DENTAL AND MEDICAL JOURNAL - REVIEW

e-ISSN 2667-7288 **Vol** 8, **Issue** 1, (2026) ***Review Article / Derleme Makale***

Stem Cell Therapy in Maxillofacial Surgery: A Literature Review

Maksillofasiyal Cerrahide Kök Hücre Tedavisi: Bir Literatür İncelemesi

A.F.M. Shakilur RAHMAN[1]

[1] Department of Oral and Maxillofacial Surgery, Rajshahi Medical College Dental Unit, Rajshahi/Bangladesh,

ORCID ID: 0000-0001-6995-8434

Corresponding Author:

Lecturer. Dr. A.F.M. Shakilur RAHMAN (BDS, FCPS)

Adress: Department of Oral and Maxillofacial Surgery, Rajshahi Medical College Dental Unit, Rajshahi/Bangladesh

e-mail: *raselblackpearl@gmail.com*

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Abstract

Stem cell therapy has emerged as a transformative approach in maxillofacial surgery, offering novel solutions for the regeneration of bone and soft tissues lost due to trauma, congenital anomalies, infection, or tumor resection. Stem cell–based therapy utilizes diverse cell populations—including mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs), oral-derived stem cells, and induced pluripotent stem cells (iPSCs)—each offering distinct regenerative and immunomodulatory advantages. These cells may be applied independently or in combination with bioactive scaffolds and growth factors to enhance tissue regeneration. These cells exhibit remarkable multipotency, immunomodulatory properties, and capacity for tissue repair. Clinical and preclinical studies demonstrate that stem cell-based therapies—especially when combined with advanced biomaterials and scaffolds—can enhance bone regeneration, improve vascularization, and reduce complications compared to conventional grafting. Dental-derived MSCs, in particular, are gaining traction due to their accessibility and strong regenerative potential. Despite promising results, challenges remain regarding standardization of protocols, long-term safety, and regulatory approval. This review critically examines the sources, mechanisms, clinical applications, and future directions of stem cell therapy in maxillofacial surgery, highlighting the convergence of biotechnology, regenerative medicine, and tissue engineering in advancing patient care.

Keywords: *Stem cell therapy, Maxillofacial surgery, Bone regeneration, Mesenchymal stem cells, Regenerative medicine.*

Özet

Kök hücre tedavisi, travma, konjenital anomaliler, enfeksiyon veya tümör rezeksiyonu nedeniyle kaybedilen kemik ve yumuşak dokuların rejenerasyonu için yeni çözümler sunan maksillofasiyal cerrahide dönüştürücü bir yaklaşım olarak ortaya çıkmıştır. Kök hücre tedavisi, mezenkimal kök hücrelerin (MSC'ler), yağdan türetilen kök hücrelerin (ADSC'ler), oral kaynaklı kök hücrelerin ve indüklenmiş pluripotent kök hücrelerin (iPSC'ler) potansiyelinden yararlanan umut verici bir alternatif olarak ortaya çıkmıştır. Bu hücreler, dikkate değer çok yönlülük, immünomodülatör özellikler ve doku onarımı kapasitesi sergiler. Klinik ve klinik öncesi çalışmalar, kök hücre bazlı tedavilerin, özellikle gelişmiş biyomalzemeler ve iskelelerle birleştirildiğinde, geleneksel greftlemeye kıyasla kemik rejenerasyonunu artırabileceğini, vaskülarizasyonu iyileştirebileceğini ve komplikasyonları azaltabileceğini göstermektedir. Özellikle diş kaynaklı MSC'ler, erişilebilirlikleri ve güçlü rejeneratif potansiyelleri nedeniyle ilgi görmektedir. Umut verici sonuçlara rağmen, protokollerin standardizasyonu, uzun vadeli güvenlik ve düzenleyici onay konusunda zorluklar devam etmektedir. Bu inceleme, maksillofasiyal cerrahide kök hücre tedavisinin

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kaynaklarını, mekanizmalarını, klinik uygulamalarını ve gelecekteki yönlerini eleştirel bir şekilde inceleyerek, hasta bakımının ilerlemesinde biyoteknoloji, rejeneratif tıp ve doku mühendisliğinin entegrasyonunu vurgulamaktadır.

