Maxillofacial Reconstruction: From Autogenous Bone Grafts to Bone Tissue Engineering

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Abstract Maxillofacial reconstruction (using autogenous bone grafts, biomaterials, growth factors, distraction osteogenesis, dental implants, and bone tissue engineering) is complex and poses significant challenges to surgeons. The use of these techniques has profoundly improved patients' function, form, and quality of life. Several techniques are currently being used to treat bone defects of the jaws (ranging from minor to major defects), including autogenous bone grafting, guided bone regeneration, the use of growth factors with biomaterials, and distraction osteogenesis. Dental implants have become a routine treatment for the final and total rehabilitation of patients. Bioengineering of autologous bone is an exciting minimally invasive alternative to bone harvesting techniques to replace missing bone of any part of the skeleton. Advances in the field of bone tissue engineering over the past few decades offer promising new treatment alternatives using biocompatible scaffold materials, autologous mesenchymal stem cells, and growth factors. The purpose of this chapter is to provide a variety of different current evidence-based treatment options, as well as novel tissue engineering technologies for the reconstruction of minor and major jaw defects.

Keywords Maxillofacial reconstruction · Autogenous bone graft · Biomaterials · Growth factors · Distraction osteogenesis · Dental implants · Tissue engineering

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R. S. Chaughule, R. Dashaputra (eds.), *Advances in Dental Implantology using Nanomaterials and Allied Technology Applications*,
https://doi.org/10.1007/978-3-030-52207-0_14

1 Introduction

Management of clinical cases in the field of maxillofacial reconstructive surgery is complex and poses significant challenges to surgeons. The use of techniques such as autogenous bone grafting, guided bone regeneration, growth factors, distraction osteogenesis (DO), dental implants, and bone tissue engineering (BTE) has profoundly improved patients' function, form, and quality of life. Maxillofacial defects can result from, but not limited to, congenital abnormalities, post-trauma, tumor resection, periodontal disease, severe ridge atrophy following tooth extraction, and infections [1–3].

The primary goal of reconstructive surgeries is to provide form and function. Autogenous bone, harvested from a variety of donor sites, is considered the gold standard. Donor site morbidity remains significant [4–6]. Resorption of grafted autogenous bone is a common and unwanted complication, and may compromise the long-term stability [3, 7].

Guided bone regeneration (GBR) [8, 9], the use of different growth factors such as platelet rich plasma (PRP), platelet rich fibrin (PRF), and bone morphogenetic protein (BMP) have shown promising preclinical and clinical results to promote and improve wound healing and bone regeneration [10–15]. Emerging technologies such as tissue engineering (TE) may represent a minimally invasive alternative to autogenous bone graft procedures. Tissue engineering would also provide patient-specific treatments [15–17]. The purpose of this chapter is to provide a variety of evidence-based treatment options, as well as novel TE technologies.

2 Maxillofacial Reconstruction

2.1 Autogenous Bone Grafts

Autogenous bone is still considered the "gold standard" [18]. Autogenous cortico-cancellous bone blocks from both membranous or endochondral origin can be harvested from jaws or distant sites. The choice of the donor site depends on aspects such as patient-specific conditions, donor site morbidity, and amount of bone required for reconstruction [3, 19–21]. In addition, the decision will also be driven by the size of the defect that needs to be reconstructed (i.e., alveolar regeneration versus reconstruction of major bone defects with bone discontinuity).

Intraoral autologous bone blocks can be safely harvested from the lateral zygomatic buttress, retromolar area, and the mandibular ramus [19, 20], and bone chips can be obtained using a bone scraper [22]. They are used for minor alveolar ridge reconstruction.

Severe alveolar ridge defects as well as bone discontinuity defects require larger bone quantity and, therefore, harvesting from distant sites. [iliac crest (anterior/posterior), calvaria, fibula, ribs, vascularized and non-vascularized]. However, this

treatment is more costly with more patient morbidity [4, 5, 23, 24]. Implant placement following grafting with autologous bone blocks usually is performed after a healing period of 3–5 months, which allows revascularization of the graft [19, 20]. Vascularized free grafts (for large bone defects) allow for immediate implants. Evidence from retrospective cohort studies demonstrates that implants placed in areas reconstructed with autogenous bone blocks have survival rates consistent with implants placed in native bone [19, 20, 25]. Despite the higher success rate of autogenous bone reconstruction, significant donor site morbidity is a major consideration [4, 5, 19, 20, 23, 25]. Graft resorption is also expected with grafts; therefore, many recommend overcorrection of defects to compensate this [26]. In some situations, in which there is insufficient implant coverage due to graft resorption or inadequate primary augmentation, secondary grafting may be required [19, 20].

