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Role of Stem Cells in Orthodontics

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ABSTRACT:

The field of tissue engineering involves the interdisciplinary application of principles of medicine, the biological sciences, and engineering toward the replacement or augmentation of a damaged or compromised tissue or organ. The purpose of this article is to highlight the importance of the use of tissue engineering in the field of Orthodontics. Tissue engineering and Orthodontics are two broad fields that share a common objective of applying scientific principles in association with existing best technology to restore the tissue function and esthetics. Both the fields have witnessed a significant surge in the technological aspect over the past century. The concept of tissue engineering has been used in Orthodontics for regeneration of the tissues in correcting the defects associated with craniofacial syndromes and temporomandibular disorders, root resorption, periodontal defects, in rapid maxillary expansion to aid in the stability of the achieved expansion , in Distraction Osteogenesis and in accelerating orthodontic tooth movement.

Keywords: stem cells, orthodontic application, craniofacial regeneration

1.INTRODUCTION

Stem cells (SCs) have the ability to build every tissue in the human body, hence have great potential for future therapeutic uses in tissue regeneration and repair. In order for cells to fall under the definition of "stem cells," they must display two essential characteristics. First, stem cells must have the ability of unlimited self-renewal to produce progeny exactly the same as the originating cell. This trait is also true of cancer cells that divide in an uncontrolled manner whereas stem cell division is highly regulated. Therefore, it is important to note the additional requirement for stem cells; they must be able to give rise to a specialized cell type that becomes part of the healthy animal **.[1]**

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Various sources for harvesting SCs have been introduced such as muscle, dermis, bone marrow, adipose tissue, periosteum, blood, umbilical cord, synovial membrane and teeth**.[2]**Among these sources, some are easily accessible in orthodontics. As extraction of primary teeth or permanent premolar or wisdom teeth is common interventions in orthodontic treatment of malocclusions, SCs sources from the teeth could be gained without extra morbidity. Several studies have revealed differentiation and proliferation potential of mesenchymal stem cells (MSCs) obtained from dental pulp, periodontal ligament or human exfoliated deciduous teeth **.[3,4]**

All stem cells, regardless of their source, have three general properties, which make them different from other cells in the body:

a) Stem cells are unspecialized/ undifferentiated and such character is one of their essential properties.

b) Unspecialized stem cells can give rise to specialized cell types through differentiation process.

c) Stem cells are able to divide and renew themselves- unlike muscle cells, blood cells or nerve cells, which normally do not replicate themselves, stem cells may duplicate many times. If the resulting stem cells continue to be unspecialized, like the parent stem cells, the cells are said to be capable of long term self renewal **.[5,6]**

From the twentieth century, cell biology and genetics began to contribute as diagnostic tools and therapies aimed at treating many of the ills that afflict humanity. The term stem cell was proposed for scientific use by Russian histologist Alexander Maksimow in 1909. He was the first to suggest the existence of hematopoietic stem cells (HSC) with the morphological appearance of a lymphocyte, capable of migrating throughout the blood to micro ecological niches that would allow them to proliferate and differentiat .**[6,7]**

In the 1950s, it was carried out, by Edward Donnall Thomas, the first bone marrow transplant. In 1961, James Till and Ernest McCulloch pointed to the existence of hematopoietic stem cells in the bone marrow of mice, opening a perspective for understanding the mechanisms involved in these transplants. Between the 1970s and 1980s, Professor Alexander Friedenstein's team, studying mesenchymal stem cells, demonstrated the capacity for self-renewal and differentiation of these cells **. [1-3]**

In year 2012, Shinya Yamanaka and John Gurdon have won Noble prize award for their excellent work on induced pluripotent stem cells (IPSCs) derived from adult somatic cells. This work has resulted into development of innovated technology to make an IPSCs from individual patient who needs treatment for specific disease. It is proposed that dental pulp stem cells (DPSCs) can develop IPSCs which can be used for therapies of various diseases,

In the decade between 2010 and 2019, the first wave of stem cell start-ups emerged, alongside research and development programmes at many large pharmaceutical companies, leading to innovation and the first human clinical trials for SCs and other related therapies **.**

Stem cells classified according to characteristics**.[1-5]**

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1. Totipotency: Is the ability of definite type of cells to produce all types of cells as well as germ cells or Embryonic Stem Cells ESCs, which also named omnipotent. Totipotent SCs are derived from the zygote, and can form embryonic and extra-embryonic tissues, including the ability to generate the placenta. **[1-7]**

2. Pluripotency: Is the ability of producing all types of cells apart from cells of the embryonic membrane. Pluripotent SCs include embryonic SCs (ESCs) and are derived from the inner cell mass of the developing blastocyst. Notably, ESCs can differentiate into the three main germ layers of the organism including the endoderm, mesoderm and ectoderm.[8,9]

3. Multipotency: Is the ability to distinguish into more than one adult cell type such as Mesenchymal Stem Cells MSCs. Postnatal/adult SCs are regarded as being multipotent and include populations of hematopoietic and mesenchymal SCs (MSCs).[9]

4. Unipotency: And called also dedicated progenitors: produce one particular cell type.[9-11]

Human stem cells can be categorized into three main categories embryonic, germinal and somatic **,[12-15]**

1)Embryonic stem cells ESCs originate from the inner cell mass of the blastocyst. ESCs are omnipotent having unlimited power of division and have indefinite replicative life span.[16]

2) Germinal stem cells GSCs are derived from primary germinal layers of embryo. They differentiate into progenitor cells to produce specific organ cells. [15,16]

3) Somatic/adult stem cells are progenitor cells as they are less totipotent less replicative life span than ESCs. They exist in mature tissues such as hematopoietic, neural, gastrointestinal and Mesenchymal tissue.[17]

Dental stem cells can differentiate into different types of cells. Dental pulp stem cells, stem cells from human exfoliated deciduous teeth, periodontal ligament stem cells, stem cells from apical papilla, and dental follicle progenitor cells are five different types of dental stem cells that have been identified during different stages of tooth development. The availability of dental stem cells from discarded or removed teeth makes them promising candidates for tissue engineering**.[18]**

Dental Pulp tissue is extracted from the teeth recovered during routine dental procedure throughout the life and these teeth are the most convenient and valuable source of DPSCs which are well characterized as a MSCs, It is a noninvasive process of extraction of MSCs from dental pulp tissue. DPSCs can be cryopreserved and revived whenever; they are needed for future regenerative therapies. Some of the diseases which are being cured by DPSCs include type 1 diabetes, neurological diseases, Immunodeficiency diseases and diseases of bone and cartilages it has been shown that DPSCs can be differentiated by modulation with growth factors, transcriptional factors, extracellular matrix proteins and receptor molecules into different cell types include odontoblast, osteoblast, chondrocyte, cardiomyocytes, neuron cells, adipocyte, corneal epithelial cell, melanoma cell and insulin secreting Beta cells **.[19,20]**

Stem cells can be isolated from the pulp of human exfoliated deciduous teeth. These cells induce bone formation and differentiate into other non-dental mesenchymal cells in vitro.