Anahtar Kelimeler: *Kök hücre tedavisi, Maksillofasiyal cerrahi, Kemik rejenerasyonu, Mezenkimal kök hücreler, Rejeneratif tıp.*

OVERVIEW / GENEL BAKIŞ

Maxillofacial surgery encompasses the diagnosis and treatment of a diverse range of defects and diseases affecting the craniofacial region. These conditions may arise from trauma, congenital anomalies, infections, tumors, or degenerative diseases, often resulting in significant functional and aesthetic impairments (1, 2). Traditional reconstructive approaches, such as autologous bone grafting and the use of alloplastic materials, have long been the mainstay of maxillofacial reconstruction. However, these methods are frequently associated with several limitations, including donor site morbidity, limited tissue availability, risk of infection, and unpredictable graft integration or resorption (3, 4). These challenges highlight the need for more effective and reliable treatment modalities.

In recent years, regenerative medicine has emerged as a transformative field in maxillofacial surgery, with stem cell therapy at the forefront of innovation. Unlike conventional techniques that primarily focus on repairing or replacing damaged tissues, regenerative strategies aim to restore the structure and function of native tissues through biological processes (5, 6). Stem cells, characterized by their self-renewal capacity and multilineage differentiation potential, offer unique advantages for tissue regeneration. Mesenchymal stem cells (MSCs), in particular, have demonstrated the ability to differentiate into osteogenic, chondrogenic, and adipogenic lineages, making them highly suitable for craniofacial bone and soft tissue engineering (7, 8).

The application of stem cell-based therapies in the maxillofacial field involves harnessing the regenerative properties of various stem cell populations—such as bone marrow-derived MSCs, adipose-derived stem cells, and dental pulp stem cells—to promote the regeneration of bone, cartilage, and soft tissues (9, 10). These cells can be delivered alone or in combination with bioactive scaffolds and growth factors to create a conducive microenvironment for tissue regeneration (11). Advances in scaffold technologies, including the development of hydrogels, bioceramics, decellularized matrices, and 3D-printed constructs, have further enhanced the clinical potential of stem cell therapies by providing structural support and promoting cell survival, proliferation, and differentiation (12, 13).

Despite these promising developments, the clinical translation of stem cell-based regenerative therapies is not without challenges. Issues such as variability in stem cell sources, lack of standardized

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protocols, regulatory and ethical concerns, and the need for robust long-term safety and efficacy data remain significant barriers to widespread adoption (1, 5). Moreover, the integration of digital technologies and artificial intelligence is beginning to play a pivotal role in optimizing scaffold design, personalizing treatment strategies, and predicting regenerative outcomes (7, 14).

The purpose of this review is to provide a clinically focused and evidence-based synthesis of human applications of stem cell–based therapies in maxillofacial surgery. Specifically, it aims to identify which stem cell types have been used clinically, the maxillofacial conditions they have been applied to, the delivery systems employed, and the clinical outcomes reported. By critically evaluating study quality and comparing outcomes across cell sources, scaffold technologies, and defect types, this review seeks to address the current heterogeneity and predominantly preclinical focus of the literature. Ultimately, the study aims to clarify the therapeutic potential, limitations, and translational readiness of stem cell therapies, while outlining key priorities needed to advance their safe and standardized clinical integration.

Sources and Types of Stem Cells in Maxillofacial Surgery

Mesenchymal Stem Cells (MSCs)

MSCs are multipotent stromal cells capable of differentiating into osteoblasts, chondrocytes, and adipocytes. They can be isolated from bone marrow, adipose tissue, dental pulp, periodontal ligament, gingiva, and other oral tissues (2, 15, 16). MSCs are favored in maxillofacial applications due to their immunomodulatory properties, trophic factor secretion, and low immunogenicity (1, 7).

