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Ministry of Higher Education
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College of Dentistry

Stem Cells in Orthodontic Treatment
A review

A Project Submitted to
The College of Dentistry, University of Baghdad, Department of Orthodontics in Partial Fulfillment for the Bachelor of Dental Surgery

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Certification of the Supervisor

I certify that this project entitled **" Stem Cells in Orthodontic Treatment; A Review"** was prepared by fifth-year student **Noor Maytham Mahdi** under my supervision at the College of Dentistry/University of Baghdad in partial fulfilment of the graduation requirements for the Bachelor degree in dentistry.

Dr. Alan Issa Saleem

The Supervisor

25-4-2022

Dedication

I dedicate this work to my creator, my strong pillar, my source of inspiration, wisdom.

Mam & dad,

Thank you for teaching me to believe in myself, in God and in my dreams.

To my family members

For raising me to believe that anything was possible.

To my best friends

Whose make the world a better place, just by being in it……

Noor Maytham Mahdi

Acknowledgment

First, I thank **"Allah"** almighty for granting me the will and strength to accomplish this project and I pray that his blessings upon me may continue throughout my life.

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List of Abbreviations

BMMSCs	Bone Marrow Mesenchymal Stem Cells
CLP	Gleft Lip and Palate
DFSCs	Dental Follicle Stem Cells
DO	Distraction Osteogenesis
DPSCs	Dental Pulp Stem Cells
ERR	External Root Resorption
ESCs	Embryonic Stem Cells
GMSCs	Gingiva-derived Mesenchyme Stem Cells
GSC	Germinal Stem Cell
GTR	Guided Tissue Regeneration
GVHD	Graft Versus Host Disease
HSC	Hematopoietic Stem Cell
HUCM	Human Umbilical Cord Matrix
IPSCs	Induced Pluripotent Stem Cells

MSC	Mesenchyme Stem Cell
OESCs	Oral epithelial progenitor/stem cells
OTM	Orthodontic Tooth Movement
PDL	Periodontal Ligament
PDLSCs	Periodontal Ligament Stem Cells
PSCs	Periosteum-derived stem cells
RME	Rapid Maxillary Expansion
RME	Rapid Maxillary Expansion
SCAP	Stem Cells from Apical Papilla
SCs	Stem Cells
SGSCs	Salivary Gland Stem Cells
SHEDs	Stem Cells from Human Exfoliated Deciduous Teeth
TGPSCs	Tooth germ progenitor cells
TMD	Tempromandibular Joint Disorder

Introduction

Stem cells are the foremost attention grabbing cells in cell biology. They have the potential to evolve as one of the most powerful technologies in the future. Stem cells are often used therapeutically in every field of health science.
In fact, several procedures are reformed after stem cells come into play **(Kathade *et al*., 2019).**

Stem cells are unspecialized cells having a property of self renewal and further differentiate into various types of specialized cells **(Potdar and Deshpande, 2013).** Stem cells are identified in a number of adult tissues including skin, adipose tissues, peripheral blood, bone marrow, pancreas, intestine, brain, hair follicles, as well as in the dental pulp cells**,** Stem cell research has expanded well due to their usefulness in regenerative therapies for improving the life of patients suffering from various genetical and neurological diseases (**Shi and Gronthos, 2003; Potdar and Kumar, 2013).**

Faster orthodontic treatment is one among the main demands of the patient population, that isn't adequately met by the orthodontists. The traditional method that was used to reduce treatment time were low friction, self-ligating bracket systems, robot preformed archwires, rapid canine retraction, and alveolar corticotomies. These procedures have positively brought better results, however, newer and higher technologies are perpetually welcome. Technologies such as stem cell therapy hold good potential and can bring a revolutionary change within the field of health science. The information of stem cells and its implications can facilitate the orthodontists to modify their treatment planning, which is able to acknowledged by the patient **(Kathade *et al*., 2019).**

Nowadays, mesenchyme stem cell (MSCs) could be considered as “research trends” in the field of biology and medicine and their application in regenerative medicine is growing. Some modalities involve direct plantation of MSCs into the defect site while others use proper scaffolds to support the cells. In bone tissue engineering, MSCs are carried by an osteoconductive scaffold and differentiated toward osteogenic cells using osteoinductive growth factors **(Motamedian *et al.*, 2016).**

Aims of the study

The aims of the present study are:

1) To give clue about the applications of stem cells (SCs) in treatment of dentofacial defects and deformities.
2) Proposing possible advantages of SCs therapy in enhancing orthodontic treatments.

Chapter One: Review of Literatures

1.1 Stem Cells

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 **(Biehl and Russell, 2009).**

Various sources for harvesting SCs have been introduced such as muscle, dermis, bone marrow, adipose tissue, periosteum, blood, umbilical cord, synovial membrane and teeth **(Chang *et al.,* 2021).** 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 (**Gay *et al.,* 2007; Khojasteh *et al.,* 2015; Motamedian *et al*., 2017).**

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 **(Ramalho-santos and Willenbring, 2007; Kabir *et al*., 2014).**

1.2 History of Stem Cells

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 differentiate **(Ramalho-Santos and Willenbring, 2007).**

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 **(Ferreira and Greck, 2020).**

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 **(Estrela *et al.*, 2011).**

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 **(Moradi, 2020).**

1.3 Characteristics of Stem Cells:

Stem cells classified according to characteristics **(Lakshmipathy and Verfaillie, 2005; Singh *et al.*, 2014).**

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

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.

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).

