Review Article

The role of stem cells in oral bone regeneration

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Abstract

Oral bone regeneration has revolutionized implant dentistry by enhancing both the quantity and quality of the available bone, ultimately leading to improved treatment outcomes. In recent years, the use of stem cells for regenerative purposes has shown promising results. The aim of this study was to review the current literature concerning the clinical applications of Mesenchymal Stem Cells (MSCs) and/or Adipose Stem Cells (ASCs), for the treatment of oral osseous defects. An electronic search of Ovid Medline database was conducted. All types of human studies that applied MSCs and/or ASCs for implant site development were included. Pre-clinical and in vitro studies were excluded. Out of the initial 282 identified records, 22 were considered for inclusion. Even though most reports showed some benefit after the use of MSCs/ASCs, the review indicated that there is lack of consensus, regarding the methodology and the outcomes assessment. The clinical significance and the feasibility should be further studied with standardized techniques.

Keywords: Bone defects, Bone regeneration, Stem cells

Introduction

Bone defects in the oral cavity differ greatly, ranging from limited alveolar bone loss to large-scale bone atrophy. A “jaw (bone) defect” is defined as the lack of bone volume where it should normally exist\textsuperscript{1}. A variety of reasons can cause jaw deformities such as extractions/ tooth loss, periodontitis, periapical infections, injuries due to facial trauma, tumors or cyst resections, congenitally missing teeth or developmental conditions (cleft palate defects), osteomyelitis, osteoradionecrosis and drug-induced osteonecrosis\textsuperscript{2}. The most common cause is the post-extraction alveolar ridge collapse, which is inevitable and leads to bone loss in both horizontal and vertical dimensions\textsuperscript{3}. The above is clinically relevant when implant replacements are to be inserted as their position in the jaws should be driven by the restorative plan\textsuperscript{4}.

Regardless of the cause of jaw deficiencies, reconstruction of the maxilla and the mandible is imperative for the return to form and function. Reconstructive jaw surgery may involve a multitude of different bone grafting materials such as autografts, allografts, xenografts and alloplasts\textsuperscript{5}. Autologous bone grafts are considered to be the gold standard for bone regeneration because of histocompatibility and their osteogenic, osteoconductive and osteoinductive properties\textsuperscript{6}. However, autografts show some disadvantages due to their limited supply, donor-site morbidity and potential infections\textsuperscript{7}. On the other hand, allografts and xenografts do not have the problem of limited supply and do not require a donor site but they have poor osteoinductive properties due to the absence of cell populations\textsuperscript{8}. To overcome these difficulties, new advanced techniques have been employed and one of the most promising is the use of stem cells\textsuperscript{9}.

By the term “stem cells” we define the cells with the ability to grow into anyone of the human body’s more than 200 cell types, responsible for the foundation of each and every organ and tissue\textsuperscript{10}. They have two defining characteristics; the ability of unlimited self-renewal and the ability to differentiate into specialized adult cell type with specific functions, when stimulated by both external and internal signals\textsuperscript{11}.

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Based on their biological properties, stem cells can be divided into pluripotent and multipotent. The former, have the ability to differentiate into all cell types in the body. They are only present in the fetus before differentiating into the more specialized multipotent stem cells. In reference to the origin of stem cells, they can be obtained from the inner cell mass of the blastocyst (pre-implantation embryos), fetal tissue and adult tissue\textsuperscript{12,13}. Adult stem cells - also called somatic - are found in the mesenchyme of many tissues and organs (Mesenchymal Stem Cells/MSCs) and they are responsible for their maintenance and repair when damaged or lost cells must be replaced. MSCs, apart from the bone marrow where they exist in abundance, have also been isolated from other tissues such as the skin, lung, adipose tissue (ASCs) and teeth (dental pulp, periodontal ligament and exfoliated deciduous teeth)\textsuperscript{14,15}.

In 2006, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposed the following minimal criteria to define human MSCs\textsuperscript{16}:
- they must be plastic-adherent in standard culture conditions;
- they must express CD105, CD73 and CD90;
- they must not express CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-Dr surface molecules;
- they must differentiate to osteoblasts, adipocytes and chondroblasts \textit{in vitro}.

