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# Potential therapeutic applications of mesenchymal stem cells in the oral and maxillofacial tissues

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**Abstract. – Over the past decades, we have noted that the study of stem cells is of interest to scientists because it offers great promise for the development of cell-based therapies and establishes basic models for studying the pathogenesis of diseases, overcoming all the challenges it encounters. The majority of craniofacial tissues are derived from mesenchymal tissues, so it makes the mesenchymal stem cells (MSCs) an attractive candidate for regenerating damaged or diseased craniofacial structures. Mesenchymal stem cells (MSCs) do not have the same obstacles as embryonic stem cells. Mesenchymal stem cells can be used to conduct research and treat diseases, as they do not require embryonic destruction. MSCs possess unique properties such as self-renewal, the ability to differentiate into different cell types, and the modulation of immune cells. The present review article provided an overview of MSCs isolated from both nondental and dental tissues and highlighted the available information regarding the significant progress in both experimental and clinical trials of MSCs and their potential therapeutic application in the oral and maxillofacial regions. This review sheds light on the experimental research and clinical applications that have led to the development of new MSCs therapies for a variety of diseases. Moreover, we have highlighted the experiments that proved that MSCs are an effective tool for tissue regeneration in the oral and craniofacial regions. This could pave the way for scientists to improve the surgical methods of oral and maxillofacial and treatment of craniofacial malformations.**

*Key Words:*
Stem cell types and sources, Mesenchymal stem cells, Regenerative medicine, Regeneration of oral-maxillofacial tissues, TMJ, Salivary glands, Oral mucous membrane, Dental pulp, Periodontium.

## Introduction

Regenerative medicine is a rapidly evolving interdisciplinary field concerned with the therapeutic application of biological materials to degenerated tissues and organs in order to restore their structure and function. Tissue regeneration achieves clinical efficacy by utilizing tissue grafting, cell implantation, and structured scaffolds[1].

Stem cells in regenerative medicine are a method of choice due to their ability to self-renew and their proliferation and differentiation to diverse types of cell lineage, so they are able to restore degenerated tissues and organs[2].

## Basic Principles of MSC Therapy

### Stem Cells Sources and Classifications

Types of stem cells according to their differentiation potential are totipotent, pluripotent, multipotent, uni-potent, and oligo potent. Also, regarding their origin, there are 4 main types: embryonic, fetal, infantile, and adult[3].

### Classification of Stem Cells According to Their Differentiation Potential

The totipotent state of stem cells refers to their ability to differentiate and produce all adult cell types. They differentiate into both embryonic and extraembryonic cell types. Totipotent stem cells can be extracted from the fertilized eggs *in vitro* fertilization[4].

The pluripotent is the capacity of stem cells to differentiate into almost all cell types extracted from the early embryo's three primary germ cell


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layers. Many distinctions between pluripotent stem cell types have been identified, including gene expression profiles, morphology, and required growth factors[5].

When the stem cells are able to specialize into a closely related cell family, this will be referred to as multipotency. Examples of multipotent cells are mesenchymal stem cells that can produce a mesenchymal type of cells, hematopoietic stem cells that specialize in various neural stem cells, and blood cells which differentiate into astrocytes, and neurons[6].

Unipotent is the ability to produce a limited number of cells of their own type. Due to their constrained lineage, they are considered to be either multipotent, as they can produce a limited range of cells, or unipotent, with the capability to produce only 1 type of cell. Skin cells are the most plentiful type of unipotent stem cells[7].

Oligopotent stem cells: these cells can differentiate into a limited number of cell types, like cells comprising the lymphoid system[8].

## Classification of Stem Cells According to Their Origin

The origin of stem cells is divided into two wide categories. The first is the prenatal type, which includes embryonic and fetal stem cells. The second is postnatal stem cells, which include infant and adult stem cells.

Embryonic stem cells (ES cells) are extracted from the inner cell mass of the blastocyst. The embryos are three to five days old. These cells have a high capacity for regenerative medicine because they can differentiate into almost any cell or tissue[9].