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SHED have higher proliferation rates, form a sphere-like clusters and differentiate into osteoblasts but they are not able to regenerate complete dentin and pulp-like complexes in vivo. These cells can repair calvarial defects in mice due to their ability to differentiate into osteoblasts. SHED secretes neurotrophic factor for repair of motor neurons following dental injury and therefore it has proposed that SHED can be useful for the treatment of neurodegenerative diseases **(Verma et al., 2014).**

Stem cells from apical papilla are the cells which are found at the tooth root apex. They have higher proliferation rates as well as have a differentiation property in vitro similar to DPSCs. They are capable of differentiating into odontoblast cells and produce dentin in vivo. Due to their higher proliferative potential, SCAPs are also suitable for cell-based therapy for formation of apex roots **(Verma et al., 2014).**

Human periodontal ligament stem cells (PDLSCs) exhibit osteoblast-like characteristics and are able to differentiate into osteoblasts. They are also considered as the optimal seed cells for periodontal regeneration and they have a capacity to form connective tissue which is riched in collagen I fiber. Human PDLSCs when seeded on 3D scaffolds such as fibrin sponge, generate bone in vivo and retain stem cell properties and tissue regeneration capacity **.[21]**

The dental follicle is the connective tissue surrounding the enamel organ and dental papilla that forms a vascular fibrous sac isolated DFPCs from the dental follicle of human third molar teeth, which were found to express the stem cell markers Notch and Nestin. Their potential for osteogenic, adipogenic, chondrogenic, and neural differentiation was further confirmed. Subsequently, DFPCs were applied for tissue regeneration, such as the regeneration of the salivary glands, dental roots, and bone tissue **.[22,23]**

Orthodontics involves treatment of dental malocclusions and correction of dentofacial deformities. The aim of orthodontic treatment is to achieve facial aesthetics and improve oral health related quality of life . The prevalence of dental malocclusion varies in different communities and have been reported to be 22.5% to 93% **.[24,25]**

Orthodontic treatment of malocclusions has several shortcomings such as prolonged treatment time, apical root resorption, tooth movement limited to alveolar bone and difficulties to overcome periodontal defects. Although facial anomalies and jaw base deformities are less frequent compared to simple dental malocclusions, they are more burdensome, Current treatment modalities of craniofacial deformities can reduce the severity of these deformities but their final aesthetic outcomes are still not pleasing. Stem cells (SCs) are self-renewal cells that could differentiate toward various cells under suitable conditions **.[18-22]**

This review focuses specifically on craniofacial bone, teeth, periodontium, and the temporomandibular joint (TMJ)within the craniofacial complex, interpreting the critical roles of adult stem cells in postnatal growth/development as well as, remodeling and regeneration of the craniofacial tissues or organs.

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2.APPLICATIONS IN DENTOFACIAL ORTHOPEDICS

2.1.Dentofacial anomalies

Craniofacial anomalies may be congenital, developmental or may result from a plethora of factors like trauma, tumor resection or fracture malunion or non union. These defects usually require surgical correction with assisted grafting of autogenic,

allogenic or prosthetic materials. However all these may be associated with problems like donor site morbidity, contour irregularities, postoperative pain,

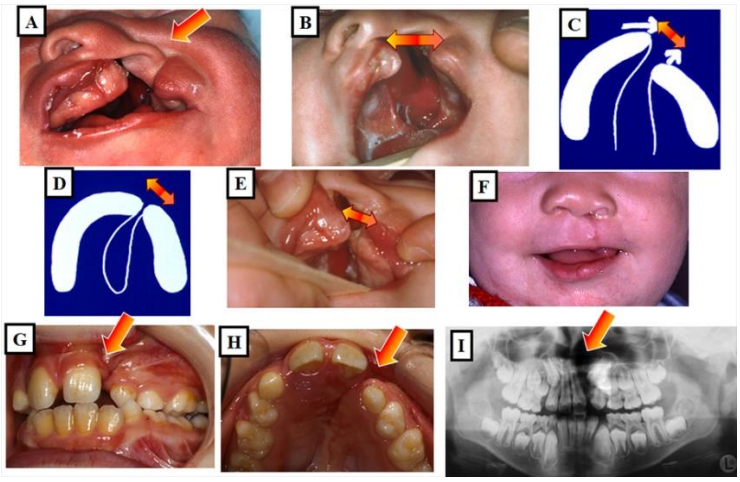
additional cost, long surgical time and postsurgical reabsorption, disease transmission, major histo incompatibility, graft versus-host disease (GVHD), immunosuppression, unpredictable outcome for tissueformation and infection of foreign material**.[27,28]** Thesechallenges can be avoided if stem cell based

regenerative techniques are used .Cleft lip and palate is one of the most predominant craniofacial deformity discussed in literature. These are associated with alveolar clefts which are predominantly treated by use of autologous cancellous bone grafts. Stem cell regenerative techniques aregrowing as a promising treatment modality for correction of alveolar clefts .

Autogenous osteoblasts cultured on demineralized bone matrix showed more reduction in defect size in comparison to control group. About 90% defect

correction of soft palate defect has been reported 14 d after injection of autologous MSCs.[30] Biomaterial seeded with autogenous osteogenic cells into the

alveolar cleft resulted in spontaneously eruption of canine in its proper place after eighteen months **(Fig 1 A-O)** [31] Poly-L-lactic acid with osteogenically differentiated fat-derived stem cells showed substantial bone regeneration in palatal defect**.[32]** The mean pain score, including both intensity and pain frequency and donor site morbidity was greatest at all time points in traditional iliac crest bone graft and least at all-time points in tissue engineering**.[31]**



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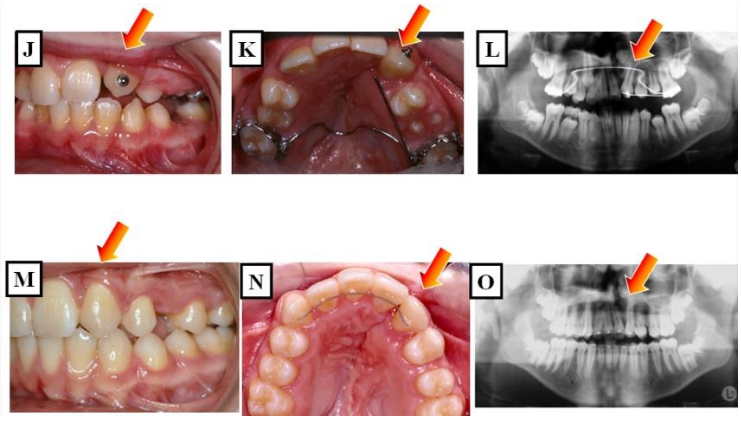