4. Unipotency: And called also dedicated progenitors: produce one particular cell type.

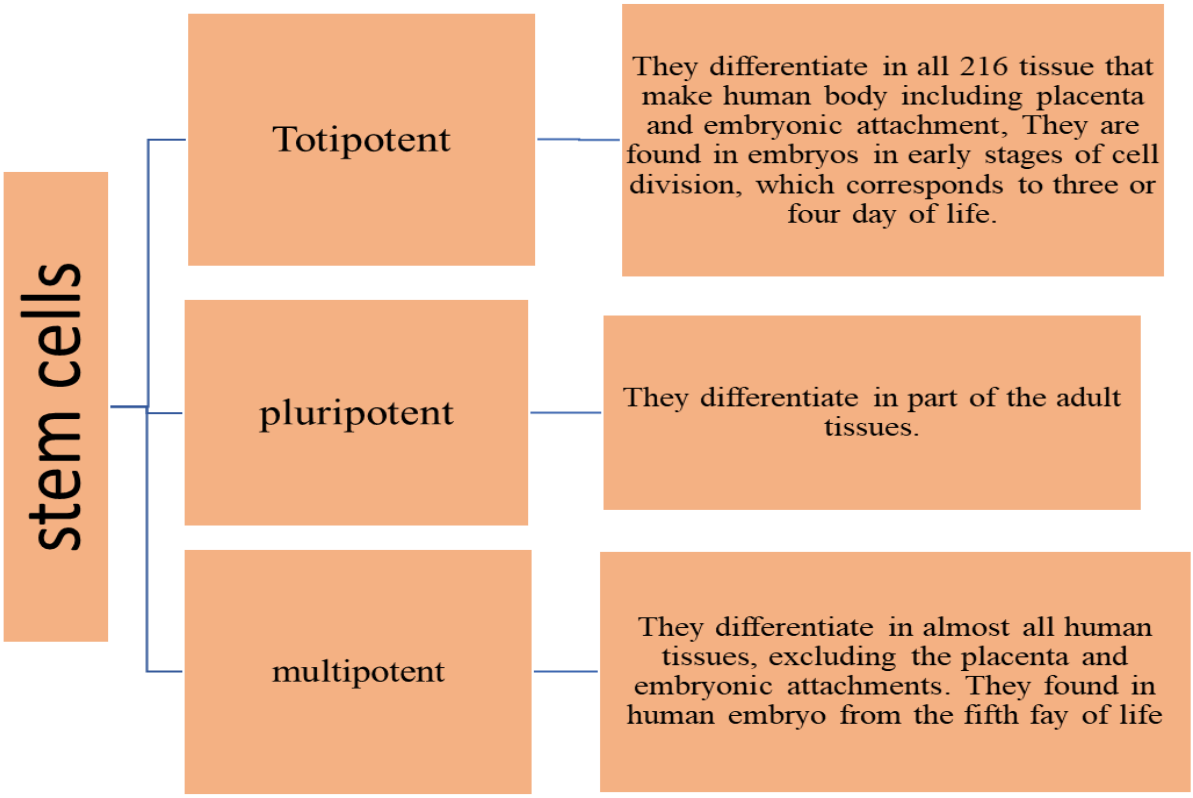

Fig 1: Characteristic of stem cells according to their potential differentiation (Ferreria and Greck, 2020)

1.4 Types of Stem Cells

Human stem cells can be categorized into three main categories embryonic, germinal and somatic **(Kabir *et al.*, 2014).**

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.

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

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.

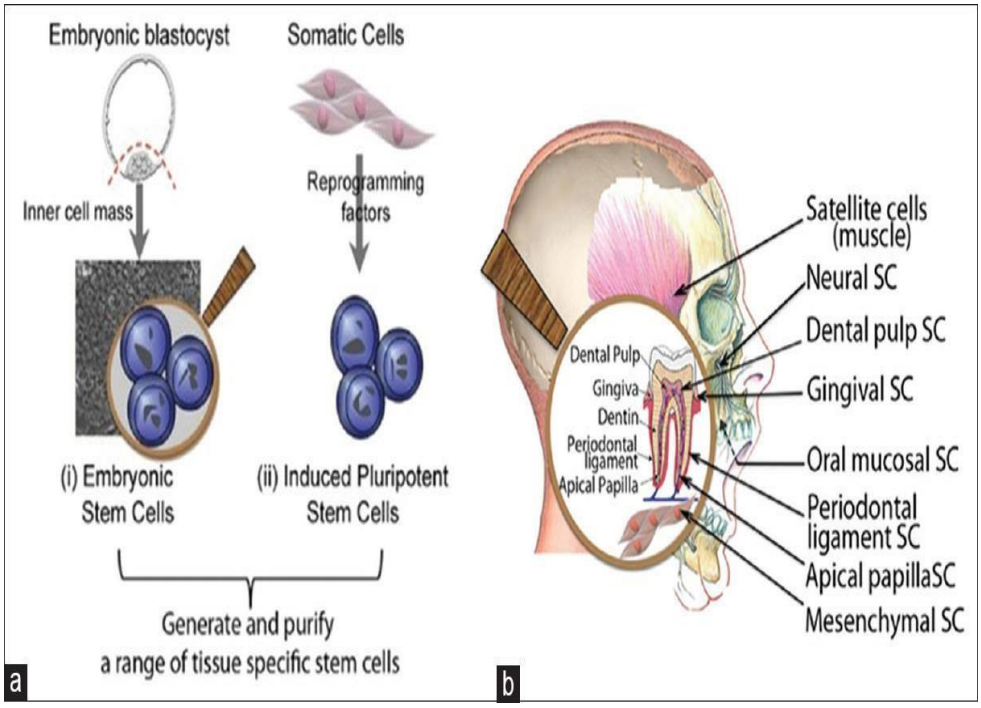

Figure 2: (a) Pluripotent stem cells (b) adult stem cells (Kumar *et al*., 2020)

1.5 Dental Stem Cells

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 **(Hsiao *et al*., 2021).**

1.5.1 Dental Pulp Stem Cells

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 **(Potdar and Jethmalani, 2015).**

1.5.2 Stem Cells from Human Exfoliated Deciduous Teeth (SHED)

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.* 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).**

1.5.3 Stem Cells from Apical Papilla (SCAP)

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).**

1.5.4 Periodontal Ligament Stem Cells (PDLSCs)

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 **(Li *et al.*, 2021).**

1.5.5 Dental Follicle Stem Cells

The dental follicle is the connective tissue surrounding the enamel organ and dental papilla that forms a vascular fibrous sac. **Morsczeck *et al*. (2005)** 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 **(Chen *et al*., 2015; Xu *et al*., 2017).**

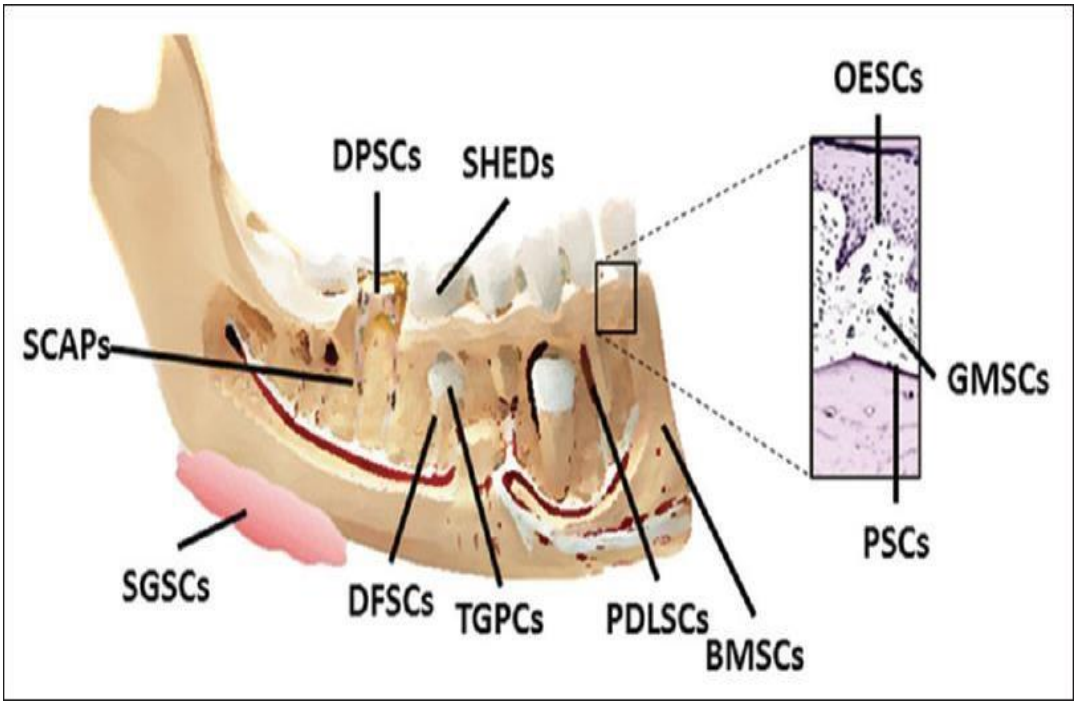

Figure 3: The locations of developmental and postnatal stem cell populations in the dental and craniofacial region indicating sources for isolation from the mandible and teeth (Kumar *et al*., 2020).