Fetal stem cells are cell types present in the fetus's organs. They can produce 2 types of stem cells: hematopoietic and pluripotent[10].

### Infant stem cell

Umbilical cord ones: the blood of the umbilical cord contains stem cells that differ from those derived from bone marrow and adult peripheral blood as the umbilical cord contains a high concentration of hematopoietic stem cells, which can be used to rebuild the blood system. Recently, umbilical cord stem cells, which have been shown[11] to be multipotent, have the ability to produce non-hematopoietic cells such as osteogenic, nerve, and endothelial cells.

Adult stem cells are postnatal ones that are present in a lot of tissues and organs. They achieve self-renewal and differentiation to keep the tissues healthy and restore their damage. When compared to embryonic stem cells, adult stem cells have a more limited capacity to give rise to various cells of the body[12].

Adult stem cells can be extracted from different types of tissues, such as bone marrow, the central nervous system, the retina, skeletal muscle, and dental tissues. The application of adult stem cells in research and treatment does not necessitate embryonic destruction, so, it does not show obstacles like embryonic stem cells. Furthermore, there is essentially no risk of tissue rejection in these situations, as adult stem cells are sometimes available from the recipient (autologous graft) of interest[13].

Induced pluripotent stem (iPS) cells are pluripotent stem cells that have been derived from adult somatic cells. They have been reprogrammed by inducing genes and transcription factors to be pluripotent[14].

## Stem Cells from Dental Sources

Stem cells obtained from dental sources have displayed massive potencies that share in a variety of tissue regenerative capabilities.

Dental stem cells can be isolated from multiple sources, e.g., human shed primary teeth (SHED)[15], alveolar bone mesenchymal stem cells[16], periodontal ligament stem cells (PDLSCs)[17], dental sac precursor cells[18], stem cells from apical papilla (SCAP)[19], and gingiva tissue (GSCs)[20].

The most significant advantages of stem cells from the oral and maxillofacial regions are their high degree of plasticity, their utility as stem cell banking because they can be cryopreserved for a very long period of time, their interaction with scaffold and growth factors, and that they offer a promising source of autologous cells[21].

## Stem Cell Niche

The stem cells niche was first proposed as a unique specific microenvironment required for the maintenance of "stemness", also, signals are released by supporting cells[22]. The stem cell niche is thought to provide a complex array of physical signals to stem cells in a temporal and spatial manner. Cell-matrix adhesions, cell-cell contacts, and biochemical signals such as growth factors are examples of physical signals. Stem cell niche is important in regulating tissue homeostasis and enhancing tissue regeneration to restore damaged tissues and rehabilitates their function, in addition to regulating the survival, self-renewal, and differentiation of stem cells[23]. The nature and location of stem cell niches differ depending on the tissue type. Many adult organs and tissues

contain stem cell niches, including bone marrow (which serves as the primary reservoir for many types of stem cells), blood vessels, skin, teeth, peripheral blood, heart, gut, liver, ovarian epithelium, brain, skeletal muscle, and testis. The bone marrow is crucial under steady-state conditions. This is critical for maintaining niche and stem cell fitness and ensuring a dynamic balance[24].

Shi and Gronthos[25] demonstrated that stem cells of dental pulp fiber nerves are restricted to their perivascular region and the perineurium, while they are not present in the odontoblastic layer and surrounding fibrous tissue. Similarly, damage to dental pulp tissue will attract the stem/progenitor cells located in perivascular areas to the injury site[26].

## Mesenchymal Stem Cells

Mesenchymal stem cells are non-hematopoietic adult stem cells that were initially isolated from bone marrow but now can be isolated from nearly all tissues in the body, including dental and oral tissues, amniotic fluid, placenta, umbilical cord, endosteum, adipose tissue, joint synovium, synovial fluid, and periosteum. They have immunomodulatory properties, as well as the capacity for self-renewal and differentiation into many cell strains. All of these features make them an appealing source for regenerative therapies depending on new generations of stem cells[25,26].