Fig. 1 (A–O). Clinical course of a patient with unilateral cleft lip and palate

A–C: Initial condition at birth and prior to any orthodontic intervention. **D–F:** Six months after the orthodontic presurgical intervention aimed at reducing the cleft width by modulating the growth of the maxillary segments in preparation for primary lip closure.
G–I: Clinical situation in the mixed dentition. A persistent alveolar bone defect is present in the cleft region. Tooth 12 is congenitally missing, and tooth 13 is unable to erupt due to the bony deficiency.
J–L: Condition following maxillary expansion and subsequent alveolar bone grafting in the cleft area. This enabled the active eruption of the canine.
M–O: Final outcome after completion of comprehensive orthodontic treatment. After successful bone augmentation, proper alignment of the canine in the position of the lateral incisor was achieved.

Thus it can be concluded that SCs seem to possess favorable potential for bone regeneration in oral and maxillofacial region and use of them in alveolar defect repair, reduce defect size by bone formation, have less postoperative morbidity compared to autogenous bone grafting and help the teeth in the defect area to erupt in their proper position**.[32-34]**

Autologous fat grafting is considered to reconstruct soft tissue defect in the treatment of congenital malformations as well as post traumatic malformations. To overcome problems associated with fat grafting, such as unpredictable clinical results and a low rate of graft survival, many innovative efforts and refinements of surgical techniques have been reported. Use of adipose derived stromal cells (ASCs) for tissue regeneration has attracted attention recently. Patients with HFM which have been grafted with supplementation of ASCs Showed 88% of fat volume surviving after 6 months in comparison to control group which was 54%. [35,36]Also, residual graft volumes of ASCs enriched grafts was significantly higher in comparison to control group.[36]

2.2.Temporomandibular joint tissue engineering and stem cells

The temporomandibular joint (TMJ) comprised both osseous and cartilaginous structures. It is enclosed in a capsule that is lubricated with synovial fluid and serves as an important growth site during postnatal development with two articular

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surfaces that can adapt to changing environment conditions. The mandibular condyle grows by proliferation of the progenitor/SCs that differentiate into chondrocytesleading to formation and increase of cartilage matrix, which

will be replaced with lamellar trabecular bone.[28.28] As SCs possess the ability to differentiate into chondrogenic and osteogenic cells, they could be used for both maintenance of mandible in new position and repair of TMJ lesions.

therapy, leads to increase in the number of mesenchymal cells (stem/progenitor cells) in the temporal fossa, which resulted in new cortical bone formation. TMJ is prone to injuries, tumors, osteoarthritis, rheumatoid arthritis and congenital anomalies. Temporomandibular disorder manifest as pain, myalgia, headaches, and structural destruction, collectively known as degenerative joint disease. The primary

methods used to reconstruct the TMJ includes autogenous bone grafting such as harvesting from the rib, or the use of alloplastic materials, with neither being ideally suited for the task and sometimes leading to unwanted adverse effects.

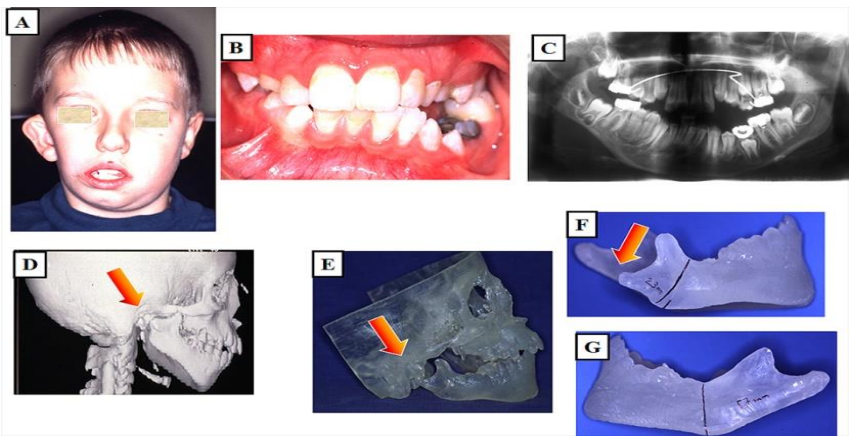
Recently, these cells have attracted much interest to joint reconstruction. Engineering a TMJ-like osteochondral graft has been studied in several studies. In one study, Combination **o**f polylactide acid discs with adipose tissue SC demonstrated the potential to development a tissue-engineered TMJ disc.

These data revealed possibility of application of SCs in combination with different scaffolds as a promising approach to regenerate osteochondral tissues of TMJ and ultimately the joint disk.[27-29]

2.3.Distraction Osteogenesis

DO which is regarded as “endogenous bone tissue engineering” has been widely applied in orthopedic surgery for correction of limb length and also in the

treatment of many craniofacial deformities. [37,38] DO is done by creating a corticotomy, placing a rigid distractor across the cut bone and gradually activating the device.[38] Long treatment periods and fibrous union or even non-union of bone are possible major draw backs impeding its widespread clinical application **(Fig. 2 A-N)**.



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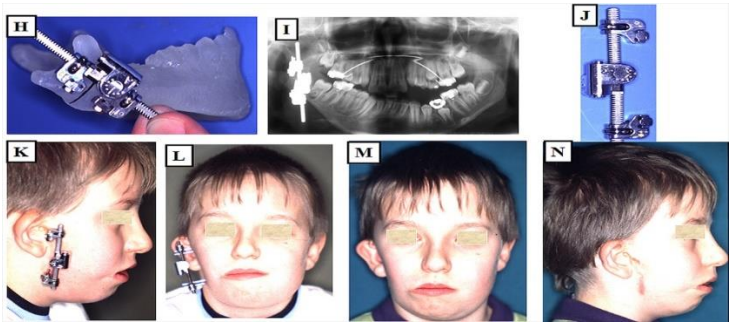

Fig. 2 (A–N). Mandibular reconstruction using distraction osteogenesis in a patient with Goldenhar syndrome

A–C: Pre-treatment clinical and radiographic presentation of a patient with Goldenhar syndrome exhibiting pronounced unilateral mandibular ramus hypoplasia consistent with hemifacial microsomia. The deficient vertical ramus height and altered mandibular morphology are clearly identifiable.

D: CT scan providing a detailed depiction of the affected anatomical region, including the pathological alterations involving the right condyle.