1.6 Stem Cells in Orthodontics and Orthopedics

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 **(Kiyak, 2008)**. The prevalence of dental malocclusion varies in different communities and have been reported to be 22.5% to 93% **(Silva and Kang, 2001)**.

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 **(Khojasteh and Motamedian, 2016).**

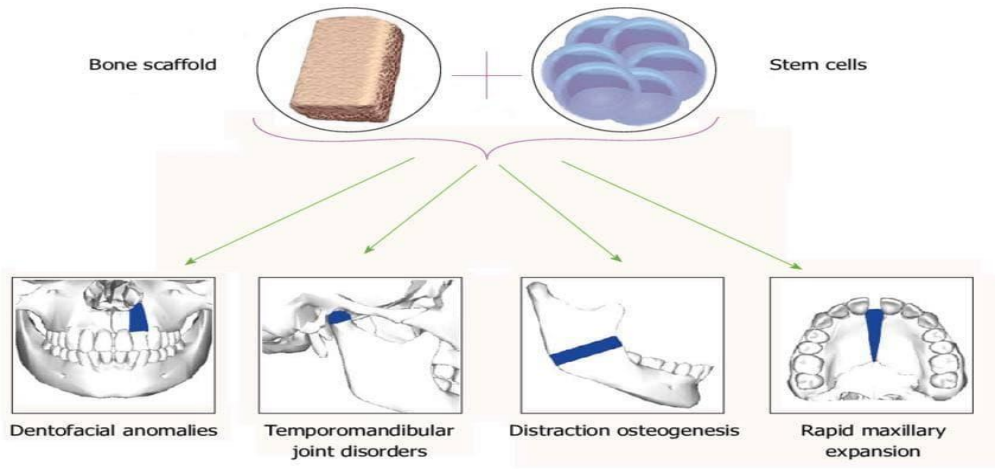

Figure 4 Applications of stem cells in dentofacial orthopedics (Safari *et al.*, 2018).

1.6.1 Dentofacial Orthopedics

1.6.1.1 Dentofacial Anomalies

There are many congenital and dentofacial deformities which results from trauma, tumour resection, non-resection, non- fusion of fractures and they are difficult to treat. Currently there are numerous techniques like autogenous, allogenic and various prosthetic material can be used to reconstruct the hard and soft tissues **(Kathade *et al.*, 2019).**

These approaches have several complications such as insufficient autogenous resources, donor site morbidity, contour irregularities, postoperative pain, additional cost, long surgical time and postsurgical reabsorption, disease transmission, major histoincompatibility, graft versus-host disease (GVHD), immunosuppression, unpredictable outcome for tissue formation and infection of foreign material. In order to overcome these complications, stem cell-based tissue regeneration offers a promising approach to provide an advanced and reliable therapeutic strategy for craniofacial tissue reconstruction **(Bayerlein *et al.*, 2006)**.

In the current review, regenerative approaches for craniofacial anomalies; cleft lip and palate (CLP) is one of the most prevalent congenital anomalies which results from fusion failure of nasal process and oropalatal shelves. The prevalence of this malformation is 0.36-0.83 in 1000 live-born infant. Alveolar bone defect, problem in swallowing, facial deformity, missing teeth, and maxillary deformity can be seen in CLP patients **(Luaces-Rey *et al*., 2010).**

Repair of the malformed alveolar bone is critical for oronasal fistula closure, maxilla unification and tooth eruption. The gold standard treatment for alveolar reconstruction in CLP patients is autogenous cancellous bone grafts **(Nwoku *et al.*, 2005; Brito *et al.*, 2012)**. Since they are immunologically inert and potential

suppliers of cells with osteoconductive and osteoinductive properties, the commonest site for acquiring autogenous bone for grafting is the anterior iliac crest, alternatives to the traditional iliac crest bone grafting techniques are available. MSCs have been shown to have the ability to form new bone when transplanted **(Horswell and Henderson, 2003; Gimbel *et al*., 2007).**

Some case reports and case series studies reported results of MSCs usage to regenerate alveolar cleft **(Khojasteh *et al*., 2015).**

1) In one case of cleft, the composite scaffold of demineralization bone mineral and calcium phosphate loaded in stem cells showed 34.5 % regenerated bone whereas in the other it was 25.6%. Also, in few cases about 50% bone regeneration has been seen. While in other it it was reported about 79.1 % of bone regeneration
2) In one of the studies, about 90% defect correction of soft palate defect has been reported 14 days after injection of autologous MSCs
3) Results also proved spontaneous eruption of canine after 18 months after injection of osteogenic cells in alveolar cleft
4) Bone regeneration in palatal defect after treatment with Poly- L- lactic acid with osteogenically differentiated fat- derived stem cells

Therefore, from the above study it was concluded that stem cells had favourable potential for regeneration of bone in oral and maxillofacial region and also it can be used for repair of alveolar defects, reduction of defect size, less postoperative morbidity and also help the teeth to erupt in their proper position **(Conejero *et al*., 2006; Behnia *et al*., 2009; Pradel and Lauer, 2012).**

1.6.1.2 Distraction Osteogenesis (DO):

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. Distraction osteogenesis is a biological process of new bone formation between the surfaces of osteotomized bone segments that are separated gradually by incremental traction. The pathophysiology of osteogenesis is initiated by an immediate inflammatory response that leads to the recruitment of MSCs and subsequent differentiation into chondrocytes that produce cartilage and osteoblasts which form bone (**AiAql *et al.*, 2008)**.

Despite its great advantages, long treatment periods and fibrous union or even non-union of bone are possible major draw backs impeding its widespread clinical application. Efforts have been made to accelerate osteogenesis in the distraction gap, shorten the consolidation period and reduce complications such as the development of nonunion, infection, or fracture **(McCarthy *et al.*, 2002).**

Due to the ability of MSCs in osteogenesis, many researchers have successfully documented the ability of SCs on promoting bone formation and shortening the consolidation period during DO. For this purpose various sources of SCs such as human exfoliated deciduous teeth (SHED)**,** bone marrow and adipose tissue have been used in studies (**Alkaisi *et al.*, 2013)**.