Tissue engineering combines biological components, such as cells and growth factors, with engineering principles and biomaterials\textsuperscript{17}. It is based on the ability of stem cells to be artificially guided in the direction of particular cellular phenotypes under the influence of favorable microenvironments. Currently, different technologies and application protocols are being studied on this field.

The aim of this study was to review the recent literature concerning clinical applications of MSCs and/or ASCs, utilized to enhance the regeneration of oral bone tissue prior to implant placement.

**Materials and methods**

An online research was conducted in September 2020 using the Ovid Medline Database, including articles published in English during the last twenty years. The search strategy used was as follows: ("Bone Regeneration"[Mesh] OR "Alveolar Ridge Augmentation"[Mesh] OR "Tissue Engineering"[Mesh] OR "Guided Bone Regeneration"[Mesh] OR "Osseous Repair"[All Fields]) AND ("Jaws" OR "Alveolar Process"[All Fields]) AND ("Wound Healing"[Mesh] OR "Biology"[Mesh] OR "Physiology"[Mesh] OR "Molecular"[Mesh] OR "Cellular"[Mesh][All Fields]) AND ("Barrier"[Mesh] OR "Membrane"[Mesh][All Fields]) AND ("Stem Cells"[All Fields]) AND "2000/01/01" AND "English"[Lang].

