Small. 2022;18(16):e2107354. https://doi.org/10.1002/smll.202107354.

47. Qiu B, Xu X, Yi P, Hao Y. Curcumin reinforces MSC-derived exosomes in attenuating osteoarthritis via modulating the miR-124/NF-kB and miR-143/ROCK1/TLR9 signalling pathways. J Cell Mol Med. 2020;24(18):10855-65. https://doi.org/10.1111/jcmm.15714.

48. Yuan W, Liu J, Zhang Z, Ye C, Zhou X, Yi Y, et al. Strontium-Alix interaction enhances exosomal miRNA selectively loading in synovial MSCs for temporomandibular joint osteoarthritis treatment. Int J Oral Sci. 2025;17(1):6. https://doi.org/10.1038/s41368-024-00329-5.

49. Deng H, Sun C, Sun Y, Li H, Yang L, Wu D, et al. Lipid, Protein, and MicroRNA Composition Within Mesenchymal Stem Cell-Derived Exosomes. Cell Reprogram. 2018;20(3):178-86. https://doi.org/10.1089/cell.2017.0047.

50. Lee YH, Park HK, Auh QS, Nah H, Lee JS, Moon HJ, et al. Emerging Potential of Exosomes in Regenerative Medicine for Temporomandibular Joint Osteoarthritis. Int J Mol Sci. 2020;21(4):1541. https://doi.org/10.3390/ijms21041541.

51. Zhang S, Teo KYW, Chuah SJ, Lai RC, Lim SK, Toh WS. MSC exosomes alleviate temporomandibular joint osteoarthritis by attenuating inflammation and restoring matrix homeostasis. Biomaterials. 2019;200:35-47. https://doi.org/10.1016/j.biomaterials.2019.02.006.

52. AbuBakr N, Haggag T, Sabry D, Salem ZA. Functional and histological evaluation of bone marrow stem cell-derived exosomes therapy on the submandibular salivary gland of diabetic Albino rats through TGFβ/ Smad3 signaling pathway. Heliyon. 2020;6(4):e03789. https://doi.org/10.1016/j.heliyon.2020.e03789.

53. Yang Y, Li J, Xia Z, Tang B, Li Y. Mesenchymal stem cells-derived exosomes alleviate temporomandibular joint disc degeneration in temporomandibular joint disorder. Biochem Biophys Res Commun. 2024;726:150278. https://doi.org/10.1016/j.bbrc.2024.150278.

54. Bousnaki M, Bakopoulou A, Grivas I, Bekiari C, Pich A, Rizk M, et al. Managing Temporomandibular Joint Osteoarthritis by Dental Stem Cell Secretome. Stem Cell Rev Rep. 2023;19(8):2957-79. https://doi.org/10.1007/s12015-023-10628-9.

55. Zhou JP, Peng SS, Xu J, Cheng XW, Wang XH, Tao JL, et al. Exploring the therapeutic potential of urine-derived stem cell exosomes in temporomandibular joint osteoarthritis. FASEB J. 2024;38(15):e23852. https://doi.org/10.1096/fj.202400448RR.

56. Tzng E, Bayardo N, Yang PC. Current challenges surrounding exosome treatments. Extracell Vesicle. 2023;2:100023. https://doi.org/10.1016/j.vesic.2023.100023.

57. Köhnke R, Ahlers MO, Birkelbach MA, Ewald F, Krueger M, Fiedler I, et al. Temporomandibular Joint Osteoarthritis: Regenerative Treatment by a Stem Cell Containing Advanced Therapy Medicinal Product (ATMP)-An In Vivo Animal Trial. Int J Mol Sci. 2021;22(1):443. https://doi.org/10.3390/ijms22010443.

58. Chen, YF., Luh, F., Ho, YS. et al. Exosomes: a review of biologic function, diagnostic and targeted therapy applications, and clinical trials. J Biomed Sci 2024;31(1):67. https://doi.org/10.1186/s12929-024-01055-0

59. Nahm, W.J., Thunga, S. and Yoo, J.Complications After Exosome Treatment for Aesthetic Skin Rejuvenation. Dermatological Reviews, 2024;5: e242. https://doi.org/10.1002/der2.242

60. Tawanwongsri W, Vachiramon V. Skin necrosis after intradermal injection of lyophilized exosome: A case report and a review of the literature. J Cosmet Dermatol. 2024;23(5):1597-603. https://doi.org/10.1111/jocd.16206.

61. Choi H, Kwak JH, Shin BS, Na CH, Kim MS. Foreign body granuloma caused by an injection of exosomes. JAAD, 2024

62. Kolhe R, Hunter M, Liu S, Jadeja RN, Pundkar C, Mondal AK, et al. Gender-specific differential expression of exosomal miRNA in synovial fluid of patients with osteoarthritis. Sci Rep 2017;7(1): 2029. http://dx.doi.org/10.1038/s41598-017-01905-y

63. Song JE, Shin JH, Moon KW, et al. AB0070 A role of rynovial exosomes in Osteoclast differentiation of inflammatory arthritis. Ann Rheum Dis 2016;75: 921-1.

64. Chen J, Tan Y, Chen Z, Yang H, Li X, Long X, et al. Exosomes derived from primary cartilage stem/progenitor cells promote the repair of osteoarthritic chondrocytes by modulating immune responses. Int. Immunopharmacol. 2024; 2024;143(Pt2):113397. http://dx.doi.org/10.1016/j.intimp.2024.113397

65. Wang Z, Hu Z, Niu L, Xu Y, Qi Y. Mesenchymal stem cell-derived exosomes for the treatment of knee osteoarthritis: a systematic review and meta-analysis based on rat model. Front Pharmacol. 2025;16:1588841. http://dx.doi.org/10.3389/fphar.2025.1588841.