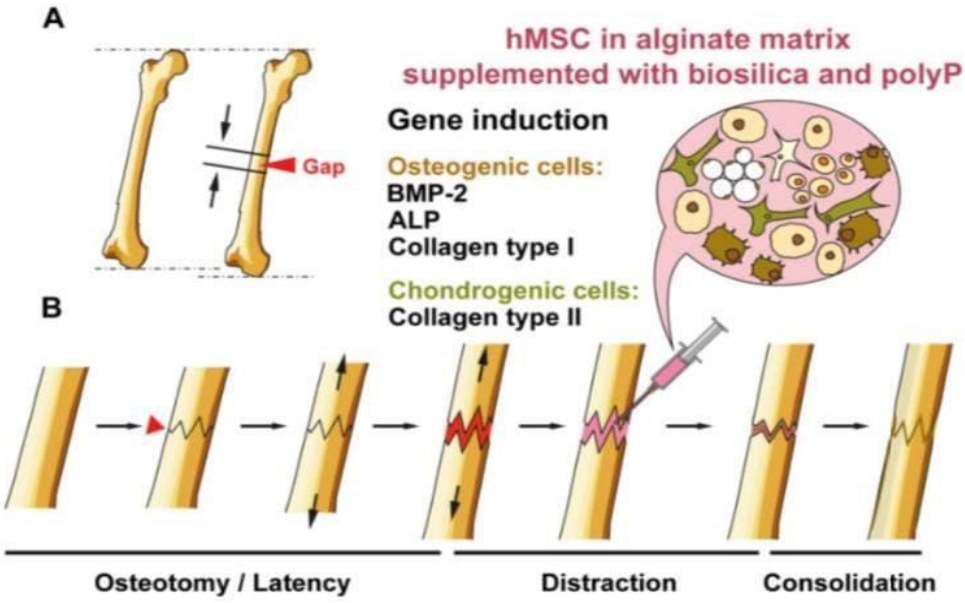

Figure 5. Distraction Osteogenesis Scheme (Wang *et al*., 2014).

(A) The healthy part of the bone is broken into two segments with an external instrument. A distraction gap is formed; (B) distraction osteogenesis phases: osteotomy/latency, distraction, consolidation. During the distraction phase, hMSCs, embedded into alginate, are proposed to be injected into the fracture zone. These supplements are hoped to accelerate the velocity of bone formation and shortening the consolidation period **(Wang *et al*., 2014).**

1.6.1.3 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 **(De Rossi *et al*., 2009; Aloufi *et al*., 2012; Vidya and Sumath, 2015**).

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 **(Mommaerts, 1999).**

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 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 **(Lagravere *et al.*, 2005; Baratieri *et al*., 2011).**

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. 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).**

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 **(Ekizer *et al.*, 2015).**

1.6.1.4 TMJ Disorder

The temporomandibular joint (TMJ) is comprised of 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 surfaces that can adapt to changing environment conditions. The mandibular condyle grows by proliferation of the progenitor/SCs that differentiate into chondrocytes leading to formation and increase of cartilage matrix, which will be replaced with lamellar trabecular bone **(Carlson, 2002; Roberts *et al*., 2004).**

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. Forward positioning of mandible, for example in functional therapy, leads to increase in the number of mesenchymal cells (stem/progenitor cells) in the temporal fossa, which resulted in new cortical bone formation **(Rabie, 2003).**

TMJ is prone to injuries, tumors, osteoarthritis, rheumatoid arthritis and congenital anomalies. Approximately 10 million individuals in the United States have been affected by temporomandibular disorders (TMD). TMD 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. The major and final option for those patients with advanced degenerative diseases is surgical replacement of the mandibular condyle. These approaches have complications such as infection, implant wear, dislocation, suboptimal biocompatibility, donor site limitation and morbidity, and potential pathogen transmission **(Shanti *et al.*, 2007).**

To overcome these disadvantages, strategies have been found to engineer osteochondral tissue, such as that found in the TMJ, will produce tissue that is both biologically and mechanically functional used. Recently, these cells have attracted much interest to joint reconstruction, engineering a TMJ-like osteochondral graft has been studied in several studies. The culture of human umbilical cord matrix (HUCM) SCs in growth medium containing chondrogenic factors, showed the HUCM SCs can outperform the TMJ condylar cartilage cells, 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 **(Bailey *et al*., 2007).**

1.6.2 Stem Cells in Orthodontics

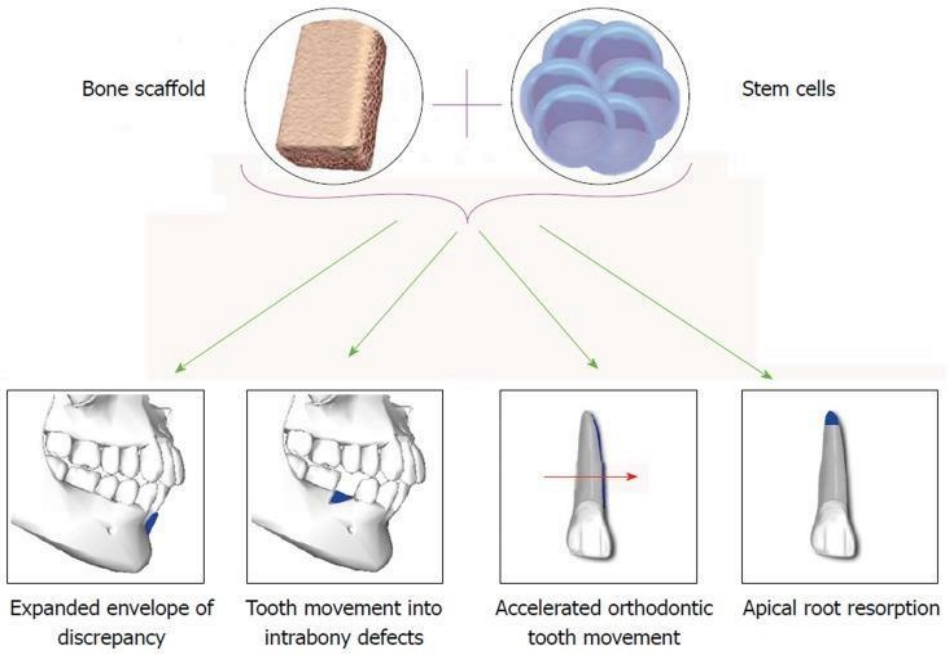

Figure 6: Possible application of stem cells (alone or in conjugation with bone scaffolds) in orthodontics (Safari *et al*., 2018).

1.6.2.1 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 **(Safari *et al*., 2018).**

The anteroposterior, vertical, and transverse millimetric range of treatment possibilities in orthodontics can be expressed as an "envelope of discrepancy" **(Proffit *et al*., 2012).** Gingival recession occurs secondarily to an alveolar bone dehiscence, if overlying tissues are stressed during OTM beyond this envelope. Sites in which the buccal or lingual bone cortex and 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 **(Preoteasa *et al*., 2012).**

Stem cells have the potential to generate different tissues, including bone, thereby stem cell therapy is a promising approach to alveolar bone regeneration **(Black *et al*., 2015).** 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 **(Miguita *et al*., 2017).**

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

1.6.2.2 Accelerated Orthodontic Tooth Movement (OTM):

OTM is achieved by the remodeling of periodontal ligament (PDL) and alveolar bone in response to mechanical loading**.** 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 **(Masella and Meiste, 2006**).