Bone Marrow-Derived MSCs (BM-MSCs)

BM-MSCs are the most extensively studied for bone regeneration. They have been shown to regenerate large craniofacial defects and enhance osseointegration of dental implants, especially when combined with scaffolds and growth factors (13, 17, 18). Clinical studies demonstrate their efficacy in maxillary sinus augmentation, alveolar ridge preservation, and mandibular reconstruction (7).

Adipose-Derived Stem Cells (ADSCs)

ADSCs are abundant, easily harvested via liposuction, and possess robust osteogenic and angiogenic potential (13). They have demonstrated effectiveness in both hard and soft tissue regeneration, including alveolar bone augmentation and periodontal repair (19).

Dental and Oral-Derived Stem Cells

Stem cells from dental tissues—such as dental pulp stem cells (DPSCs), stem cells from human exfoliated deciduous teeth (SHED), periodontal ligament stem cells (PDLSCs), and gingival-derived stem cells—are accessible and show high proliferation and differentiation capacity (20, 15). Their

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minimal harvesting morbidity and strong osteogenic potential make them attractive for oral and maxillofacial applications (16, 21).

Induced Pluripotent Stem Cells (iPSCs)

iPSCs are reprogrammed from adult somatic cells and hold promise for personalized regenerative therapies, though challenges remain regarding tumorigenicity, differentiation control, and clinical standardization (3, 22).

Mechanisms of Action

Stem cells facilitate tissue regeneration through multiple mechanisms, including direct differentiation, paracrine signaling, and immunomodulation. MSCs can directly differentiate into osteoblasts, chondrocytes, and other specialized cell types, thereby replacing lost or damaged tissue (2, 7). In addition to this direct contribution, stem cells exert paracrine effects by secreting a variety of growth factors, cytokines, and extracellular vesicles, which stimulate endogenous repair processes, promote angiogenesis, and modulate immune responses (23, 14). Furthermore, MSCs play a crucial role in immunomodulation by regulating inflammation and creating a regenerative environment, which helps reduce the risk of fibrosis and tissue rejection (3). Advances in genetic engineering, such as the overexpression of bone morphogenetic protein-2 (BMP2), have been shown to further enhance the osteogenic differentiation and regenerative capacity of MSCs.

Scaffold Technologies in Maxillofacial Regeneration

Scaffold technologies are revolutionizing maxillofacial regeneration by providing three-dimensional frameworks that support cell attachment, proliferation, and differentiation, effectively mimicking the natural extracellular matrix (24-26). These scaffolds can be constructed from natural polymers, synthetic polymers, ceramics, or composite materials, each offering unique benefits regarding biocompatibility and mechanical properties (27). Recent advances include 3D-printed, patient-specific scaffolds, which allow for precise adaptation to complex defects and improved integration with host tissues (28). Additionally, loading scaffolds with stem cells or bioactive molecules has shown promise in enhancing bone and cartilage regeneration (29). While challenges remain in optimizing degradation rates and vascularization, scaffold-based approaches hold significant promise for the future of maxillofacial reconstruction (25).

Types of Scaffolds

Hydrogels, characterized by their highly hydrated polymer networks, are extensively used in regenerative medicine to support cell encapsulation and delivery, making them particularly effective for soft tissue regeneration. Bioceramics, including materials such as hydroxyapatite and β-tricalcium phosphate, are valued for their osteoconductivity and are commonly utilized in bone regeneration

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applications (11, 13). Decellularized matrices, which are natural tissue scaffolds stripped of cellular components, maintain native tissue architecture and bioactivity, supporting cellular engraftment while reducing immunogenicity. Additionally, 3D-printed scaffolds offer customizable, patient-specific solutions that improve tissue integration and functional outcomes by allowing precise structural and mechanical adaptation to individual needs (11, 12). Scaffolds loaded with MSCs or other stem cells can be further enhanced by incorporating growth factors (e.g., BMPs, VEGF), cytokines, or nanoparticles to promote osteogenesis and angiogenesis (30).

