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Stem Cell Approach In Tmj Ankylosis: A Review

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Abstract

Temporomandibular joint (TMJ) ankylosis is a debilitating condition characterized by fibrous or bony fusion of the joint, leading to restricted mobility and functional impairment. Conventional surgical treatments, though effective in mechanical release, often fail to restore joint biology and face high recurrence rates. Stem cell–based regenerative strategies have emerged as a transformative approach, leveraging the osteogenic and chondrogenic potential of mesenchymal stem cells (MSCs) to repair and reconstruct the osteochondral interface. These cells exert therapeutic effects through differentiation, paracrine signaling, immunomodulation, and extracellular matrix remodeling, promoting functional regeneration and preventing re-ankylosis. Advanced delivery systems including hydrogels, 3D-printed scaffolds, and cell-sheet engineering enhance cell viability, localization, and integration, offering biologically driven joint restoration. While preclinical outcomes are promising, future success depends on standardized methodologies and clinical validation to translate stem cell–based therapies into effective TMJ ankylosis management.

Keywords: TMJ ankylosis, stem cells, mesenchymal stem cells, tissue engineering, osteochondral regeneration

Introduction

Temporomandibular joint (TMJ) ankylosis is a debilitating condition characterized by the pathological fusion of the mandibular condyle to the cranial base, most commonly resulting from trauma, infection, or inflammatory conditions that lead to fibrous or bony adhesions and restricted joint mobility.[1] This disorder manifests as severely limited mouth opening, impaired mastication, speech difficulties, compromised oral hygiene, and, in growing children, significant facial asymmetry and psychosocial distress. TMJ ankylosis can be classified based on the nature of the fusion (fibrous, bony, or mixed) and the severity of joint involvement, with a higher prevalence noted among pediatric populations, particularly in developing countries such as India, where cases often peak between 10 and 15 years of age and show a slight female

predominance.[2] Conventional management relies primarily on surgical interventions such as gap or interpositional arthroplasty and joint reconstruction using autogenous or alloplastic materials; however, these approaches face persistent challenges including high recurrence rates, restricted postoperative mobility, unpredictable remodeling, graft overgrowth, and infection.[3] Moreover, traditional methods fail to restore the biological function or growth potential of the joint, emphasizing the need for regenerative solutions. Recent advances in regenerative medicine have paved the way for biologically driven therapies that aim to reconstruct functional osteochondral tissues, reduce recurrence, and promote harmonious craniofacial growth. Among these, stem cell–based strategies particularly those utilizing mesenchymal stem cells (MSCs) have emerged as a promising frontier due to their inherent ability to differentiate into chondrogenic and osteogenic lineages, modulate inflammation, and support tissue integration when combined with biocompatible scaffolds and bioactive molecules.[4] This paradigm shift from mechanical correction to biological restoration represents a transformative approach in the management of TMJ ankylosis, with ongoing preclinical and pilot clinical studies exploring the potential of stem cells, tissue engineering, and gene therapy to achieve durable functional regeneration and improved long-term outcomes.[5]

Pathophysiology of Temporomandibular Joint (TMJ) Ankylosis and Rationale for Regenerative Therapy

Temporomandibular joint (TMJ) ankylosis is a complex pathological condition characterized by partial or complete fusion of the mandibular condyle to the cranial base, resulting in severe restriction of jaw movement and functional impairment. Based on the nature of the fusion, TMJ ankylosis is broadly categorized as fibrous or osseous (bony). In fibrous ankylosis, the joint space becomes filled with dense fibrous or fibrocartilaginous tissue, typically following mild trauma or articular disc displacement that leads to persistent inflammation and fibrosis without complete ossification.[6] In contrast, osseous ankylosis involves the formation of a continuous bony bridge across the joint, often resulting from severe condylar and glenoid fossa injury accompanied by chronic inflammation. This process triggers endochondral ossification, whereby cartilage and fibrous tissue are progressively replaced by bone, culminating in permanent and rigid joint immobility.[7]