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 non-vital teeth **(Zainal Ariffin *et al.*, 2011)**.

There are surgical methods like surgically-facilitated orthodontic therapy or corticotomy, periodontally accelerated osteogenic orthodontics**.** Some nonsurgical procedures such as systemic/local administration of chemical substances like epidermal growth factor, parathyroid hormone, 1,25-dihydroxy vitamin D3, osteocalcin and prostaglandins, resonance vibration, static or pulsed magnetic field, low-intensity laser irradiation therapy **(Almpani and Kantarci, 2016).**

In a study, increased PDL progenitor cells with suppressed expression of type I collagen (Col-I) were observed during orthodontic force application, whilst after force withdrawal they increase in Col-I expression, which suggests that PDLSCs are able to respond to orthodontic mechanical forces with suppressed collagen expression **(Feng *et al*., 2016).**

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 **(Safari *et al.*, 2018).**

1.6.2.3 Periodontal Regeneration

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 **(Proffit, 2012).** Periodontal regeneration has been defined as the formation of new cementum, alveolar bone, and a functional periodontal ligament on a previously diseased root surface **(Reynolds *et al.*, 2003).**

The current treatment approaches include the use of surgery, guided tissue regeneration (GTR), bone fillers and growth factors and application of bioactive molecules to induce regeneration **(Reynolds *et al.*, 2015; Khojasteh *et al.*, 2017).**

Based on the differential potential capability of SCs and their ability of renewal via mitosis they have the quality to regenerate damaged tissues, hence they can be used for regeneration of periodontium. Periodontal defects could be a challenging situation both pre and post orthodontic treatment **(Bianco *et al.*, 2010).**

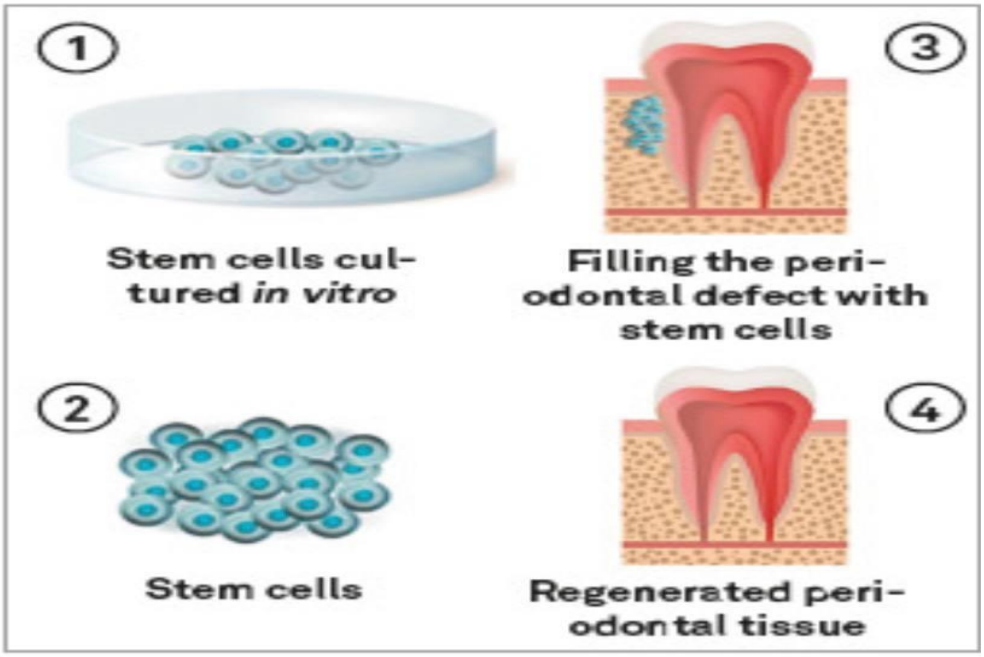

Figure 7: Mesenchymal Stem Cells for periodontal regeneration (Ferreria and Greck, 2020)

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 **(Safari *et al.*, 2018).**

1.6.2.4 External Root Resorption (ERR)

External root resorption is a common and unfavorable side effect of orthodontic treatment which any specialist may encounter. Many factors seem to be involved in ERR such as genetics, individual biological variability, age, sex, and orthodontic forces and treatment duration **(Pizzo *et al.*, 2007; Mohanty *et al.*, 2015).**

Orthodontic forces yet seem to be the main etiologic factors. ERR may lead to loss of tooth structure such as cementum and in more advanced stages, dentin, however no specific treatment has been introduced so far. One possible treatment modality could be regeneration of resorbed roots by application SCs and tissue engineering **(Zahrowski and Jeske, 2011; Guo *et al*., 2016).**

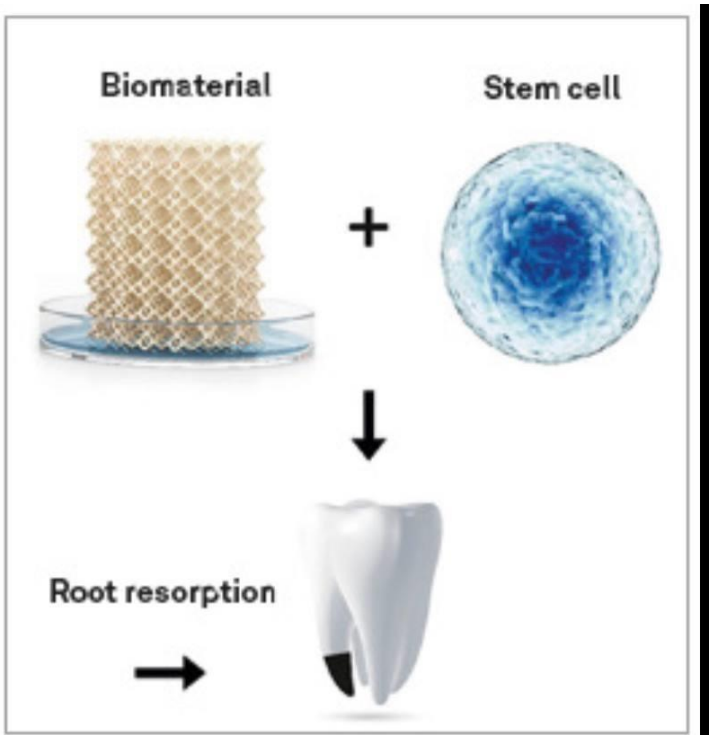

Figure 8: Mesenchymal stem cells undergoing root regeneration (Ferreria and Greck, 2020)

In severe cases, ERR may cause poor prognosis of tooth, resulting in tooth loss. Regeneration of these lesions increases the longevity of tooth and may play an important role in facilitating the treatment. In a study designed to induce de novo cementum formation by SC therapy, MSCs driven from periodontal ligament in in vivo transplantation were able to form cellular cementum-like hard tissue containing embedded osteocalcin-positive cells **(Shinagawa *et al*., 2017).**

According to studies in which the whole tooth structure has been bioengineered and transplanted into Rodent and beagle dogs models, it might be possible to regenerate the damaged tooth structure such as dentin and cementum and in the future to achieve a bioengineered functional human tooth structure. Although it seems that there is a long way until regeneration of the teeth materials, cementogenesis and regeneration of dental structures through stem cellbased therapies could be anticipated **(Oshima *et al.*, 2011).**

Chapter two

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 **(Mazzetti *et al.*, 2018).**

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 **(Caplan, 2017).**

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 **(Mishra, 2016).**

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 **(Marques and Martins, 2012).**

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 **(Amuk *et al*., 2016).**

Accelerated wound healing: Bone marrow mesenchymal stem cell BMMSCs treated wounds exhibit significantly accelerated wound closure, with increased re-epithelialization, cellularity, and angiogenesis **(Wu *et al*., 2007).**

Chapter three

Conclusions and Suggestions

3.1. Conclusions

1) Stem cell open the door for new nonsurgical and minimally invasive treatment for orthopedic injury.