### *Mesenchymal Stem Cells Surface Markers*

MSC isolation is also influenced by biological properties like its ability to form colonies, colony-forming unit fibroblasts (CFUFs), its plastic adherence, its higher proliferative ability, self-renewal, and capacity to produce many types of cells.

The International Society for Cellular Therapy (ISCT) has identified a set of cell surface markers that must be expressed or absent in MSCs as one of the minimal requirements for human MSC (hMSC) identification. The expressed markers are CD105, CD90, CD73, while human leukocyte antigen (HLA)-DR and CD11b, CD14, CD19, CD34, CD45, CD79a, are not. Ullah et al[27] published a more specific combination of markers to identify MSCs according to their tissue of origin.

Adipose tissue: the positive surface markers are CD13, CD29, CD44, CD71, CD73, CD90, CD105, CD166, STRO-1 while the negative surface markers are CD14, CD31, CD34, CD45.

Bone marrow: the positive surface markers are CD73, CD90, CD105, CD106, CD146, STRO-1, While the negative surface markers CD14, CD34, CD45, HLA-DR

Dental pulp: the positive surface markers are CD29, CD44, CD90, CD105 while the negative surface marker is CD45, CD34, CD14,

Peripheral blood: the positive surface markers are CD44, CD90, CD105, HLA ABC, while the negative markers are CD133, CD45.

Skin: the positive surface markers are Vimentin, CD44, CD90, CD166, SSEA-4, CD105, CD73, While the negative markers are CD34, CD45, HLA-DR[28].

## Biological Properties of MSCS Stem Cell Culture

### *Homing of MSCs*

As stem cells circulate in the blood, after certain stimuli, they leave their niche and migrate to an injured site or organ, where they can initiate their differentiation program and speed up the regeneration process under certain microenvironmental conditions[29].

Several studies[30,31] have demonstrated that MSCs migrate into the injured organ, differentiate into target cells, and then participate in regenerative procedures. Such cases have been documented in the fields of cartilage, muscle, cardiac, and bone regeneration. Furthermore, they emigrate across the forebrain and cerebellum without interfering with the host brain architecture. When the stem cells come to homing, it is widely assumed that they follow the same steps as leukocytes. In the first step, tethering and rolling will enable the cells to contact the endothelium, causing the cells to decelerate in the blood flow. G-protein-coupled receptors activate the cells in the second stage, followed by an integrin-mediated, activation-dependent arrest in the third stage. Finally, the cells migrate through the endothelium and the underlying basement membrane in the fourth step[32].

### *MSCs Differentiation and Plasticity*

The term stem cell plasticity has been coined to describe how stem cells from one tissue appear to have "differentiated or transdifferentiated to produce progeny of another tissue". Furthermore, plasticity can be defined as stem cells' ability to self-renew and differentiate into multiple tissue lineages under the influence of local environmental factors and is thus also

known as transdifferentiation.

MSCs can be expanded in culture without losing their differentiation potential, forming an infinite pool of transplantable cells. They can differentiate and trans-differentiate, which has a direct impact on stem cell plasticity. They have the ability to differentiate into a variety of cell types like chondroblasts, odontoblasts, fibroblasts, osteoblasts, cementoblasts, and adipocytes[33].

### Autocrine and Paracrine Mechanisms in Stem Cell Maintenance

The functional improvements obtained by stem cells occur mostly as a result of paracrine actions in the host tissue, not due to cell differentiation and repopulation. Notably, bone marrow BM-MSCs are known to secrete functional autocrine secretions of bioactive factors that can have significant effects on local cellular dynamics, as well as paracrine biological factors like cytokines, vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2) and phosphatidylinositol-glycan biosynthesis class F protein (PIGF)[34].

Adult MSCs may have a remedial effect *via* paracrine-mediated mechanism, and proteins secreted by MScs have been shown[35] to be antimicrobial, antifibrotic, and prodegenerative, with effects on certain processes such as angiogenesis, immunomodulation, and tissue differentiation and regeneration.