E–G: Stereolithographic 3D reconstructions of the skull and mandible, enabling precise visualization of the defective right mandibular condyle and spatial assessment of the osseous defect morphology.

H–L: Placement and activation of an external distraction device to perform distraction osteogenesis. Following corticotomy, gradual distraction was initiated according to standard latency and activation protocols, allowing controlled neo-osteogenesis and progressive elongation of the mandibular ramus in both vertical and horizontal dimensions.

M, L: Sequential follow-up and final treatment outcome after consolidation. The images demonstrate successful ossification within the distraction gap, restoration of mandibular vertical height, and notable improvement in lower facial symmetry and skeletal contour

In some studies, alone MSCs,[39,40] in the others, gene transferred MSCs [41,42] and factors [43,44] have been used to enhance bone regeneration following distractionosteogenesis. The modifications such as use of scaffolds,[45]] demineralized bone matrix [46] and Plateletrich Plasma [47] have been done in some studies. MSCs transfected with bFGF showed excellent boneformation and higher BMD and bone mineral content (BMC) in the distracted callus.[46]

2.4.Expanded Envelope of Discrepancy

There are several factors that limit the extent of orthodontic movement including the anatomy of the alveolar bone, pressures exerted by soft tissues, periodontal tissue attachment levels, neuromuscular forces and lip–tooth relationships[48]**.**

The anteroposterior, vertical, and transverse millimetric range of treatment possibilities in orthodontics can be expressed as an “envelope of discrepancy” **.[49]** Gingival recession occurs secondarily to an alveolar bone dehiscence, if overlying tissues are stressed during OTM beyond this envelope **(Fig. 3, Fig. 4 A-D).** Sites in which the buccal or lingual bone cortex and

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covering gingival tissue are thin, such as lower incisors in patients with a prominent chin and compensation in the form of lingual tipping of these teeth are at particular risk of bone defects like fenestrations and dehiscence.[50]

Stem cells have the potential to generate different tissues, including bone, thereby stem cell therapy is a promising approach to alveolar bone regeneration.[51] Some researches have applied stem cell therapy in case of bone ridge augmentation in humans and mainly used bone marrow cells. The outcome of alveolar bone regeneration showed a tendency to enhance bone formation**.[52]**

Hence, bone regeneration methods using SCs might provide an approach for expanding limitations of envelope of discrepancy.

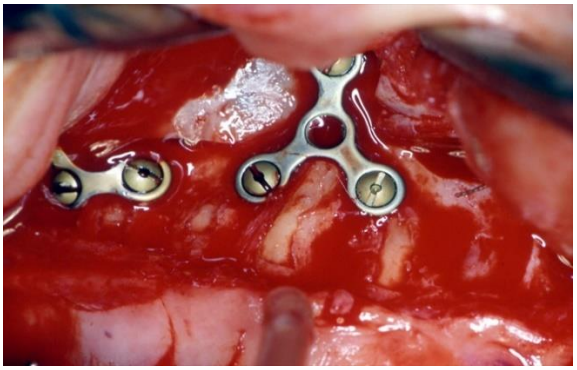

Fig. 3. Periodontal osseous defects observed during maxillary osteotomy following orthodontic transverse maxillary expansion

Intraoperative view during maxillary osteotomy after mucoperiosteal flap elevation. Distinct alveolar bone dehiscences and fenestrations of the buccal cortical plate are evident—periodontal osseous defects that developed as a consequence of prior orthodontic transverse maxillary expansion. These periodontal defects illustrate the expansion-induced thinning of the buccal alveolar housing and emphasize the anatomical limitations and potential periodontal risks associated with orthodontically driven maxillary widening.

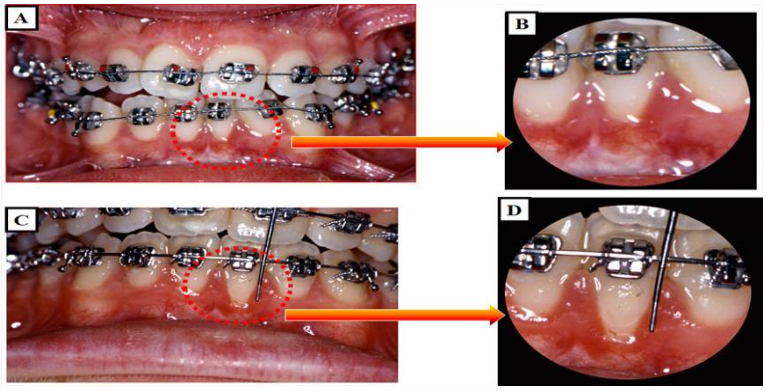

Fig. 4 A-D. Gingival recession and buccal alveolar bone dehiscence induced by excessive protrusion of the mandibular incisors

Power System Technology
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A, B: Baseline examination immediately after initiation of orthodontic treatment. Although no clinical recession was present, the mandibular incisors were positioned at the buccal cortical boundary, indicating a high-risk periodontal phenotype. **C, D:** At 5 months, continued labial displacement resulted in a **site-specific gingival recession** and a **buccal alveolar bone dehiscence**, illustrating the breakdown of periodontal support due to orthodontic movement beyond the physiologic limits of the alveolar housing.

2.5.Periodontium tissue regeneration and stem cells

Periodontal complications are one of the most actual side effects linked to the orthodontics. It can be found in various forms, from gingivitis to periodontitis, dehiscence, fenestrations, interdental fold, gingival recession or overgrowth, black triangles. Periodontal regeneration has been defined as the formation of new cementum, alveolar bone, and a functional periodontal ligament (PDL) on a

previously diseased root surface. The current treatment approaches include the use of surgery, GTR, bone fillers and growth factors and application of bioactive molecules to induce regeneration **(Fig. 5 A-F, Fig. 6 A-C, Fig. 7 A-E, Fig. 8 A-E)**. On the one hand, because of the increasing number of adult patients seeking orthodontic treatment, encountering the periodontally involved patients may be a potential problem for every practitioner. It has been suggested that, by moving the teeth into infrabony defects, we can achieve the regeneration of the attachment apparatus.

The periodontal defects such as fenestration, dehiscence and attachment loss are among common complications of orthodontic treatments. In a study, induced pluripotent SCs have been implanted into a mouse periodontal fenestration defect model with a silk fibroin scaffold in combination with EMD gel. Thus, the use of PDLSC transplantation in periodontal therapies can reduce treatment time and better outcomes followed by patient comfort; however, due to complex structure of periodontium, regeneration is a feasible and yet complicated procedure and may need pluripotent SCs and more investigations.