2) Reduce duration of treatment.

3) Preserve periodontal health.

4) Reduction of root resorption risk.

5) Accelerated wound healing.

3.2. Suggestions

1) Realize the value of these cells and exploit them to solve many orthodontic problems and reduce patients' fears of orthodontics

2) More research should be conducted to evaluate the safety and efficacy of stem cells

3) Used stem cells more in the future, and that there will be promotional and awareness campaigns about the importance of stem cells and their locations, especially in the primary teeth.

Reference:

A

- Ai-Aql, Z.S., Alagl, A.S., Graves, D.T., Gerstenfeld, L.C. and Einhorn, T.A. (2008) Molecular mechanisms controlling bone formation during fracture healing and distraction osteogenesis. Journal of *dental research*, *87*(2), 107-118.
- Alkaisi, A., Mutum, S.S., Ahmad, Z.A.R., Masudi, S.A. and Abd Razak, N.H. (2013) Transplantation of human dental pulp stem cells: enhance bone consolidation in mandibular distraction osteogenesis. Journal of *Oral and Maxillofacial Surgery*, *71*(10), 1758.
- Almpani, K. and Kantarci, A. (2016) Nonsurgical methods for the acceleration of the orthodontic tooth movement. *Tooth movement*, *18*, 8091.
- Aloufi, F., Preston, C.B. and Zawawi, K.H. (2012) Changes in the upper and lower pharyngeal airway spaces associated with rapid maxillary expansion. *International Scholarly Research Notices*, *2012*.
- Amuk, N., Kurt, G., Baran, Y., Seyrantepe, V., Yandim, M., Adan, A., Demir, S., Kiraz, Y. and Sonmez, M. (2016) Effects of cell-mediated osteoprotegerin gene transfer and mesenchymal stem cell applications on orthodontically induced root resorption of rat teeth. *The European Journal of Orthodontics*, *39*(3), 235-242.

B

- Bailey, M., Wang, L., Bode, C., Mitchell, K. and Detamore, M. (2007) A Comparison of Human Umbilical Cord Matrix Stem Cells and Temporomandibular Joint Condylar Chondrocytes for Tissue Engineering Temporomandibular Joint Condylar Cartilage. *Tissue Engineering*, 13(8), pp.2003-2010.
- Baratieri, C., Alves Jr, M., de Souza, M.M.G., de Souza Araujo, M.T. and Maia, L.C. (2011) Does rapid maxillary expansion have long-term effects on airway dimensions and breathing. *American Journal of Orthodontics and Dentofacial Orthopedics*, *140*(2), 146-156.
- Bayerlein, T., Proff, P., Heinrich, A., Kaduk, W., Hosten, N. and Gedrange, T. (2006) Evaluation of bone availability in the cleft area following secondary osteoplasty. *Journal of Cranio-Maxillofacial Surgery*, *34*, 57-61.

Behnia, H., Khojasteh, A., Soleimani, M., Tehranchi, A., Khoshzaban, A., Keshel, S.H. and Atashi, R. (2009) Secondary repair of alveolar clefts using human mesenchymal stem cells. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and endodontology*, *108* (2), e1-e6

- Bianco, P., Robey, P.G., Saggio, I. and Riminucci, M. (2010) Mesenchymal" stem cells in human bone marrow (skeletal stem cell): a critical discussion of their nature, identity, and significance in incurable skeletal disease. *Human gene therapy*, *21*(9), 1057-1066.
- Biehl, J. K. and Russell, B. (2009) Introduction to stem cell therapy. The *Journal of cardiovascular nursing*, 24(2), 98.
- Black, C.R., Goriainov, V., Gibbs, D., Kanczler, J., Tare, R.S. and Oreffo, R.O. (2015) Bone tissue engineering. Curr Mol Biol Rep 1: 132–140.
- Brito, L.A., Paranaiba, L.M., Bassi, C.F., Masotti, C., Malcher, C., Schlesinger, D., Rocha, K.M., Cruz, L.A., Bárbara, L.K., Alonso, N., Franco, D., Bagordakis E., Martelli, H.Jr., Meyer, D., Coletta, R.D. and Passos-Bueno, M.R. (2012) Region 8q24 is a susceptibility locus for nonsyndromic oral clefting in Brazil. *Birth Defects Research Part A: Clinical and molecular Teratology*, *94*(6), 464-468

C

- Caplan, A.I. (2017) Mesenchymal stem cells: time to change the name!. *Stem cells translational medicine*, *6*(6), 1445-1451.
- Carlson, D.S. (2002) Biological rationale for early treatment of dentofacial deformities. *American journal of orthodontics and dentofacial orthopedics*, *121*(6), 554-558.
- Chang, D., Fan, T., Gao, S., Jin, Y., Zhang, M. and Ono, M. (2021) Application of mesenchymal stem cell sheet to treatment of ischemic heart disease. *Stem Cell Research & Therapy*, *12(1), 1-10*
- Chen, G., Chen, J., Yang, B., Li, L., Luo, X., Zhang, X., Feng, L., Jiang, Z., Yu, M., Guo, W. and Tian, W. (2015) Combination of aligned PLGA/Gelatin electrospun sheets, native dental pulp extracellular matrix and treated dentin matrix as substrates for tooth root regeneration. Biomaterials, 52, 56-70.
- Conejero, J.A., Lee, J.A., Parrett, B.M., Terry, M., Wear-Maggitti, K.,

Grant, R.T. and Breitbart, A.S. (2006) Repair of palatal bone defects using osteogenically differentiated fat-derived stem cells. *Plastic and Reconstructive Surgery*, 117(3), 857-863.

D

- De Rossi, M., De Rossi, A., Hallak, J.E., Vitti, M. and Regalo, S.C. (2009) Electromyographic evaluation in children having rapid maxillary expansion. *American Journal of Orthodontics and Dentofacial Orthopedics*, 136(3), 355-360.