All levels of evidence were included, except reviews. The following exclusion criteria were applied:
- Pre-clinical studies.
- \textit{In vitro} studies.
- Temporomandibular joint (TMJ) regeneration.
- Regeneration of dental and periodontal defects.
- Studies that involved the use of stem cells for distraction osteogenesis.
- Reconstruction of defects following removal of benign and malignant tumors/cysts.
### Table 1. List of the selected clinical trials included in the analysis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Stem cell type</th>
<th>Collection</th>
<th>Subculture</th>
<th>Origin</th>
<th>N</th>
<th>Carrier</th>
<th>Defect type</th>
<th>Graft location</th>
<th>Cover</th>
<th>Control</th>
<th>Time for analysis</th>
<th>Analysis</th>
<th>Primary outcomes</th>
<th>Implants</th>
<th>Restoration</th>
<th>Follow-up after restoration</th>
<th>Implant survival rate</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khojasteh et al 2016*</td>
<td>ASC</td>
<td>SAT</td>
<td>Yes</td>
<td>BFP</td>
<td>4+4</td>
<td>FDBA</td>
<td>Alveolar Reconstruction</td>
<td>M+Mn, CM</td>
<td>CS</td>
<td>6 or 12 weeks</td>
<td>R+HyCT+H</td>
<td>Bone width gain: control 3.01±0.8% vs test 3.94±1.62</td>
<td>YES</td>
<td>N/S</td>
<td>N/A</td>
<td>N/A</td>
<td>N/S</td>
<td>1 year</td>
</tr>
<tr>
<td>Khojasteh et al 2018*</td>
<td>ASC</td>
<td>SAT</td>
<td>Yes</td>
<td>BFP</td>
<td>7+7</td>
<td>ABBM</td>
<td>Horizontal + Vertical</td>
<td>PMn, TM</td>
<td>Autologous bone</td>
<td>6 months</td>
<td>CT</td>
<td>Area of new bone formation: 169.5±5.9 mm² (test) vs 168.0±10.69 mm² (control)</td>
<td>YES</td>
<td>N/S</td>
<td>N/A</td>
<td>N/A</td>
<td>N/S</td>
<td>1 year</td>
</tr>
<tr>
<td>Marx et al 2014*</td>
<td>MSC</td>
<td>BMA</td>
<td>No (whole aspirate)</td>
<td>IB</td>
<td>20±20</td>
<td>CS - BMP-2 + Allogenic bone</td>
<td>Alveolar Reconstruction</td>
<td>Mn, TM</td>
<td>Bone density: Trabecular Bone Area 36±10% (test) vs 67±13% (control)</td>
<td>CT+H</td>
<td>40% of contr achieved regeneration of implantable bone vs 100% of test/Mean bone volume (test)</td>
<td>YES</td>
<td>N/S</td>
<td>N/A</td>
<td>N/A</td>
<td>N/S</td>
<td>1 year</td>
<td>100%</td>
</tr>
<tr>
<td>Prins et al 2016*</td>
<td>ACS</td>
<td>SAT</td>
<td>NO</td>
<td>AW</td>
<td>10 Pat. (5±5)/16 sites (6 split mouths)</td>
<td>TCP or BCP</td>
<td>Sinus Lift</td>
<td>PM</td>
<td>NO</td>
<td>TCP or BCP</td>
<td>5 - 6 - 9 months</td>
<td>Panoramic x-ray</td>
<td>boned osteid percentage in study biopsies vs 19.6%</td>
<td>YES (44)</td>
<td>YES</td>
<td>More than 2.5 years</td>
<td>97.70%</td>
<td>1 implant failure</td>
</tr>
<tr>
<td>Rickert et al 2013*</td>
<td>MNC</td>
<td>BMA</td>
<td>NO</td>
<td>IB</td>
<td>12 - 20 implants/24 sinuses</td>
<td>BBM</td>
<td>Sinus Lift</td>
<td>PM</td>
<td>CM</td>
<td>BBM + Autologous graft</td>
<td>14.8±0.7 weeks</td>
<td>Histology</td>
<td>new bone: 17.7±7.3% (test) vs 12.16±6.6% (control)</td>
<td>YES (66)</td>
<td>YES</td>
<td>N/S</td>
<td>N/S</td>
<td>3 implant failures</td>
</tr>
<tr>
<td>Reference</td>
<td>Study design</td>
<td>Stem cell type</td>
<td>Collection</td>
<td>Subculture</td>
<td>Origin</td>
<td>N</td>
<td>Carrier</td>
<td>Defect type</td>
<td>Graft location</td>
<td>Cover</td>
<td>Time for analysis</td>
<td>Analysis</td>
<td>Primary outcomes</td>
<td>Implants</td>
<td>Restoration</td>
<td>Follow-up after restoration</td>
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<td>Complications</td>
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</tr>
<tr>
<td>Ahn et al 2018</td>
<td>CR</td>
<td>MSC</td>
<td>BMA</td>
<td>No (whole aspirate)</td>
<td>IB</td>
<td>1</td>
<td>PCL</td>
<td>Clef Palate</td>
<td>AM</td>
<td>NO</td>
<td>6 months</td>
<td>CT</td>
<td>oronasal fistula closure+BV of newly formed 45% of total defect volume</td>
<td>NO</td>
<td>NO</td>
<td>N/A</td>
<td>N/A</td>
<td>4 months: exposure of PCL and removal of plate+ screws</td>
</tr>
<tr>
<td>Behnia et al 2009</td>
<td>CS</td>
<td>MSC</td>
<td>BMA</td>
<td>Yes (2 wks manually/no induction)</td>