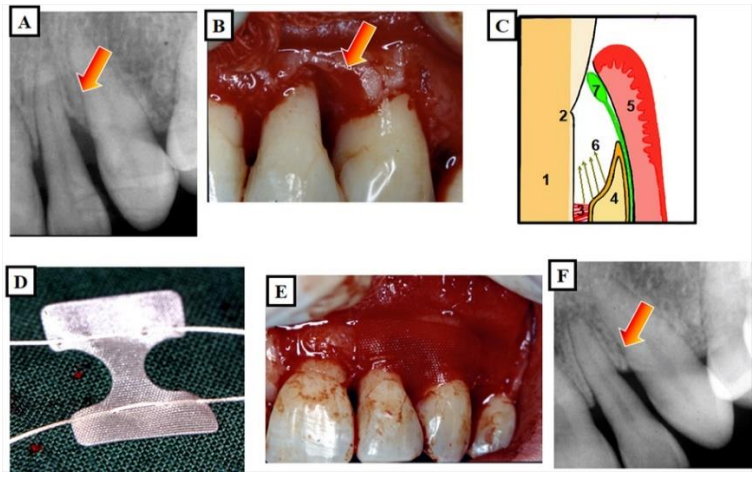

Fig. 5 (A–F). Guided Tissue Regeneration (GTR) with resorbable membrane

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A, B: Initial radiographic and clinical view of an infrabony defect distal to the lateral incisor. **C, D:** Principle of GTR: barrier membrane separates the defect from soft tissue to allow selective periodontal regeneration. **E:** Intraoperative placement of the membrane. **F:** Six-month radiograph showing defect fill and successful regenerative outcome.

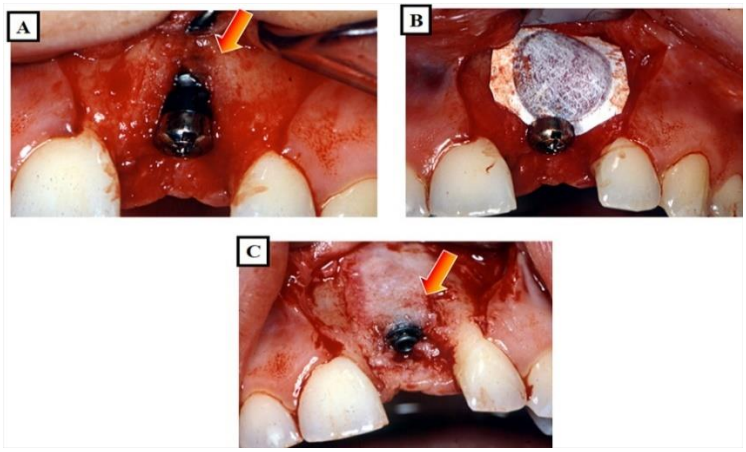

Fig. 6 (A–C). Guided Bone Regeneration (GBR) using a non-resorbable membrane to reconstruct a buccal peri-implant bone defect

A–C: Clinical and surgical presentation of Guided Bone Regeneration (GBR) performed to treat a pronounced buccal peri-implant bone defect. A non-resorbable barrier membrane (e.g., ePTFE) was placed to maintain space, stabilize the blood clot, and prevent soft-tissue ingrowth into the defect. By providing a long-term, stable barrier environment, the membrane enables selective repopulation of the site by osteogenic cells, supporting predictable new bone formation along the buccal aspect of the implant.

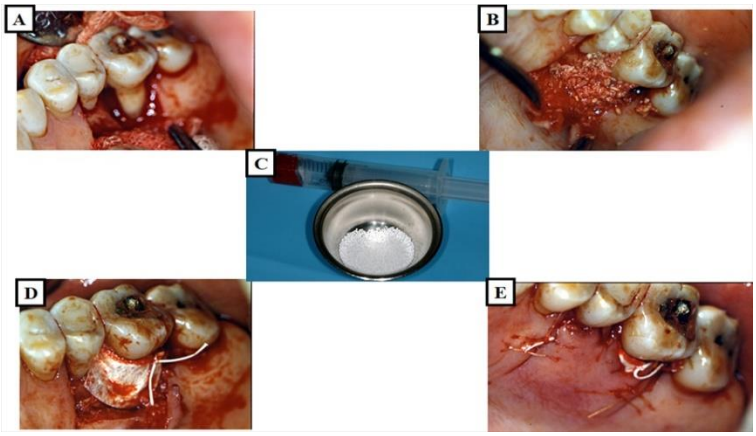

Fig. 7 (A–E). Guided Bone Regeneration (GBR) using bone substitute material and a non-resorbable membrane

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A–E: Clinical sequence of GBR performed to treat an alveolar bone defect. The defect was augmented with a bone substitute material and covered with a non-resorbable membrane (e.g., ePTFE) to maintain space, prevent soft-tissue ingrowth, and promote predictable new bone formation within the defect.

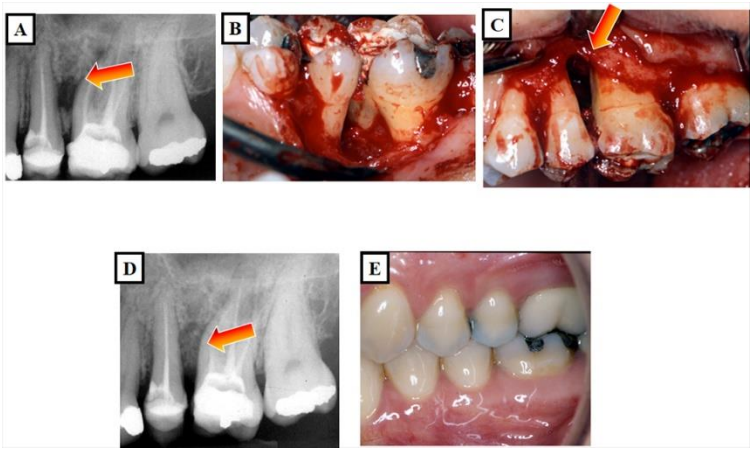

Fig. 8 (A–E). GBR with autogenous bone for regeneration of a mesial defect at tooth 26

A: Radiograph showing an infrabony defect with a sequestrum mesial to tooth 26. **B, C:** Clinical presentation of the defect after thorough surgical debridement. **D:** Six-month postoperative radiograph demonstrating substantial bone fill. **E:** Final clinical outcome showing restored periodontal tissues and stable regenerative result.