E

- Ekizer, A., Yalvac, M.E., Uysal, T., Sonmez, M.F. and Sahin, F. (2015) Bone marrow mesenchymal stem cells enhance bone formation in orthodontically expanded maxillae in rats. *The Angle Orthodontist*, *85*(3), 394-399.
- Estrela, C., Alencar, A.H., Kitten, G.T., Vencio, E.F. and Gava, E. (2011) Mesenchymal stem cells in the dental tissues: perspectives for tissue regeneration. *Brazilian Dental Journal*, 22(2), 91-98.

F

- Feng, L., Yang, R., Liu, D., Wang, X., Song, Y., Cao, H., He, D., Gan, Y., Kou, X. and Zhou, Y. (2016) PDL progenitor–mediated PDL recovery contributes to orthodontic relapse. *Journal of Dental Research*, *95*(9), 10491056.
- Ferreira, J. and Greck, A. (2020) Adult mesenchymal stem cells and their possibilities for Dentistry: what to expect? *Dental Press Journal of Orthodontics*, 25(3), 85-92.

G

- Gay, I.C., Chen, S. and MacDougall, M. (2007) Isolation and characterization of multipotent human periodontal ligament stem cells. *Orthodontics & craniofacial research*, *10*(3), 149-160.
- Gimbel, M., Ashley, R.K., Sisodia, M., Gabbay, J.S., Wasson, K.L., Heller, J., Wilson, L., Kawamoto, H.K. and Bradley, J.P. (2007) Repair

of alveolar cleft defects: reduced morbidity with bone marrow stem cells in a resorbable matrix. *Journal of Craniofacial Surgery*, 18(4), 895-901.

Guo, Y., He, S., Gu, T., Liu, Y. and Chen, S. (2016) Genetic and clinical risk factors of root resorption associated with orthodontic treatment. American Journal of Orthodontics and Dentofacial Orthopedics, 150(2), 283-289.

H

- Horswell, B.B. and Henderson, J.M. (2003) Secondary osteoplasty of the alveolar cleft defect1. *Journal of oral and maxillofacial surgery*, *61*(9), 1082-1090.
- Hsiao, H., Nien, C., Hong, H., Cheng, M. and Yen, T. (2021) Application of dental stem cells in three-dimensional tissue regeneration. *World Journal of Stem Cells*, 13(11),1610-1624.

K

- Kabir, R., Gupta, M., Aggarwal, A., Sharma, D., Sarin, A. and Kola, M. (2014) Imperative role of dental pulp stem cells in regenerative therapies: a systematic review. Nigerian journal of surgery, 20(1), 1-8.
- Kathade, D. P., Toshniwal, D.N.G., Mani, D.S., Mote, D.N., & Dhanjani, D.V. (2019) Stem Cells in Orthodontics. *International Journal of Innovative Science and Research Technology*, *4*(11), 1–1.
- Khojasteh, A. and Motamedian, S.R. (2016) Mesenchymal Stem Cell Therapy for Treatment of Craniofacial Bone Defects: 10 Years of Experience. Journal of" Regeneration, Reconstruction & Restoration" 1: 1-7
- Khojasteh, A., Kheiri, L., Motamedian, S.R. and Khoshkam, V. (2017) Guided bone regeneration for the reconstruction of alveolar bone defects. Annals of maxillofacial surgery, 7(2), 263.
- Khojasteh, A., Motamedian, S.R., Rad, M.R., Shahriari, M.H. and Nadjmi, N. (2015) Polymeric vs hydroxyapatite-based scaffolds on dental pulp stem cell proliferation and differentiation. *World journal of stem cells*, *7*(10), 1215.
- Kiyak, H.A. (2008) Does orthodontic treatment affect patients' quality of life? *Journal of dental education*, *72*(8), 886-894.

Kumar, I.G., Pradeep, S., Ravi, S., Kiran, H.J. and Raghunath, N. (2020) Stem cells in orthodontics and dentofacial orthopedics: Current trends and future perspectives. International Journal of Orthodontic Rehabilitation, 11(1), p.21.

L

- Luaces Rey, R., Arenaz Búa, J., López-Cedrún Cembranos, J.L., Herrero Patiño, S., Sironvalle Soliva, S., Iglesias Candal, E. and Pombo Castro, M. (2010) Is PRP useful in alveolar cleft reconstruction? Platelet-rich plasma in secondary alveoloplasty.
- Lagravere, M.O., Major, P.W. and Flores-Mir, C. (2005) Long-term dental arch changes after rapid maxillary expansion treatment: a systematic review. The Angle Orthodontist, 75(2), 155-161.
- Li, J., Wang, Z., Huang, X., Wang, Z., Chen, Z., Wang, R., Chen, Z., Liu, W., Wul, B. and Qiu, W. (2021) Dynamic proteomic profiling of human periodontal ligament stem cells during osteogenic differentiation. Stem cell research & therapy, 12(1), 1-16.
- Lakshmipathy, U. and Verfaillie, C. (2005) Stem cell plasticity. Blood reviews, 19(1), pp.29-38.

M

- Marques, L., Júnior, P. (2012) Root resorption in orthodontics: An evidence-based approach. *Orthodontics-Basic Aspects and Clinical Considerations.* 1th ed. InTech: Shangai, 429-446
- Masella, R.S. and Meister, M. (2006) Current concepts in the biology of orthodontic tooth movement. American Journal of Orthodontics and Dentofacial Orthopedics, 129(4), 458-468.
- Mazzetti, M., Alonso, N., Brock, R., Ayoub, A., Massumoto, S. and Eça, L. (2018) Importance of Stem Cell Transplantation in Cleft Lip and Palate Surgical Treatment Protocol. *Journal of Craniofacial Surgery*, 29(6), pp.1445-1451.
- McCarthy, J.G., Katzen, T.J., Hopper, R. and Grayson, B.H. (2002) The first decade of mandibular distraction: lessons we have learned. *Plastic and Reconstructive surgery*, 110(7), 1704-1713.

Miguita, L., Mantesso, A., Pannuti, C.M. and Deboni, M.C.Z. (2017) Can stem cells enhance bone formation in the human edentulous alveolar ridge? A systematic review and meta-analysis. *Cell and Tissue Banking*, 18(2), 217-228.

- Mike, Moradi (2020) why stem cells could be the medical innovation of the century, (world economic forum annual meeting)
- Mishra, S. (2016) Stem Cells: A Step Ahead in Regenerative Dentistry with Accent on Orthodontics. *British Journal of Medicine and Medical Research*, 14(12), pp.1-7.
- Mohanty, P., Prasad, N.K., Sahoo, N., Kumar, G., Mohanty, D. and Sah, S. (2015) Reforming craniofacial orthodontics via stem cells. Journal of *International Society of Preventive & Community Dentistry*, 5(1), 13.
- Mommaerts, M.Y. (1999) Transpalatal distraction as a method of maxillary expansion. *British Journal of Oral and Maxillofacial Surgery*, 37(4), 268-272.
- Motamedian, S.R., Iranparvar, P., Nahvi, G. and Khojasteh, A. (2016) Bone tissue engineering: a literature review. Journal of*" Regeneration, Reconstruction & Restoration*"(Triple R), 1(3), 103-120.
- Motamedian, S.R., Tabatabaei, F.S., Akhlaghi, F., Torshabi, M., Gholamin, P. and Khojasteh, A. (2017) Response of Dental Pulp Stem Cells to Synthetic, Allograft, and Xenograft Bone Scaffolds. *International Journal of Periodontics & Restorative Dentistry*, 37(1)

N

- Nwoku, A.L., Al Atel, A., Al Shlash, S., Oluyadi, B.A. and Ismail, S. (2005) Retrospective analysis of secondary alveolar cleft grafts using iliac of chin bone. *Journal of Craniofacial Surgery*, 16(5), 864-868.