The underlying mechanisms involve a cascade of inflammatory and osteogenic processes. Following trauma or infection, sustained inflammation releases cytokines such as IL-1β, TNF-α, and TGF-β, along with growth and angiogenic factors like VEGF and HIF-1α, which collectively promote fibroblast activation, chondrocyte proliferation, and aberrant osteogenesis. The recruitment of progenitor and osteoprogenitor cells into the joint space further accelerates bone formation and bridging.[8] Histological studies reveal higher angiogenic and osteogenic activity in osseous ankylosis than in fibrous types, reflecting the increased expression of bone-promoting proteins and enzymes such as matrix metalloproteinases (MMPs) and type I/II collagen involved in matrix remodeling. At the molecular level, several key signaling pathways orchestrate this pathological transformation. The TGF-β (Transforming Growth Factor-β) pathway plays a pivotal role by driving fibrosis and chondrogenesis, stimulating excessive extracellular matrix deposition within the joint. Bone Morphogenetic Proteins (BMPs) further potentiate cartilage and bone formation by inducing differentiation of local stem and progenitor cells into chondrocytes and osteoblasts. Meanwhile, upregulation of the Wnt/β-catenin pathway contributes to the cartilage-to-bone transition, reinforcing progressive ossification and joint immobilization. Additional mediators, including VEGF, MMPs, and collagen subtypes, facilitate angiogenesis, tissue turnover, and remodeling during the ankylotic process.[9]

Conventional treatment modalities such as gap arthroplasty, interpositional arthroplasty, joint reconstruction, and distraction osteogenesis aim to mechanically restore joint mobility but often fail to re-establish normal joint architecture or prevent recurrence. Gap arthroplasty, though effective in immediate release, carries a high risk of re-fusion without biological support. Interpositional arthroplasty using autogenous grafts (e.g., temporalis fascia, dermis) may reduce recurrence but is associated with donor site morbidity and unpredictable long-term remodeling. Joint reconstruction using costochondral or alloplastic materials presents issues of growth mismatch, resorption, infection, and prosthesis-related complications, while distraction osteogenesis is complex, time-intensive, and requires prolonged rehabilitation.[10] Given

these limitations, stem cell–based regenerative approaches have emerged as a promising therapeutic paradigm. Mesenchymal stem cells (MSCs) and engineered constructs possess the ability to differentiate into chondrocytes and osteoblasts, facilitating the simultaneous regeneration of articular cartilage and subchondral bone. Beyond their regenerative potential, MSCs exhibit potent immunomodulatory and anti-fibrotic properties, helping to suppress pro-inflammatory cytokines and inhibit aberrant signaling cascades such as TGF-β, BMP, and Wnt, which drive pathological ossification.[11]

Stem Cell Sources and Their Therapeutic Potential in TMJ Ankylosis

A variety of stem cell types are currently being explored for the management of temporomandibular joint (TMJ) ankylosis, each offering unique biological properties, advantages, and translational challenges. Among them, bone marrow–derived mesenchymal stem cells (BM-MSCs) remain the most extensively studied due to their strong osteogenic and chondrogenic potential, which supports effective bone and cartilage regeneration; however, their clinical application is limited by the invasive nature of bone marrow harvesting and the relatively low cell yield.[12] Adipose-derived stem cells (ADSCs), isolated from the buccal fat pad or subcutaneous fat, present a less invasive and more abundant alternative, though their differentiation potential can vary depending on donor factors. Dental pulp stem cells (DPSCs), obtained from extracted teeth, are of neural crest origin and exhibit dual osteogenic and chondrogenic capabilities, yet their limited quantity per donor restricts scalability. Synovial MSCs, derived from the synovial membrane or fluid, closely resemble native joint cells and show a high affinity for cartilage regeneration, but their isolation is technically demanding and typically yields few viable cells. Induced pluripotent stem cells (iPSCs), generated from reprogrammed somatic cells, offer an unlimited, patient-specific cell source for TMJ tissue engineering, though concerns about tumorigenicity and ethical considerations remain significant barriers to clinical use.[13] Wharton's Jelly–derived MSCs (WJ-MSCs), sourced from umbilical cord tissue, are emerging as a promising option due to their potent anti-inflammatory and neuroprotective effects, yet logistical and ethical issues continue to limit widespread adoption. In addition, mesenchymal stem cells (MSCs) from bone marrow, synovium, and umbilical cord play a pivotal role in cartilage regeneration because of their multilineage differentiation potential (Minervini et al., 2022; Abaasa et al., 2022),[14,15] while human stem cells (HSCs) have shown encouraging in vitro results, enhancing osteogenesis and chondrogenesis in TMJ-associated tissues (Gong et al., 2022).[16] Thus, successful clinical translation of these cell-based approaches depends on balancing regenerative efficacy with practical considerations such as donor morbidity, cell availability, reproducibility of differentiation, and overall safety profile.[13]