Clinical Applications

Bone Regeneration

Stem cell-based therapies have made significant strides in the field of bone regeneration, particularly within maxillofacial applications. These therapies have demonstrated efficacy in regenerating alveolar bone, facilitating maxillary sinus augmentation, and reconstructing bone defects following tumor resection or traumatic injury (7, 17, 18). Systematic reviews and meta-analyses consistently report that stem cell therapies—especially those utilizing MSCs—result in improved bone volume, density, and implant survival rates when compared to traditional bone grafting techniques (3).

Clinical trials employing bone marrow-derived MSCs (BM-MSCs) and adipose-derived stem cells (ADSCs) have shown not only increased bone quality but also successful osseointegration of dental implants, with minimal reported complications (17, 18). Furthermore, dental-derived MSCs, such as dental pulp stem cells (DPSCs) and stem cells from human exfoliated deciduous teeth (SHED), have been effectively used to restore mandibular bone defects (31, 32). These studies have provided evidence of compact bone formation and enhanced mechanical stability at the defect site, underscoring the regenerative potential of these cell sources (33). Collectively, these findings highlight the transformative impact of stem cell-based therapies in maxillofacial bone regeneration, offering improved outcomes and fewer complications compared to conventional approaches (31-33).

Soft Tissue and Periodontal Regeneration

Stem cell-based approaches have emerged as a promising strategy for the regeneration of soft tissues and periodontal structures in the oral cavity. Stem cells derived from dental pulp, gingiva, and the periodontal ligament (PDL) have demonstrated the capacity to regenerate key components of the periodontium, including the periodontal ligament itself, alveolar bone, cementum, and gingival tissues (15, 16). Dental pulp stem cells (DPSCs) and gingival mesenchymal stem cells (GMSCs) are particularly notable for their ability to differentiate into fibroblasts, osteoblasts, and other cell types essential for the repair and regeneration of oral soft tissues and mucosa (16).

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Beyond their differentiation potential, these stem cells possess significant immunomodulatory properties, which play a critical role in regulating local inflammation and promoting a favorable environment for tissue healing (20). By secreting anti-inflammatory cytokines and growth factors, stem cells can modulate the immune response, reduce chronic inflammation, and accelerate the resolution of tissue injury—factors that are essential for successful periodontal and soft tissue regeneration. Preclinical and clinical studies have shown that the transplantation of these stem cell populations leads to improved attachment levels, reduced probing depths, and enhanced regeneration of both soft and hard periodontal tissues (15). Collectively, these findings underscore the therapeutic potential of stem cell-based therapies for restoring periodontal health and function.

Temporomandibular Joint (TMJ) and Complex Reconstructions

Bioengineering approaches for temporomandibular joint (TMJ) reconstruction are advancing rapidly, with stem cell-based therapies—particularly those utilizing MSCs—showing significant promise for regenerating both cartilage and bone components of the joint (34, 35). MSCs, which can be derived from tissues such as bone marrow, synovium, and umbilical cord, possess self-renewal and multilineage differentiation capabilities, enabling them to contribute to chondrogenic and osteogenic tissue repair in TMJ osteoarthritis (TMJ-OA) and other degenerative conditions (36, 37). These cells not only differentiate into cartilage and bone but also exert trophic, anti-inflammatory, and immunomodulatory effects that support tissue regeneration and modulate the joint environment (38, 39). When MSCs are delivered directly into the joint or seeded onto advanced scaffolds—such as hydrogels, decellularized extracellular matrix (dECM), or composite 3D-printed constructs—they can form tissue structures that closely mimic the biomechanical and biochemical properties of the native TMJ, supporting both cell proliferation and differentiation (34, 40). The use of bioactive molecules, including transforming growth factor-beta (TGF-β) and bone morphogenetic proteins (BMPs), further enhances these regenerative processes by promoting matrix synthesis and cellular activity (35, 38). Preclinical and early clinical studies have reported that intra-articular administration of MSCs can effectively reduce joint pain and improve mouth opening, with some studies showing an average pain reduction of 85% and a 40% increase in maximum mouth opening over six months, although most clinical evidence remains preliminary and at high risk of bias (36, 37). Overall, stem cell-based and tissue engineering strategies offer a promising alternative to traditional autogenous grafts and alloplastic prostheses, with the potential to restore TMJ function and integrity while reducing donor site morbidity and postoperative complications. However, further long-term clinical studies are needed to validate these findings and optimize protocols for widespread clinical application (34, 36).