<td>IB</td>
<td>2</td>
<td>DBM + Calcium Sulfate</td>
<td>Clef Palate</td>
<td>AM</td>
<td>NO</td>
<td>4 months</td>
<td>CT</td>
<td>oronasal fistula closure+25-6-34.5% bone defect fill</td>
<td>NO</td>
<td>NO</td>
<td>N/A</td>
<td>N/A</td>
<td>N/S</td>
</tr>
<tr>
<td>Behnia et al 2012</td>
<td>CS</td>
<td>MSC</td>
<td>BMA</td>
<td>Yes (2 wks manually/no induction)</td>
<td>IB</td>
<td>4</td>
<td>HA / TCP + PDGF</td>
<td>Clef Palate</td>
<td>AM</td>
<td>Fibrin clot</td>
<td>3 months</td>
<td>CT</td>
<td>oronasal fistula closure+51.3% bone defect fill</td>
<td>NO</td>
<td>NO</td>
<td>N/A</td>
<td>N/A</td>
<td>N/S</td>
</tr>
<tr>
<td>Cerruti et al 2007</td>
<td>CS</td>
<td>MNC</td>
<td>BMA</td>
<td>No (whole aspirate)</td>
<td>IB + SB</td>
<td>32</td>
<td>AB + PPP + PRP</td>
<td>Vertical, Horizontal, Sinus lift</td>
<td>AM + PM</td>
<td>N/S</td>
<td>4 months</td>
<td>H+CT</td>
<td>Width 6-14mm Height 10mm (AM) and 6-15mm (PM)</td>
<td>YES</td>
<td>YES</td>
<td>4 years</td>
<td>100%</td>
<td>1 graft not integrated+1 sinus infection</td>
</tr>
<tr>
<td>Ahn et al 2018</td>
<td>CR</td>
<td>MSC</td>
<td>BMA</td>
<td>Yes (2 wks manually/osteogenic induction)</td>
<td>IB</td>
<td>1</td>
<td>PRP</td>
<td>Clef Palate</td>
<td>TM</td>
<td>3-6-9 months</td>
<td>CT</td>
<td>79.1% bone coverage</td>
<td>NO</td>
<td>NO</td>
<td>N/A</td>
<td>N/A</td>
<td>N/S</td>
<td></td>
</tr>
<tr>
<td>Kuper et al 2010</td>
<td>CR</td>
<td>MSC</td>
<td>BMA</td>
<td>Yes (1.2 days manually/no induction)</td>
<td>IB</td>
<td>1</td>
<td>GS</td>
<td>Extraction Socket</td>
<td>N/S</td>
<td>OM</td>
<td>6 weeks</td>
<td>µCT+H</td>
<td>Bone defect fill</td>
<td>NO</td>
<td>NO</td>
<td>N/A</td>
<td>N/A</td>
<td>N/S</td>
</tr>
<tr>
<td>Khojasteh et al 2009</td>
<td>CS</td>
<td>ASC</td>
<td>SAT</td>
<td>Yes (manually/no induction)</td>
<td>BFP</td>
<td>2</td>
<td>BBM</td>
<td>Horizontal + Vertical</td>
<td>M + Mh</td>
<td>OM</td>
<td>6 months</td>
<td>CT+H</td>
<td>Newly formed bone</td>
<td>YES</td>
<td>NO</td>
<td>48 months</td>
<td>100%</td>
<td>N/S</td>
</tr>
<tr>
<td>Rajan et al 2014</td>
<td>CR</td>
<td>MSC</td>
<td>BMA</td>
<td>Yes (1.2 days manually/no induction)</td>
<td>IB</td>
<td>1</td>
<td>TCP</td>
<td>Horizontal + Vertical</td>
<td>AM</td>
<td>OM</td>
<td>4-6-12 months</td>
<td>CT+Hm</td>
<td>Width 5-6 mm gain+80% regeneration Height</td>
<td>YES</td>
<td>YES</td>
<td>6 months</td>
<td>100%</td>
<td>N/S</td>
</tr>
<tr>
<td>Shayesteh et al 2006</td>
<td>CS</td>
<td>MSC</td>
<td>BMA</td>
<td>Yes (4 wks manually/no induction)</td>
<td>IB</td>
<td>7</td>
<td>HA / TCP</td>
<td>Sinus Lift</td>
<td>PM</td>
<td>OM</td>
<td>3-12 months</td>
<td>R+Hm</td>
<td>New bone: 41.34%/radiographic bone height: 2.25-12.08-10.83 (baseline-postgraft-1y)</td>
<td>YES⑩</td>
<td>YES</td>
<td>6 months</td>
<td>93%</td>
<td>2 implants lost</td>
</tr>
<tr>
<td>Smiler et al 2007</td>
<td>CS</td>
<td>N/S</td>
<td>BMA</td>
<td>No (whole aspirate)</td>
<td>IB</td>
<td>5 (7 sites)</td>
<td>Xenograft, Allograft or Alloplast</td>
<td>Sinus Lift or Horizontal</td>
<td>PM</td>
<td>CM + TM</td>
<td>4-7 months</td>
<td>H+Hm</td>
<td>23-45% new bone formation / No difference between carriers are statically reported</td>
<td>NO</td>
<td>NO</td>
<td>N/A</td>
<td>N/A</td>
<td>N/S</td>
</tr>
<tr>
<td>Valdivia et al 2018</td>
<td>CR</td>
<td>MSC + Monocytes</td>
<td>BMA</td>
<td>NO</td>
<td>IB</td>
<td>1</td>
<td>Xenograft</td>
<td>Horizontal + Vertical</td>
<td>AM</td>
<td>CM + TM</td>
<td>7 months</td>
<td>CT+Hm</td>
<td>New bone formation / presence of osteocytes</td>
<td>YES</td>
<td>NO</td>
<td>N/A</td>
<td>N/A</td>
<td>N/S</td>
</tr>
<tr>
<td>Yamada et al 2013</td>
<td>CR</td>
<td>MSC</td>
<td>BMA</td>
<td>Yes (4 wks manually/osteogenic induction)</td>
<td>IB</td>
<td>1</td>
<td>PRP</td>
<td>Horizontal + Vertical</td>
<td>PMh</td>
<td>CM + TM</td>
<td>7 months</td>
<td>CT+H</td>
<td>4.2mm height bone gain /new mature bone</td>
<td>Yes (3)</td>
<td>YES</td>
<td>2 years</td>
<td>100%</td>
<td>N/S</td>
</tr>
</tbody>
</table>