### Immune Modulation by MSCs

MSCs have immunomodulatory and immunosuppressive properties that inhibit immune cell activation and proliferation[36].

MSCs have been proposed to have therapeutic ability for many human immunological disorders. To avoid self-attack, they may promote inflammation when the immune system is under-activated and suppress inflammation when the immune system is over-activated. This activity is also known as the immune system's "sensor and switcher". To obtain the maximum advantages of MSC-dependent immune regulation while minimizing patient risks, all potential side effects of MSC use must be carefully considered when selecting the tissue origin, cell dose, administration route, and treatment schedule of MSC[37].

## Application of Mesenchymal Stem Cells

Stem cell therapy seeks to repair damaged tissue that is unable to heal on its own. It is critical to maintain ongoing research processes on stem cell therapies so that patients can not only reduce the symptoms of their chronic diseases but also receive standard treatment to cure their illness. Stem cell-based therapies can be performed by simply implanting stem cells into the body and instructing them to develop new, healthy tissue, and they can now work by convincing stem cells already in the body to collaborate and grow new tissues[38].

When stem cells are used in tissue regeneration, two important goals must be met: first, injured tissue should be repaired efficiently and second is the biocompatible scaffolds without immunological reactions. MSCs are regarded as an important source for cell and gene therapy applications in congenital disorders and destructive diseases due to their higher proliferation ability, differentiation into multiple cell lineages, and immune regulation effects[39].

## Clinical Application of Mesenchymal Stem Cell in the Oral and Maxillofacial Region

Targeted structures in the oral and maxillofacial region are dental and supporting tissue, temporomandibular joint, craniofacial bones, skeletal muscles, skin, and salivary glands[40].

Orofacial structure formation and function are quite distinct. The neural crest and paraxial mesoderm both contribute to the formation of orofacial bones. Skeletal bones, on the other hand, are entirely composed of mesoderm. Furthermore, as a result of various masticatory muscles, orofacial bones are subjected to tremendous stress and strain, and they respond to growth factors and mechanical stimuli in a distinct way[41].

Furthermore, the ability to regenerate orofacial tissues is limited and varies. Because tooth enamel is an acellular dental structure, it lacks reparative capacity and loses the function of its formative cells after a complete crown. Because the pulp is encased in dentine and has a limited apical blood supply, dentine and pulp have some regenerative capacity. Cement, unlike bone, is an avascular dental structure with a low regenerative capacity[42,43].

### Regeneration of Dentin Pulp Complex

The maintenance of dental pulp function is an important factor in the preservation of tooth well-being; necrosis of dental pulp always leads to fracture of the tooth and/or inflammation of

periapical tissues, then lastly, the tooth will be lost. In cases of infected dental pulp, the immune system has a difficult time getting rid of the infection due to the pulp's reduced blood supply. Partial pulpectomy attempts have proven[44] ineffective because infecting organisms may still be present in the canals.

Therefore, infected dental pulp due to trauma or caries almost always needs root canal treatment, which involves removing all pulp tissue, disinfecting the cavity, then filling it with an artificial material[45]. Generally, the pulp tissue presents regeneration difficulty because of its anatomical location and its unique structures with complex innervation. The specific location of dentin and its highly organized structure are also other causes[40,46].

As a result, regenerative endodontics was introduced as an alternative to root canal treatment, a technique in which the replacement of necrotic pulp tissues by regenerated ones that have the ability for tooth revitalization occurs[47].

Complete pulp regeneration with newly formed innervation and vasculature was achieved in an adult canine experimental model[48] of pulpectomy in dogs using autogenous transplantation of pulp CD105+ side population cells with stromal cell-derived factor-1 (SDF-1). When side population CD105+ cells were transplanted in combination with SDF-1, pulp-like tissue by day 14 was deposited, and closure of the apex completely occurred, while less amount of pulp tissue was obtained with CD105+ cells or SDF-1 alone. This was the first study[48] to report complete *in situ* pulp regeneration. Furthermore, hard tissue was formed after direct pulp capping using autologous mesenchymal BMSCs[49].