Treatment of Osteonecrosis and Osteoradionecrosis

Stem cell therapy represents a promising approach for managing challenging conditions like medication-related osteonecrosis of the jaw (MRONJ) and osteoradionecrosis, which often resist conventional treatments due to impaired vascularity, chronic inflammation, and compromised bone

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healing (41). ADSCs and their exosomes have demonstrated significant potential in addressing these pathologies. ADSCs promote tissue regeneration through multiple mechanisms: they secrete pro-angiogenic factors (e.g., VEGF) to improve blood supply, modulate inflammation by reducing pro-inflammatory cytokines (e.g., TNF-α, IL-6), and enhance osteoblast differentiation to stimulate new bone formation (23, 42). Exosomes derived from ADSCs further amplify these effects by delivering bioactive molecules (microRNAs, proteins) that suppress osteoclast activity, reduce tissue fibrosis, and activate endogenous repair pathways (23). Clinical studies report reduced bone exposure, decreased pain, and radiographic evidence of bone regeneration following local administration of ADSCs or exosomes, offering a minimally invasive alternative to surgical debridement (41, 42). These therapies address the core pathophysiology—promoting vascularization, dampening inflammation, and restoring bone homeostasis—making them particularly valuable for radiation-induced or bisphosphonate-compromised tissues.

Distraction Osteogenesis

Distraction osteogenesis is a widely used surgical technique for lengthening bones and correcting craniofacial defects, but it is often limited by the lengthy consolidation period required for new bone formation. Recent research indicates that stem cell therapy can significantly enhance the outcomes of distraction osteogenesis by accelerating bone regeneration and potentially reducing the overall treatment duration (43; 44). MSCs, when introduced into the distraction gap, contribute to osteogenesis both through direct differentiation into osteoblasts and by secreting growth factors that stimulate endogenous bone formation and angiogenesis (43).

Studies have shown that the local application of MSCs or their derivatives, such as exosomes, leads to increased bone density, improved mineralization, and more rapid consolidation compared to traditional distraction osteogenesis protocols (44). These effects are attributed not only to the osteogenic potential of the transplanted cells but also to their ability to modulate the local microenvironment, enhance vascularization, and reduce inflammation. As a result, stem cell-enhanced distraction osteogenesis offers the promise of faster recovery, fewer complications, and better functional and aesthetic outcomes for patients undergoing craniofacial reconstruction.

Oral Cancer and Immunomodulation

Mesenchymal stem cells (MSCs) are emerging as multifunctional agents in oral cancer therapy, extending their role beyond tissue regeneration to include targeted drug delivery and immunomodulation. Owing to their intrinsic tumor-homing capacity, MSCs can migrate toward malignant tissues (45), enabling their use as biological carriers that transport anti-tumor agents—such as oncolytic viruses, pro-apoptotic factors, or chemotherapeutic compounds—directly to cancer sites with reduced off-target toxicity (45, 46). For example, MSCs engineered to express TRAIL (tumor necrosis factor–related apoptosis-inducing ligand) have demonstrated selective induction of apoptosis

in oral squamous cell carcinoma models, resulting in measurable tumor reduction in preclinical studies (46).

In addition to targeted delivery, MSCs influence the tumor microenvironment through modulation of immune pathways. They can downregulate pro-tumorigenic inflammation and suppress immunosuppressive cell populations, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), thereby enhancing endogenous anti-cancer immune activity (47, 48). However, their immunological plasticity necessitates careful control, as MSCs may inadvertently promote tumor progression by secreting cytokines such as PGE2 and IL-10 when not appropriately engineered or regulated (49).