O

- Oshima, M., Mizuno, M., Imamura, A., Ogawa, M., Yasukawa, M., Yamazaki, H., Morita, R., Ikeda, E., Nakao, K., Kasugai, S., Saito, M. and Tsuji, T. (2011) Functional tooth regeneration using a bioengineered tooth unit as a mature organ replacement regenerative therapy. PloS one, 6(7), e21531.

P

- Pizzo, G., Licata, M.E., Guiglia, R. and Giuliana, G. (2007) Root resorption and orthodontic treatment. Review of the literature. *Minerva stomatologica*, 56(1-2), 31-44.
- Potdar, P. and Kumar, K.S. (2013) Establishment and molecular characterization of human dermal mesenchymal-like stem cells derived from human scalp biopsy of androgenetic alopecia patient.
- Potdar, P.D. and Deshpande, S. (2013) Mesenchymal stem cell transplantation: New, avenues for stem cell therapies. *Journal of Transplantation Technologies Research*, 3(122), 2161-0991.
- Potdar, P.D. and Jethmalani, Y.D. (2015) Human dental pulp stem cells: Applications in future regenerative medicine. *World journal of stem cells*, 7(5), 839.
- Pradel, W. and Lauer, G. (2012) Tissue-engineered bone grafts for osteoplasty in patients with cleft alveolus. *Annals of AnatomyAnatomischer Anzeiger*, 194(6), 545-548.
- Preoteasa, C.T., Ionescu, E. and Preoteasa, E. (2012) Risks and complications associated with orthodontic treatment. *Orthodontics-basic aspects and clinical considerations*, *2012*, 403-428.
- Proffit, W.R., Fields, H., Sarver, D. and Ackerman, J. (2012) *Contemporary Orthodontics.* 5th ed. Mosbey Philadelphia, 691

R

- Rabie, A.B.M., She, T.T. and Hägg, U. (2003) Functional appliance therapy accelerates and enhances condylar growth. *American Journal of Orthodontics and Dentofacial Orthopedics*, 123(1), 40-48.
- Ramalho-Santos, M. and Willenbring, H. (2007) On the origin of the term "stem cell*". Cell stem cell, 1*(1), 35-38.
- Reynolds, M.A., Aichelmann-Reidy, M.E., Branch-Mays, G.L. and Gunsolley, J.C. (2003) The efficacy of bone replacement grafts in the treatment of periodontal osseous defects. A systematic review. *Annals of periodontology*, 8(1), 227-265.

Reynolds, M.A., Kao, R.T., Camargo, P.M., Caton, J.G., Clem, D.S., Fiorellini, J.P., Geisinger, M.L., Mills, M.P., Nares, S. and Nevins, M.L. (2015) Periodontal regeneration–intrabony defects: a consensus report from the AAP Regeneration Workshop. *Journal of Periodontology*, 86,S105-S107.

- Roberts, W.E., Huja, S. and Roberts, J.A., (2004) June. Bone modeling: biomechanics, molecular mechanisms, and clinical perspectives. *In Seminars in orthodontics* (Vol. 10, No. 2, pp. 123-161). WB Saunders.

S

- Safari, S., Mahdian, A. and Motamedian, S.R. (2018) Applications of stem cells in orthodontics and dentofacial orthopedics: Current trends and future perspectives. *World journal of stem cells*, 10(6), p.66.
- Shanti, R.M., Li, W.J., Nesti, L.J., Wang, X. and Tuan, R.S. (2007) Adult mesenchymal stem cells: biological properties, characteristics, and applications in maxillofacial surgery. *Journal of Oral and Maxillofacial Surgery*, 65(8),1640-1647.
- Shi, S. and Gronthos, S. (2003) Perivascular niche of postnatal mesenchymal stem cells in human bone marrow and dental pulp. *Journal of bone and mineral research*, 18(4),696-704.
- Shinagawa-Ohama, R., Mochizuki, M., Tamaki, Y., Suda, N. and Nakahara, T. (2017) Heterogeneous human periodontal ligamentcommitted progenitor and stem cell populations exhibit a unique cementogenic property under in vitro and in vivo conditions. *Stem cells and development*, 26(9),632-645.
- Silva, R.G. and Kang, D.S. (2001) Prevalence of malocclusion among Latino adolescents. *American Journal of Orthodontics and Dentofacial Orthopedics*, 119(3),313-315.
- Singh, H., Bhaskar, D.J., Rehman, R., Jain, C.D. and Khan, M. (2014) Stem cells: An Emerging future in dentistry. *Int J Adv Health Sci*, 1(2),17-23.

V

- Verma, K., Bains, R., Bains, V.K., Rawtiya, M., Loomba, K. and Srivastava, S.C. (2014) Therapeutic potential of dental pulp stem cells in regenerative medicine: An overview. *Dental research journal*, *11*(3), 302.
- Vidya, V.S. and Sumathi, F.A. (2015) Rapid maxillary expansion as a standard treatment for obstructive sleep apnea syndrome: a systematic review. *J Dental Med Sci*, 14(2),51-55.

W

- Wang, X., Schröder, H.C., Grebenjuk, V., Diehl-Seifert, B., Mailänder, V., Steffen, R., Schloßmacher, U. and Müller, W.E. (2014) The marine sponge-derived inorganic polymers, biosilica and polyphosphate, as morphogenetically active matrices/scaffolds for the differentiation of human multipotent stromal cells: potential application in 3D printing and distraction osteogenesis. *Marine drugs*, 12(2),1131-1147.
- Wu, Y., Chen, L., Scott, P.G. and Tredget, E.E. (2007) Mesenchymal stem cells enhance wound healing through differentiation and angiogenesis. *Stem cells*, 25(10),2648-2659.

X

- Xu, Q.L., Furuhashi, A., Zhang, Q.Z., Jiang, C.M., Chang, T.H. and Le, A.D. (2017) Induction of salivary gland–like cells from dental follicle epithelial cells. *Journal of Dental Research*, 96(9),1035-1043.

Z

- Zahrowski, J. and Jeske, A. (2011) Apical root resorption is associated with comprehensive orthodontic treatment but not clearly dependent on prior tooth characteristics or orthodontic techniques. *The Journal of the American Dental Association*, 142(1),66-68.
- Zainal Ariffin, S.H., Yamamoto, Z., Abidin, Z., Megat Abdul Wahab, R. and Zainal Ariffin, Z. (2011) Cellular and molecular changes in orthodontic tooth movement. *The Scientific World Journal*, 11,17881803.