Shiehzadeh et al[50] confirmed a shift toward a biological approach by creating an environment conducive to tissue regeneration. They treat necrotic/immature pulp in teeth with periradicular periodontitis (that had not responded to traditional apexification procedures) with MSC. All cases presented bone healing and mature apices within 3 to 4 months after the beginning of treatment, with no side effects and at a much faster rate than traditional treatments.

Regeneration endodontic procedures (REPs), including cell-based and cell-free, are being observed as an alternative strategy for treatment of immature permanent teeth with pulp necrosis. Cell-free REP therapies, such as revascularization and cell homing with molecules that recruit endogenous (MSCs), have shown promise in the treatment of periapical lesions and enhancing root growth in clinical trials. The regenerated pulp-dentin complex, however, is still missing in these cases. Dental MSCs are important seed cells in regenerative medicine because they are one of the essentials of tissue engineering. Dental MSC-based REPs have shown promising effects for pulp-dentin regeneration in many animal studies and clinical trials[51].

According to Liu et al[52], biomaterial scaffolds (blood clots, autologous platelet concentrates, platelet-rich plasma (PRP), platelet plasma-rich fibrin (PRF), decellularized extracellular matrix, collagen, alginate, chitosan, and hyaluronic acid) have demonstrated clinical potential as an armamentarium in regenerative endodontic procedures and have achieved remarkable advancements. Furthermore, Liu et al[52] stated that for pulp-dentin complex regeneration, cell-based regenerative endodontic therapy has shown in histological analyses of animal studies promising clinical outcomes of this procedure.

### *MSC in Periodontal Regeneration*

Regenerative dentistry is particularly interested in the periodontology and implantology fields as alveolar bone and tooth loss frequently occur as a result of periodontal diseases[53].

Regeneration of periodontal tissues initially depended on using scaffolds of two generations. In the first generation, cells will migrate into the periodontal tissue by using the osteoconductive membranes and bone graft materials as a framework, thereby enhancing its regeneration. In the second generation, osteoinductive materials, such as growth factors, were used to enhance the periodontal tissues to grow faster[54].

BMSCs were used by Kawaguchi et al[55] to enhance periodontal tissue regeneration and periodontal defects' healing. MSCs from beagle dogs' bone marrow were isolated, expanded *in vitro*, then mixed with atelocollagen (2 percent type I collagen), and auto-transplanted into Class III defects in the lab. As a control, telocollagen alone was implanted into the defects. After 1 month of transplantation, histological and morphometric analyses of periodontal tissue healing were performed. In the MSC-atelocollagen group, the defects were clearly regenerated with periodontal tissues, while in the control group, less periodontal tissue regeneration was observed. By using morphometric analysis, the percentage of new cementum length in the 5 x 10 (6) and 2 x 10 (7) cells/ml groups and the percentage of new bone area in the 2 x 10 (7) cells/ml group were signifi-

cantly higher than in the control group ($p < 0.01$). Thus, BMSCs provide an alternative source for the treatment of periodontal diseases.

Research studies[56] proved that periodontal regeneration could be achieved by a combination of platelet-rich plasma (extracted from peripheral blood) and autologous mesenchymal stem cells (obtained from the iliac crest). After one year of follow-up, improvement of attachment level, noticeable closure of the bone defect, and good healing and regeneration of interdental papilla were achieved.

In their experimental research on goats, Marie et al[57] used autologous bone marrow stem cells with scaffold to regenerate periodontal tissues around titanium implants. MSCs-PRP/3 dimensional woven-fabric composite scaffold presented a highly safe and effective regenerative treatment strategy for periodontitis when applied in ten patients with intra-bony defects[58].

Chen et al[59] confirmed the notably increase in alveolar bone height after using autologous periodontal ligament mesenchymal stem cells (PDLSCs) as an accessory grafting material in guided tissue regeneration (GTR) to treat periodontal intra-bony defects.