2.6.Accelerated orthodontic tooth movement

Orthodontic tooth movement (OTM) is achieved by the remodeling of PDL and alveolar bone in response to mechanical loading.[**32]** The initiating inflammatory event at compression sites is caused by constriction of the PDL microvasculature,

resulting in a focal necrosis, followed by recruiting of osteoclasts from the adjacent marrow spaces. These osteoclasts are mostly derived from hematopoietic SCs. Hence, SCs could be used to accelerate OTM by providing progenitor cells. The development of new methods to accelerate OTM has been sought by clinicians as a way to shorten treatment times, reduce adverse effects such as pain, discomfort, dental caries, and periodontal diseases, and minimize iatrogenic damages such as root resorption and the subsequent development of nonvital teeth. There are surgical methods like surgically-facilitated orthodontic therapy or corticotomy, periodontally accelerated osteogenic orthodontics **(Fig. 9 A-F)** and some nonsurgical procedures such as systemic/local administration of chemical substances such as epidermal growth factor, parathyroid hormone, 1,25-dihydroxyvitamin D3, osteocalcin and prostaglandins, resonance vibration, static or pulsed magnetic field, low-intensity laser irradiation therapy. This ability of SCs could be used to accelerate OTM in response to orthodontic forces. When orthodontic force is applied, tooth

movement is hindered until the necrosis is removed, leading to the clinical manifestation of a delay period. Hypothetically, transplantation of SCs in pressure sites may speed up the process, resulting in accelerated OTM. Hypothetically,

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transplantation of SCs in pressure sites may speed up the process, resulting in accelerated OTM.

2.7.External apical root resorption

Root resorption is a common and unfavorable side effect of orthodontic treatment, [53,54] which any specialist may encounter. Many factors seems to be involved in ERR such as genetics, individual biological variability, age, sex, and orthodontic forces and treatment duration.[55,56] Orthodontic forces are one of the main etiological factors for external root resorption. There are currently no treatment modalities for root resorption .

Stem cells and tissue engineering are being studied for repair of root resorption after orthodontic tooth movement by regeneration of the tissues like dentin and cementum and it was found that some amount of regeneration could be achieved. Bioengineering of the entire tooth is being studied and is still under research. .[55,56]

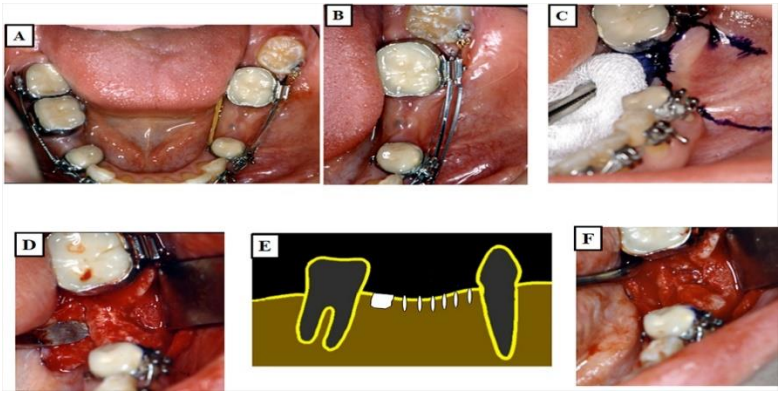

Fig. 9 (A–F). Corticotomy-assisted mesialization of tooth 37

A, B: Treatment plan showing mesialization of tooth 37 to optimize the position of tooth 38 with minimal effects on the anterior teeth.
C, D: Incision design and elevation of a mucoperiosteal flap for cortical bone exposure.
E: Schematic illustration of the planned corticotomy perforations.
F: Intraoperative view of the completed corticotomy to facilitate accelerated orthodontic tooth movement.

2.8.Mandibular growth in mandibular hypoplasia using

stem cells:

Viral vectors carrying vascular endothelial growth factor (rAAV-VEGF) have been shown to stimulate mandibular growth in vivo in rats**.[57]** Yet, more research is needed to optimize the technique and detailed toxicity evaluation of viral and non viral vectors (both local and systemic), and testing optimized techniques in higher animals before clinical trials can be conducted. The hypothesis underlying local injection of vector-loaded VEGF into mandibular condyles is that this VEGF can modulate mandibular growth through added VEGF effect that has been shown to be correlated to mandibular growth stimulation**.[58,59]** VEGF may stimulate mandibular growth through two mechanisms:

Power System Technology
ISSN:1000-3673
Received: 06-10-2025 Revised: 15-11-2025 Accepted: 25-12-2025

(1) through stimulation of endochondral bone growth and

(2) through recruitment of new replicating mesenchymal stem cells, which is correlated to mandibular growth**[60,61]** Gene therapy as well as LLL (Laser) or LED (Light emtting diode) seems to be promising approaches in stimulating mandibular growth. However, detailed toxicity investigations of these techniques are required before potential clinical trials can be performed.

2.9.Cleft lip and palate

Cleft lip and palate is a congenital malformation that requires a multidisciplinary treatment that evolves pediatrician, obstetrics, fetal medicine, genetics, plastic surgery, orthodontics, speech therapist, nursery, and psychology. The intrauterine diagnosis leads to preborn parental orientation and better parental collaboration to accept a precocious multidisciplinary treatment. New ideas to use SCs and blood from the umbilical cord and also blood from placenta are discussed to improve final surgical results**.[62,63]** Maternal SCs are easy to collect, there are no damage to the patient and mother, it is autologous and it could be very useful in the authors' protocol. A technique using umbilical cord blood SCs could be a promising new approach for repairing cleft palate in infants, Performed as part of reconstructive surgery when the infant is a few months old, the procedure provides good results in growing new bone to close the upper jaw cleft and may prevent the need for later bone graft surgery, the researchers report.[64] Umbilical cord blood is a rich source of various types of SCs, which have the potential to develop into many different types of specialized cells, including bone and cartilage. Umbilical cord SCs also have greater regenerative potential, according to the researchers**.[65]** For the first few months, the infant underwent nonsurgical nasoalveolar shaping procedure to align the soft tissues of the upper jaw. At the age of 5 months, the SCs were thawed for use as part of boneless bone grafting surgery, or gingivoperiostioplasty. The SCs were placed in a pocket of soft tissue bridging the gap in the upper jaw.[**65-68**] It has potential complications and subjects the child to one or more additional surgeries. The study is the first to use SCs as part of primary surgery to repair cleft palate in an infant. The researchers say that their patient will need further monitoring to ensure adequate bone thickness in the upper jaw. Also, the researchers emphasize the need for further studies evaluating their SC technique in a large number of patients, including steps to confirm that bone formation results from the SCs and not from the initial boneless bone graft surgery.[**62-68**] **(Fig. 1 A-O)**

2.10.Rapid Maxillary Expansion

Maxillary constriction can be associated with several problems that include occlusal disharmony and esthetics as well as such functional difficulties as narrowing of the pharyngeal airway, increased nasal resistance, and alterations in tongue posture, resulting in retroglossal airway narrowing and mouth breathing.[**69**]

Maxillary constriction can be corrected with slow orthodontic expansion, rapid maxillary expansion (RME), surgically assisted rapid palatal expansion or a two-segmented Le Fort I-type osteotomy with expansion.[**70**]