CR=Case Report, CS=Case Series, MSC=Mesenchymal Stem Cells, MNC=Mononuclear Cells, ASC=Adipose Stem Cells, N/S=Not Specified, BMA=Bone Marrow Aspirate, SAT=Subcutaneous Adipose Tissue, BI=Iliac Bone, SB=Sternum Bone, PCL=PolyCaproLactone, DBM=Demineralized Bone Marrow, HA/TCP=Hydroxyapatite/Tricalcium Phosphate, PDGF=Platelet Derived Growth Factor, AB=Allograft Block, PPP=Platelet Poor Plasma, PRP=Platelet Rich Plasma, CS=Calcium Sulfate, BBM=Bovine Bone Marrow, AM=Anterior Maxilla, PM=Posterior Maxilla, M=Maxilla, MN=Medial, PMN=Posterior Mandible, CM=Collagen Membrane, TM=Titanium Mesh, CT=Computed Tomography, H=Histology, Hm=Histomorphometry, Rx=Radiography, N/A=Not Applicable
Results

The author (GK) carried out the search in duplicate and in case of uncertainty about the inclusion of an article the decision was taken after consulting an experienced reviewer (KS). A total of 282 articles were identified by the database search. Applying the exclusion criteria at the title and abstract level, 24 articles were finally selected for full-text screening. Of those, 22 met the inclusion criteria and were considered for analysis and discussion (Figure 1). Out of the 22 articles, 10 corresponded to clinical trials (Table 1), 7 to case reports and 5 to case series (Table 2). In total, they assessed the application of MSCs in 289 patients.

Cell Type

All studies reviewed used adult stem cells from various tissues. Specifically, 16 studies reported the use of Bone Marrow Aspirate (BMA) \(^{18-33}\), 4 the use of Subcutaneous Adipose Tissue (SAT) \(^{24-37}\) and 2 used cellular bone allograft (CBA) \(^{38,39}\).

Stem cells were generally isolated from bone marrow aspirates from the iliac bone. Only one reported as a source the sternum bone along with the iliac crest \(^{26}\). This highlights that this specific harvesting technique is widely adopted. BMSCs (Bone Marrow-derived Stem Cells) from the iliac bone have been thoroughly studied and documented, as they are easily collected and expanded and retain great potential for differentiation. Gimbel et al. confirmed that BMA from the iliac crest resulted in reduced morbidity and increased patient comfort compared to the traditional harvesting technique for autologous graft, from same location \(^{19}\).

ASCs (Adipose-derived Stem Cells) are easily accessible via liposuction (less invasive harvesting procedure) from areas such as the abdominal wall or the buccal fat pad and they are much more abundant (0.5-2 x 10^6 ASCs/g adipose tissue) \(^{40,41}\). Applications in the human body \(^{24-37}\) evaluated the efficacy of ASCs for bone regeneration. In all cases, newly formed bone was seen and there was no evidence of immune response.