Božić et al[60] investigated the treatment of intra-bony defects through using hyaluronic acid in combination with deproteinized porcine bone mineral in 23 patients with 27 intra-bony defects and found that the clinical attachment level (CAL) was greatly increase of $3.65 \pm 1.67$ mm ($p < 0.001$) and pocket probing depth (PPD) was reduced.

In contrast, Lin et al[61] investigated the use of MSC culture conditioned medium (CM), which has growth factors, cytokines, chemokines, enzymes, extracellular vesicles, exosomes and secretomes; all of them provide immunomodulatory and tissue-regenerating properties, in pre-clinical and clinical studies. MSC-CM-based indirect treatment has the advantages of eliminating the obstacles in using direct MSC periodontal tissue regeneration, where the main disadvantages of using MSCs directly in periodontal tissue regeneration are its low survival rate during *in vivo* transplantation and the host immunogenic reaction against it.

### Regeneration of Craniofacial Defects

The extent and etiology of bone deficiencies in the oral cavity vary greatly. Bone loss can be divided into either: localized alveolar bone loss occurred as a result of periodontal disease or extensive bone atrophy caused by a variety of clinical diseases, such as traumatic injuries and bone resorption which accompany several benign or malignant tumors. In these cases, using of dental implants to enhance functional and esthetical rehabilitation is not enough because sufficient quantity and quality of bone should be present to provide a successful dental implant. Thus, different regenerative techniques were introduced in these situations with the aim of achieving promising results[62].

Stem cells are a method of choice for bone regeneration and correction of large craniofacial defects that occur as a result of cyst enucleation, tumor resection, and trauma. Tissue transfer is commonly used to close a bone defect, but it has many drawbacks, such as the inability to restore the specific function of the affected part and is almost always accompanied by scarring and infection donor site morbidity[63].

Langenbach et al[64] closed the critical size bone defects that will not heal spontaneously within a patient's lifetime by using microspheres (scaffold-free tissue construct) in their *in vitro* studies. They discovered osteogenically differentiated microspheres with cell growth, which can be used to repair bone defects. When compared to cell suspensions or gels, this new technique permits the transplantation of more cells and better integrity.

Freshly extracted teeth were used as autogenous grafts by Qin et al[65]. Teeth were sectioned, cut to shape, and disinfected, and to achieve good stability, they used eighteen rabbits in which the grafts were rigidly fixed to the mandibular defects by titanium screws. Each 6 rabbits were randomly euthanized at 1, 3, and 6 months after implantation, respectively. During the 1st and 3rd months, the boundaries of the grafts were clearly seen in the implanted area, while by the 6$^{th}$ month, the teeth grafts were completely covered by new bone. X-ray showed the gradual transition of the bone and grafted tooth interface from radiolucency to radiopacity over time. At the graft-bone interface, temporary fibrous integration occurred as a result of vascularization. At 1 and 3 months, the bone contact rate was greatly reduced compared to that of the 6 months. By this time, grafts were gradually resorbed and replaced by new bone. It was proved that introducing MSCs, healing-promoting factors within biomaterial carriers (hydrogel, scaffold, etc.), could enhance and speed up the functional new bone formation[65].

The incorporation of growth factors and another cell type with MSCs in various delivery vehicles is thought[66] to stimulate MSC differentiation, increase activity, and attract undifferen-

tiated osteoprogenitor cells. Another promising method for increasing osteogenic efficacy is the co-delivery of MSCs with other cell types, i.e., endothelial and osteogenic cells. The interaction of MSCs, osteoblasts, and endothelial cells is critical for new bone generation and angiogenesis[67].