RME is indicated in patients younger than 12 years, who have lateral discrepancies involving several teeth, whether the constriction is skeletal, dental or a combination of both. It is an

Power System Technology
ISSN:1000-3673
Received: 06-10-2025 Revised: 15-11-2025 Accepted: 25-12-2025

effective orthopedic procedure to open the midpalatal suture, providing appropriate and stable maxillary width increase and re-stablish balance between the width of the jaws.[**71]**

RME is similar to DO histologically. During RME, a gap in the midpalatal suture is created which is filled with blood and granulated tissue and followed by active bone formation. The expanded arch width relapses unless followed by an appropriate retention period. Therefore, providing a strategy to accelerate bone formation in the midpalatal suture might shorten treatment and retention period, achieve stability and prevent relapse **(Fig. 10 A-O, Fig. Fig. 11 A-T)**. Because of the ability of SCs to differentiate into osteogenic cells, injection of SCs seems to have the ability to accelerate the process of bone formation. This was studies in one study by Ekizer et al **(2015).[72]**

In their animal study, local injection of MSCs into intermaxillary suture after force application resulted in increased new bone formation in the suture by increasing the number of osteoblasts and new vessel formation**.** Thus, locally applied MCSs to the expanded maxilla might be a useful and practical treatment strategy to accelerate new bone formation in midpalatal suture and to shorten the treatment and retention period for patients undergoing orthopedic maxillary expansion **.[62]**

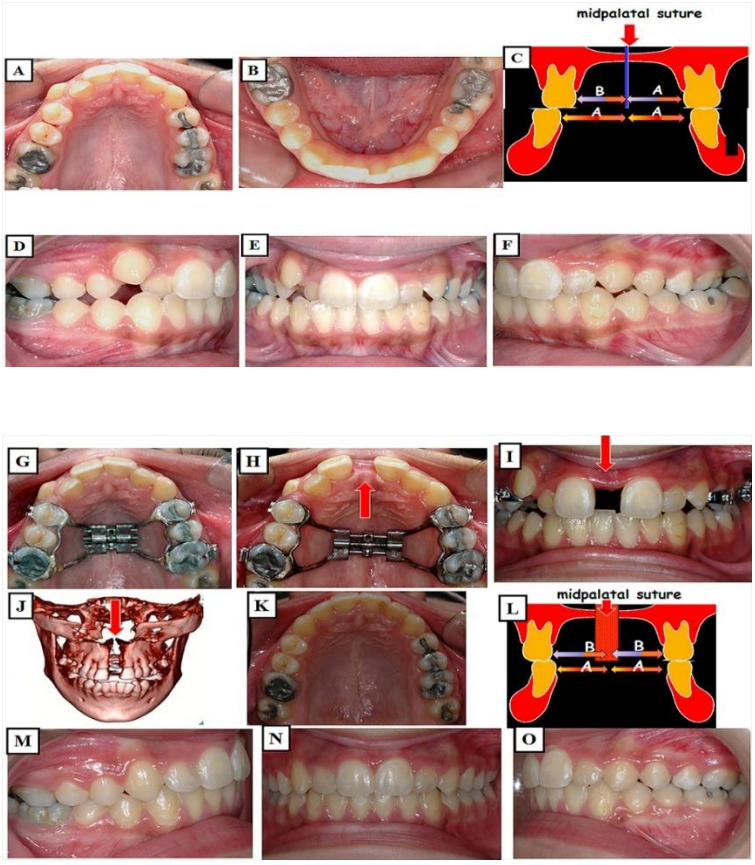

Fig. 10 (A–O): Orthodontic expansion through a conventional RPE (Rapid Palatal Expander).

A-F: Before treatment, a narrow upper jaw (A-C), and crossbite (D).

Power System Technology
ISSN:1000-3673
Received: 06-10-2025 Revised: 15-11-2025 Accepted: 25-12-2025

G: Maxillary expansion device inserted and positioned prior to activation.

H–I: Clinical views following successful skeletal maxillary expansion achieved with a Hyrax screw.

J: CBCT image providing a three-dimensional visualization of the achieved transverse expansion and the associated skeletal effects.

K–O: Clinical situation after completion of treatment.

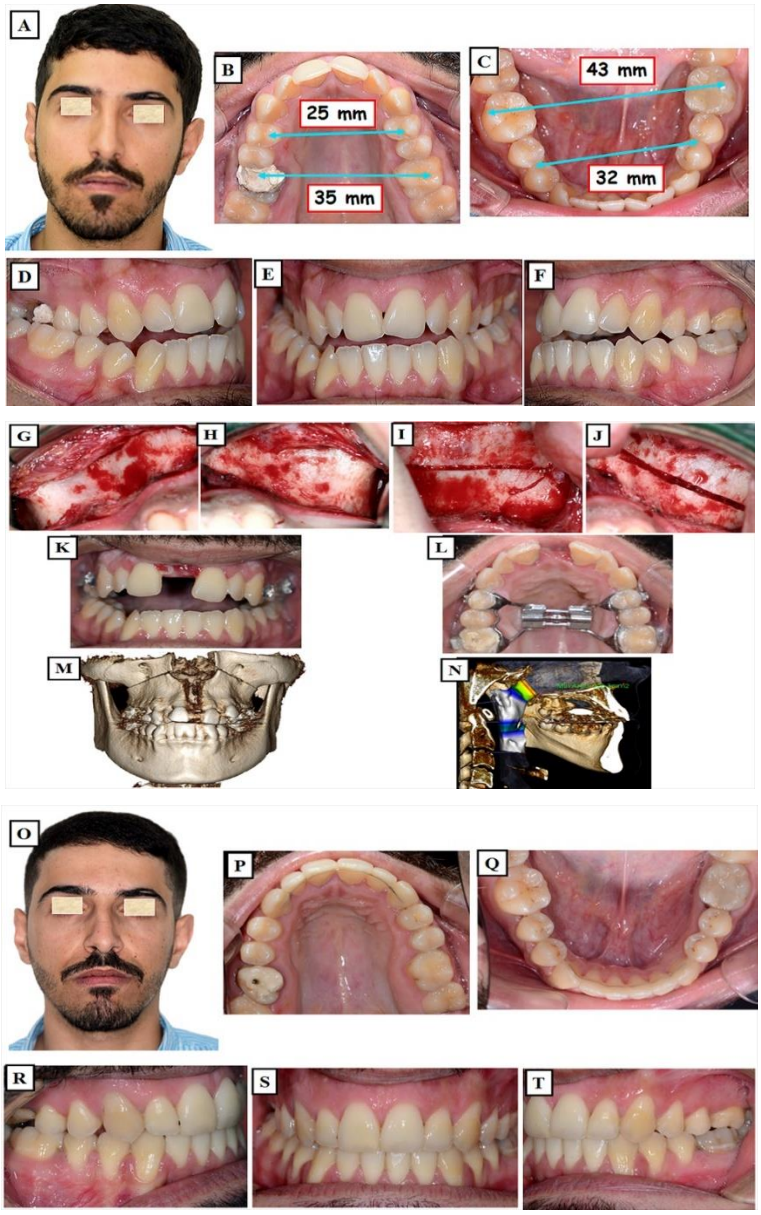

Fig. 11 (A–T): Expansion of the maxilla through Surgically Assisted Rapid Palatal Expansion (SARPE).