There are also commercially available human MSCs. Katagiri et al. \(^{39}\) applied hMSCs from Lonza Inc. (Walkersville, MD, USA) and cultured them in a mesenchymal stem cell basal medium. Following incubation, the cell culture-conditioned medium was collected, and this was defined as MSC-CM. The results in all patients showed early bone formation with increased trabecular density. This fact justified the potential of MSCs to differentiate and promote osteogenesis responding to the environment, while there is no need for autograft harvesting, protecting the patients from discomfort and possible complications in the donor-site.

Culture and Preparation methods

There are several different approaches in terms of handling the population of the collected cells. Some researchers used the whole aspirate without expansion or differentiation, loaded into scaffolds \(^{19,21,23,26,31,32,36,38}\). In other studies, stem cells were isolated and expanded, under certain conditions (in a basal medium with autologous serum/no osteogenic induction) \(^{18,24,25,28-30,34,35,37}\). Finally, other studies used an expansion protocol with osteogenic factors such as dexamethasone (100 μM), beta-glucophosphate (10 μM) and L-ascorbic acid (25-50 μg/ml) known to induce osteogenic differentiation \(^{20,27,33}\). This automated culture system expands the quantity of bone reconstruction cells (hematopoietic and mesenchymal stem cells) \(^{42}\). Although no clinical comparison has been performed between processed BMA and non-processed BMA, the outcomes from the clinical trials showed similar efficacy in terms of bone regeneration whether osteogenic induction was performed or not \(^{20,38}\).

Carriers and Membranes

Several types of materials have been used as carriers (scaffolds) to deliver the cells into the defect being treated. These vary from alloplastic (β-TCP with or without HA) \(^{18,25,29,30,36,39}\) to xenografts (mainly bovine bone) \(^{22,31,32,35,37}\), allograft (freeze-dried bone allograft/FDBA) \(^{34}\) or autografts (PRP concentrate) \(^{27,33}\).

The ideal scaffold must be biocompatible (without immune response), biodegradable (preferably the time of resorption to follow the time of bone reconstruction), porous so as to allow the cell to adhere, and with the appropriate shape for filling the bony defect \(^{25}\). One study compared the use of β-TCP to atelocollagen sponge (ACS) as carriers for MSCs \(^{19}\). Newly bone formed was seen in both cases with mild presence (β-TCP) or absence of inflammatory cells (ACS). ACS was more easily resorbed than β-TCP and its use resulted into denser bone formation.

3-D printing technology offers the possibility of patient-specific custom-made scaffolds. Ahn et al. reported in 2018 \(^{23}\) the first case of alveolar cleft palate repair using a 3D printed bioresorbable polycaprolactone (PCL) scaffold loaded with MSCs from iliac bone marrow aspirate. After 6 months 45% of the total defect volume was full of new bone.

Some studies used these carriers combined and mixed with or without additional factors such as Bone Morphogenetic Protein-2 (BMP-2) \(^{21}\) or Platelet-Derived Growth Factor (PDGF) \(^{25}\).

Cerruti et al. \(^{26}\) used bone marrow whole aspirate combined with bone allograft and platelet growth factors (PPP: platelet-poor plasma and PRP: platelet rich plasma). PPP was used to produce fibronectin and laminin, known to attract MSCs \(^{34}\). PRP was mixed with the bone allograft and the stem cells and were all placed into the grafted area. Even though some studies have shown contradictory results regarding the regenerative capacity of PRP \(^{45,46,47,48}\), it can be concluded that it presents with multiple advantages: it offers bleeding reduction \(^{49}\), rapid healing of the soft tissues \(^{50}\) and due to its contents, especially PDGF and TGFs (Transforming Growth Factors -α, -β) influences bone regeneration \(^{51}\). These factors along with VEGF (Vascular Endothelial Growth
Factor) and IGF (Insulin-like Growth Factor) play significant role in the angiogenesis, the proliferation and differentiation of MSCs, enhancing the regenerative procedure.