Katagiri et al[68] proved that MSCs had the potential for bone regeneration. Yamada et al[69] searched in patients with alveolar deficiencies whether injectable tissue-engineered bone (TEB) made of MSCs and PRP could generate new bone. These experiments were carried out on animals before being applied to patients with long-term follow-up. Consequently, Yamada et al. experiment revealed that minimally invasive MSC transplantation resulted in good bone formation. Regarding the clinical approach, all patients showed greatly improved bone volume with no side effects. After 3 months, the newly formed bone was greatly higher over the preoperational baseline ($p < .001$) and approaching levels were equal to that of the original bone, with no noticeable bone resorption during long-term follow-up. Moreover, the patient's masticatory function was restored. TEB represents an effective therapeutic approach for bone tissue regeneration, as it has the capacity to regenerate functional bone in areas of alveolar defects while also restoring masticatory function in patients.

Behnia et al[70] also found greater improvement in bone regeneration 3 months after using recombinant platelet-derived growth factor with human bone marrow mesenchymal stem cells in alveolar cleft defects in cases of cleft palate, implying that combining recombinant platelet-derived growth factors with hMSCs improves the cells' regenerative ability.

Rizzo et al[71] engineered a new natural scaffold from decellularized porcine mucoperiosteum, which was then recellularized *in vitro* with hBM-MSCs using an innovative micro-perforation procedure based on Quantum Molecular Resonance (QMR). Their findings demonstrated that decellularization treatment is effective in generating a natural, non-immunogenic scaffold with preserved collagen microenvironment that promotes hMSC engraftment, spreading, and differentiation. According to ultrastructural analysis, the micro-perforation procedure preserved the collagen mesh, increasing the osteoinductive potential of mesenchymal precursor cells.

Soft tissue reconstruction in the oro-maxillofacial region is essential when there is a significant loss of soft tissues as a result of surgery or trauma. Several ways were introduced, including graft and flap transfer, but these new techniques lead to disease of the donor site. Alhadlaq et al[72] discovered that when human MSCs are exposed to an adipogenic-inducing medium, they can transform into adipose cells. In immune-deficient mice, adipose cells with appropriately shaped scaffolds can be used to reconstruct soft tissues on the dorsum surface of the tongue.

### Salivary Gland Regeneration

Salivary gland regeneration through stem cell transplantation is critical in tumors of the head and neck region and in cases of xerostomia which occur as a side effect of radiotherapy that always negatively affect the salivary gland function. Two major regenerative methods were used to restore the damaged salivary glands' functions. The first method is achieved by using tissue engineering techniques to create an artificial salivary gland. In the second method, stem cells are injected into damaged salivary gland tissues[73].

It has been proved[74] that when adipose-derived MSCs are transplanted in irradiated submandibular glands in a mouse model, the salivary gland function is restored. Sumita et al[75] demonstrated that salivary output increased with functional restoration in post-irradiated female mice after BMDC transplantation at weeks 8 and 24 when it was transplanted from male mice into the tail vein of 18 Gy-irradiated female mice. Salivary glands harvested from BMDC-treated mice were heavier than those harvested from non-treated mice 24 weeks after irradiation. According to histological analysis, treated mice's SGs had higher levels of tissue regenerative ability, such as angiogenesis and cell proliferation, whereas non-transplanted mice had higher levels of apoptotic activity[75]. It has been demonstrated that bone marrow cell extract (known as BM Soup) can restore salivary secretion and repair irradiated salivary glands. Misuno et al[76] concluded that BM Soup is effective in renovating damaged SGs function in non-obese type I diabetic (NOD) mice.

Xu et al[77] demonstrated that BMMSc in Sjögren syndrome (SS)-like NOD/LtJ mice and human patients were defective in immune-regulatory functions. Importantly, mesenchymal stem cell therapy reduced autoimmunity in Sjögren syndrome patients and returned salivary gland secretory function in both mouse models and SS patients.

### Mandibular Condyle Regeneration

Trauma or arthritis to temporomandibular joint disc or condyle leads to its damage and makes

patients have lifelong orofacial pain and impaired masticatory function. Temporomandibular joint regeneration strategies can improve these patients' quality of life (QOL). In a goat model study[78], the combination of cartilage tissue engineering using cartilage-derived progenitor cells carried in a hydrogel and distraction osteogenesis was successful in reconstructing condylar osteochondral defects.