Clinical translation is advancing, with ongoing investigations evaluating MSC-mediated delivery of interferon-β or suicide genes—such as thymidine kinase—to improve loco-regional disease control and reduce recurrence rates (50). These strategies hold the potential to mitigate treatment-related morbidity, preserve oral function, and overcome limitations associated with conventional modalities. Future research is directed toward refining MSC specificity through advanced genetic engineering and biomaterial-guided targeting systems to optimize their therapeutic safety and efficacy (51).

Efficacy, Safety, and Limitations

Stem cell therapies have demonstrated superior bone quality, vascularization, and integration compared to traditional grafts, especially in challenging cases (7, 17, 18). Systematic reviews confirm the potential for predictable and stable outcomes in bone and soft tissue regeneration (3).

Clinical studies consistently report a favorable safety profile for stem cell therapies in maxillofacial applications, with minimal adverse effects (3). However, immune responses, especially in allogeneic transplants, require further investigation to optimize cell survival and function.

Limitations

Despite the promising potential of stem cell therapies, several limitations hinder their widespread clinical adoption. A significant challenge is the lack of standardized protocols for cell isolation, expansion, and delivery, leading to variability in outcomes across studies (1, 7). Additionally, most available research focuses on short- to mid-term results, with limited data on long-term efficacy and safety (3). Regulatory and ethical challenges related to cell sourcing, manipulation, and clinical translation also remain significant barriers (5, 22). Furthermore, the high costs and technical complexity associated with these therapies restrict their accessibility and broader clinical application. Finally, the regenerative capacity of stem cells declines with age, potentially reducing their effectiveness in older patients—a crucial consideration given the aging global population.

Advances in Scaffold and Biomaterial Technologies

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Recent innovations in scaffold design, including 3D-printed hydroxyapatite, bioactive glass, and composite hydrogels, have significantly improved stem cell delivery, survival, and differentiation (12, 24). These materials mimic the natural extracellular matrix, enhance angiogenesis, and allow for patient-specific customization (30). Integration of growth factors, nanoparticles, and gene delivery systems further boosts osteogenic and regenerative capacity (11).

Future Directions

Recent advances continue to redefine the trajectory of regenerative medicine in maxillofacial surgery. Progress in stem cell sourcing, genetic modification, and computational modeling—including applications of artificial intelligence and machine learning—is accelerating the development of personalized and precision-based regenerative strategies (5, 7). In parallel, cell-free therapies such as exosomes and secretomes are emerging as promising alternatives due to their lower immunogenicity and favorable safety profiles (14, 23).

To support meaningful clinical translation, the field urgently requires large-scale, multicenter clinical trials with standardized methodologies and long-term follow-up, which are essential for generating robust evidence regarding safety and efficacy (1, 3). Digital technologies, including AI-enhanced planning systems and algorithm-driven scaffold optimization, are expected to further improve treatment predictability and clinical outcomes (7).

Finally, international collaboration focused on regulatory harmonization and consensus guidelines is critical. Establishing unified standards for stem cell processing, delivery protocols, and outcome reporting will play a central role in translating these innovations into safe, reliable, and widely adoptable clinical therapies (5, 22).

SUMMARY / SONUÇ

Stem cell–based therapies represent a promising shift in maxillofacial reconstruction, offering new treatment avenues for challenging bone and soft-tissue defects. Mesenchymal stem cells derived from bone marrow, adipose tissue, and dental tissues have shown encouraging safety profiles and regenerative potential, with growing—though still limited—clinical evidence supporting their use. Advances in biomaterials, scaffold engineering, and emerging cell-free approaches are further strengthening the therapeutic possibilities of regenerative strategies in this field.

However, key limitations remain. Variability in cell sources and preparation methods, lack of standardized clinical protocols, small patient cohorts, and limited long-term follow-up continue to hinder broad clinical adoption. Regulatory and ethical considerations also present additional barriers to translation.

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Overall, while stem cell therapy is progressing toward wider clinical integration, its routine use in maxillofacial surgery will require continued interdisciplinary research, methodologically robust clinical trials, and harmonized standards for safety, efficacy, and reporting.

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