Another important difference was identified on the use and the type of membrane/barrier. Some studies used collagen membranes or titanium mesh to cover the grafted area while others did not use any membrane at all.

**Defect Type**

Regarding the type of defect being treated, this ranged from small sized deficiencies (post-extraction sockets) to extensive bone deformities (cleft palate). Specifically, 77 cleft palates were repaired, 115 sinus elevations were performed, 109 horizontal and/or vertical augmentations and 4 post-extraction sockets were preserved. Bone regeneration varied greatly from site to site.

**Clinical Results**

Overall, the methodologies applied were not comparable to extrapolate robust conclusions. However, several studies indicated the benefit of the use of stem cells. Gonshor et al. reported a histological advantage of using stem cells carried in a cellular bone allograft after sinus augmentation (32.5%±6.8% vs. the test group versus 18.3%±10.6% of the control group). Another study demonstrated that cell therapy accelerated the bone regeneration process. The treated sites were analyzed clinically, radiographically and histologically and after 6 weeks, the linear bone height was 55.3% in the control group versus 78.9% in the test group (p=0.01).

Another study demonstrated that cell therapy accelerated the bone regeneration. The treated sides were analyzed clinically, radiographically and histologically and after 12 weeks, it was 74.6% (control) versus 80.1% (test) (p=0.28). Katagiri et al. reported newly formed bone, early mineralization and dense trabecular bone when MSC-CM were used. Without cell loading, β-TCP was scarcely replaced, and inflammatory cells were found around the alloplastic β-TCP. A study worth mentioning was conducted by Marx and coworkers. The aim of this trial was to investigate the role of the bone marrow derived CD34+ cells in bone regeneration.

**Autogenous Bone Grafting**

In all case reports included in this review, the results of stem cell therapy were encouraging. When MSCs were used for cleft palate reconstruction, coronal fistula closure was observed and a total of 34.5% to 79.1% bone defect filling was occurred depending on the follow-up period (3 to 9 months). Where horizontal and vertical augmentation were performed, newly formed bone was present and there was a gain in both width and height ridge’s dimensions.
The role of stem cells in oral bone regeneration

Discussion

Bone regeneration is often needed prior or during dental implant placement as it has been suggested that up to 40% of implants require some kind of GBR (Guided Bone Regeneration)\(^2\). A retrospective analysis showed that especially in the anterior maxilla, which is an esthetically demanding region, 74.7% of implants inserted, required additional local bone augmentation procedure\(^3\). Implant therapy has become an integral part of restorative dentistry and there is a growing demand for reduced healing times and application in medically compromised patients. Following the principles of personalized medicine and tissue engineering, stem cells have been used to enhance the regenerative procedures with promising results.

This review was performed to evaluate the clinical applications of stem cells in the treatment of oral bone defects using clinical, radiographic and histological analyses. Most reports demonstrated a greater amount of newly formed bone in the short term, when stem cells were applied, but the majority of the studies were case reports and case series. The absence of standardized clinical protocols and the fact that until now the existent clinical trials have failed to demonstrate statistically significant differences, clearly highlights the need for further research in the field. The feasibility of the use of different cell lines and scaffolds has been established but there is limited evidence regarding the selection of optimal combination for superior results in specific defect types. In addition, financial and patient reported outcome measures have not been consistently discussed and these should be incorporated in the design of future trials in order to evaluate the long-term benefits of stem cell-based therapies both at implant- and patient-level.

Our review had some inherent limitations, the most obvious of which was the small number of included reports for analysis. We restricted our search into human studies published during the last 20 years as we attempted to report on the most updated techniques and materials. The inclusion of preclinical investigations would have offered a greater perspective on the biological mechanisms but the results cannot be directly translated into clinical practice.

Conclusion

The review of the published literature has shown the advantages of mesenchymal stem cells in the field of oral bone regeneration. However, most studies failed to show a significant difference between control and test groups. Better knowledge of MSCs potential and the use of new advanced treatment strategies being developed now could establish cell therapy as a future clinical tool and reliable solution for use on patients.

References