Power System Technology
ISSN:1000-3673
Received: 06-10-2025 Revised: 15-11-2025 Accepted: 25-12-2025

A-F: Situation before treatment, narrow face and narrow nose (A), narrow upper jaw (B) compared to the lower jaw, skeletal and dentoalveolar crossbite on the right and left (D-F).

G-L: Surgical assistance for maxillary expansion. Surgical separation of the bones on the maxilla was partially performed at the level of Lefort I.

K-N: Maxillary expansion with the screw (K, L). Cone-beam computed tomography (CBCT) after expansion shows the separation of maxillary parts (M) and the airway (N). Improvement in breathing and breathing disorders is expected in such patients.

Q-T: Condition after treatment, changes in facial width (Q), changes in jaw widths (P, Q) with occlusion correction (R-T).

2.11.Oral tissues remodeling and regenerating:

Remodelling of the alveolar bones is important in regenerating tissues.

Stem cells play an essential role in controlling this phenomenon coupled by local signaling/growth factors and systemic hormones. [**62**]

3.Discussion

SCs could be a promising new approach in orthopedic surgery especially for repairing cleft lip and palate in infants. There are some studies that can already demonstrated important results of regenerative, neovascular, anti-inflammatory and tissue neoformation part of them had stem cells injection and part had only the conventional treatment done and comparing between them, Nine patients with clef lip and palate were operated and had stem cells from umbilical cord blood and placenta blood injected into the bone and soft tissue during the procedure. The subjective analysis demonstrated that the group of patients with stem cell injection had less inflammatory response at lip soft tissue, less scar hypertrophy, there was no palate fistula or dehiscence and less fibrosis between hard and soft palate at the second palatal surgery the results have shown no adverse results and improvement at the inflammatory response. A treatment protocol with stem cells was developed**.[62]**

SCs could reduce the treatment time**,** Embryonic stem cells have been proved to differentiate into cartilage cells and have been implanted on artificially created cranial osseous defects. Mesenchymal stem cells (MSCs) express and secrete various factors and other cytokines that are important for angiogenesis. Various bioactive factors are secreted by the stem cells that suppress the local immune system, inhibit fibrosis, stimulate mitosis. Thus, by increasing the rate of healing and regeneration, treatment time hopefully could to be reduced**.[74]**

SCs preserve periodontal health, The success of orthodontic treatment is related to the health of periodontium is without any signs of diseases and defects Human PDLSCs get attached to the surfaces of the alveolar bone and tooth root when integrated into the PDL tissue. Dental pulp stem cells DPSCs have the highest osteogenic potential among bone marrow mesenchymal stem cells BMMSCs and periosteal cells**.[75]**

Power System Technology
ISSN:1000-3673
Received: 06-10-2025 Revised: 15-11-2025 Accepted: 25-12-2025

And external apical root resorption is the most common and undesirable sequelae of Orthodontic treatment. Various derivatives of stem cells may be used prior to the treatment, may prevent root resorption or post treatment to repair the damage**.[76]**

Decreased number of resorption lacuna with MSCs transfer to the PDL can be explained with proliferation and differentiation of MSCs to reparative cells like cementoblasts and cementoblast-like cells after the metabolic regeneration request and to create an antiinflammatory activity**. [77]**

Accelerated wound healing: Bone marrow mesenchymal stem cell BMMSCs treated wounds exhibit significantly accelerated wound closure, with increased re-epithelialization, cellularity, and angiogenesis.[**78**]

4. Future Perspectives of Stem Cells Therapy:

4.1. Periodontal Regeneration:

Periodontium can be regenerated successfully by transplantation of ex vivo prolonged autologous MSCs. It is also confirmed, that periodontal defects can be managed by reimplantation of these cells. Dental Pulp Stem Cells DPSCs can form ectopic dentin and related pulp tissue.[**79-82]**

4.2. Tooth regeneration:

Three key elements are involved in tooth regeneration which include: Inductive morphogenes, Stem cells and Scaffold. .[**79-86**]

Regeneration of tooth hypothesis can be carried out throughout many steps. The adult stem cellsare harvested and are arranged into a scaffold that provides optimized environment. Cells are instructed with targeted soluble molecular signals

spatially and gene expression is read. Finally, theabove mentioned mixture is incubated into a suitable conditions till the final product is produced.

4.3. Reimplantation and Transplantation of teeth can be carried out via stem cell therapy through enhanced tissue healing processes .[**79-86**]

4.4. Bioengineered Teeth:

A method has been developed to regenerate tooth buds in a single procedure by combining dental pulp and bone marrow on a scaffold and implanting this into surgically created defects. After a number of months, the construct led to organized

dentin, enamel, pulp, cementum, and periodontal ligament surrounded by regenerated alveolar bone, suggesting a method that could translate directly to

humans [**79-86**]

5.**CONCLUSION:**

Tissue engineering using stem cells is a fast emerging field and finds wide applications in the field of Orthodontics. Mesenchymal stem cells have been utilised in correcting the defects associated with craniofacial syndromes. Their increased cellula renewal and turnover can be

Power System Technology
ISSN:1000-3673
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utilised in correction of temporomandibular disorders and distraction Osteogenesis. Their ability to induce new bone formation can be used to promote the stability after. rapid maxillary expansion. This bone forming potential can help in expanding the envelope of discrepancy and thereby greater tooth movement can be achieved Orthodontically . Regenerative potential of stem cells finds its application in the treatment of root resorption and periodontal defects. Also Osteoclastic precursors can be used in accelerating tooth movement. Further research in the integrated approach of the two fields will have a wide range of applications.

ABBREVIATIONS;

-MSCs- Mesenchymal stem cells

- BMSCs- Bone marrow–derived MSCs

- DSCs- Dental stem cells

-0DPSCs- Dental pulp stem cells

-PDSCs- Periodontal ligament stem cells

-SCAP- apical papilla stem cells

-DFSCs- dental follicular stem cells

- iPSCs- induced pluripotent stem cells

CONSENT

It is not applicabl

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests

exist.

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