Mechanisms of Stem Cell–Mediated Repair in TMJ Ankylosis

Stem cell–mediated repair in temporomandibular joint (TMJ) ankylosis operates through multiple interconnected biological mechanisms and employs advanced delivery systems designed to restore joint function while preventing pathological ossification. Mesenchymal stem cells (MSCs) and related progenitor cell types play a pivotal role by exhibiting osteochondral differentiation, enabling regeneration of both articular cartilage and subchondral bone, thereby reconstituting the native osteochondral interface of the TMJ. Beyond direct differentiation, stem cells exert profound paracrine effects, secreting a wide range of cytokines, growth factors, and exosomes including insulin-like growth factor (IGF), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF) which collectively promote angiogenesis, matrix synthesis, cellular proliferation, and tissue repair.[17] Their immunomodulatory capacity further enhances therapeutic efficacy by modulating the local inflammatory microenvironment; MSCs shift macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, effectively reducing chronic inflammation and mitigating fibro-osseous progression. Additionally, stem cells contribute to extracellular matrix remodeling, stimulating the synthesis of cartilage-specific components such as type II collagen and aggrecan, which are critical for restoring the biomechanical integrity and resilience of the joint surface.[18]

Delivery Strategies of Stem Cell–Mediated Repair in TMJ Ankylosis

To optimize therapeutic outcomes, a range of delivery platforms and scaffolds have been developed to ensure effective localization, survival, and integration of transplanted cells. Hydrogels composed of materials such as alginate, fibrin, or chitosan serve as injectable, biocompatible carriers that maintain stem

cell viability, conform to irregular joint spaces, and support in situ paracrine signaling while minimizing surgical invasiveness. Three-dimensional (3D)-printed scaffolds enable the fabrication of patient-specific constructs that replicate condylar anatomy with precise porosity and mechanical properties, facilitating osteochondral regeneration and anatomical fidelity.[19] Collagen- or hyaluronic acid (HA)-based scaffolds provide a bioactive matrix that promotes layered bone and cartilage formation, while nanofiber and composite systems offer controlled release of bioactive molecules and enhanced vascularization, sustaining long-term reparative signaling. Meanwhile, cell-sheet engineering a scaffold-free approach involving layered autologous stem cell or chondrocyte sheets circumvents issues of scaffold biocompatibility and immune response, allowing direct transplantation of organized cellular constructs capable of self-integration and matrix secretion. Collectively, these synergistic cellular and biomaterial strategies advance the biological and functional restoration of the TMJ, offering a regenerative alternative that addresses the limitations of conventional surgical approaches and holds promise for durable, recurrence-free outcomes in TMJ ankylosis management.[20]

Conclusion

Stem cell–based therapies represent a promising frontier in the biological reconstruction of the temporomandibular joint, potentially overcoming the drawbacks of conventional surgery. While preclinical results are encouraging, robust clinical evidence, standardized protocols, and interdisciplinary collaboration are essential before these approaches can be integrated into mainstream TMJ ankylosis management.

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