Rat MSCs were harvested, expanded in culture, and treated with either chondrogenic or osteogenic supplements. Rat MSC-derived chondrogenic and osteogenic cells were loaded in hydrogel suspensions in two stratifications, then the integrated hydrogel layers were sequentially photopolymerized in a human condylar mold. Harvested articular condyles at 4-week *in vivo* implantation demonstrated stratified layers of chondrogenesis and osteogenesis. These findings provide proof of concept for future research into tissue-engineered mandibular condyles[79].

El-Bialy et al[80] isolated bone marrow stromal cells from skeletally mature New Zealand rabbit femoral bones and used low-intensity pulsed ultrasound to expand and differentiate them into chondrogenic and osteogenic lineages (LIPUS). The regeneration of the rabbit mandibular condyle was aided by low-intensity pulsed ultrasound after induced differentiation of BMSCs into chondrogenic and osteogenic cells.

Zhang et al[81] isolated mandibular bone marrow mesenchymal stem cells (MBMSCs) and mandibular condylar chondrocytes (MCCs) from Sprague Dawley (SD) rats to investigate the effect of moderate-intensity static magnetic fields (SMF) on chondrogenesis and proliferation of MBMSCs in the MBMSC/mandibular condyle. MBMSCs and MCCs were seeded in 1:2 ratios in the lower and upper Transwell chambers and exposed to a 280 mT SMF. MBMSCs were harvested for analysis after three, seven, or fourteen days. When compared to controls, MBMSC proliferation was significantly increased in the experimental group with MBMSCs co-cultured with MCCs under SMF stimulation. The glycosaminoglycan (GAG) content increased, as did the gene expression levels of *SOX9*, Collagen Type II Alpha 1 (*Col2A1*), and Aggrecan (*ACAN*).

### Oral Mucous Membrane Regeneration

Because the tongue is essential for speech, swallowing, and airway protection, surgical resection of tongue tissue can have a significant impact on quality of life. As a result, tongue defect reconstruction has remained a persistent challenge in dentistry. When myoblast/progenitor cells were implanted in a collagen gel into the hemi-glossectomized tongue in a rat model[82], cell-based tongue reconstruction was reported. Egusa et al[83] demonstrated that applying cyclic strain to BMSCs significantly speed up the *in vitro* skeletal myogenesis to achieve aligned myotube structures, highlighting the importance of cellular alignment in creating physiologically relevant environments for engineering skeletal muscle. Mouse BMSCs (mBMSCs) were plated on silicone sheets coated with fibronectin and subjected to cyclic 10% uniaxial strain when they reached 80-90% cell confluence. Cells cultured in a growth medium and subjected to 0.17 Hz (10 times/min) cyclic strain demonstrated a 48-hour shift in alignment from a completely random orientation to a well-aligned morphology with well-organized actin stress fibers parallel to the strain vector. The cyclic strain inhibited the motility and proliferation of the aligned mBMSCs in the growth medium, resulting in a cell population.

Rashed et al[84] reported in their experimental study that both intra-lesion injection of PRP and isolated cultured BMSCs can fasten the healing of induced oral ulcers in rats' buccal mucosa, however, BMSCs alone provided better clinical and histological results compared to PRP alone which was noticeable in the migration rate of epithelial cells, the number of inflammatory cells, thickness and organization of collagen fibers and the prefiltration of blood vessels, accompanied by complete re-epithelization on 10$^{th}$ day.

## Conclusions

This review sheds light on the experimental research and clinical applications that have led to the development of new MSCs therapies for a variety of diseases. Moreover, we have highlighted the experiments that proved that MSCs are an effective tool for tissue regeneration in the oral and craniofacial regions. This could pave the way for scientists to improve methods of oral and maxillofacial surgery and treatment of craniofacial malformations.

### Availability of Data and Materials

Not applicable.

### Conflict of Interests

Authors declared that they have no competing interest.

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