2.2 Guided Bone Regeneration (GBR)

Guided bone regeneration (GBR) has been successfully reported for over 20 years and represents a safe and reliable option for alveolar regeneration for dental implant placement [22, 27, 28]. Guided bone regeneration (GBR) consists of preventing the migration of undesired cells to the site that is intended to be reconstructed by placing a barrier membrane in conjunction with particulate grafts biomaterials. This technique restricts the entry of soft tissue into the defect, avoids nonosteogenic cell migration, and allows accumulation of growth factors, ultimately providing stability to bone grafts [22, 28].

Membranes used in GBR should possess some desirable characteristics, such as biocompatibility, cell-occlusion properties, clinical manageability, and be able to maintain proper physical and mechanical properties [8]. Non-resorbable membranes are commonly referred as the "gold-standard" material for GBR, and some examples include those composed of polytetrafluorethylene (PTFE), and titanium-reinforced expanded PTFE [8]. These require a second surgical procedure for removal. Second generation of membranes that are resorbable such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(ε-caprolactone) (PCL), inorganic compounds (i.e. calcium sulfate, calcium phosphate), and xenografic membrane (derived from bovine or porcine tissues) have been developed [8]. The GBR technique of choice depends on specific needs [22, 29].

Complications include soft tissue dehiscence, exposure of membranes, and infection [8, 30]. Exposure of resorbable membranes can occur and rapid degradation of the material may allow a spontaneous healing [8]. Major disadvantages of resorbable membranes include lack of rigidity (i.e., PLA, PGA, and PCL) and lack of plasticity (i.e., calcium sulfate, calcium phosphate) [8].

Enhancement of GBR outcomes by using growth factors such as BMP-2 and platelet-derived growth factor (PDGF) has been described. This can be obtained by soaking the membranes in a solution containing the growth factors, followed by lyophilization. Depending on additional reagents (i.e., heparin, cross-linkers), and

growth factors concentration, a faster release of factor usually occurs within the first day, followed by a phase characterized by a slower release. Blood-derived products, such as PRP or PRF membranes, have also been described as adjuncts to enhance the regenerated bone obtained by GBR [31]. Biological basis may be due to the availability of growth factors [32].

2.3 Bone Morphogenetic Proteins (BMPs)

Bone morphogenetic proteins were first described by Urist in 1965. BMPs are present in bone matrix, and there are about 30 proteins belonging to the human BMP family. Most of them constitute subfamilies in the transforming growth factor beta (TGF-β) superfamily [33].

It appears that BMP-2, BMP-6, and BMP-9 may be the most potent agents to induce osteoblast lineage-specific differentiation of MSCs [34]. BMP activates a signaling system called Smad. Smads are an important group of molecules that translocate and transmit signals from BMP-activated receptors into the cell nucleus [35, 36].

Despite the evidence showing the positive effects on bone formation, there are concerns regarding side effects of BMPs *in vivo*. Major side effects of BMP include edema, inflammation, and ectopic bone formation. Carcinogenic effects have been suggested [37].

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is placed on an absorbable collagen sponge (ACS). It has been shown that this combination can induce and support bone formation [38–40]. Bone-forming cells migrate to the area of the rhBMP-2/ACS, and infiltrate into the ACS. Mesenchymal stem cells around the rhBMP-2/ACS also increase in number. Binding of rhBMP-2 to specific receptors on the surface of the MSC causes them to differentiate into bone-forming cells (osteoblasts). As the sponge degrades or dissolves trabecular bone and/or cartilage is formed, with angiogenesis occurring at the same time. The bone formation process develops from outer surface of the sponge towards the center until the entire area is replaced by trabecular bone [39].

A clinical study examined the efficacy of two doses of rhBMP-2/ACS in 80 in post-extraction sockets [41]. Recombinant BMP at concentrations of 0.75 and 1.5 mg/cc was comparted to controls. The results demonstrated that the 1.5 mg/cc rhBMP-2/ACS treated sites had about two times the amount of bone compared to the empty control group, preserving ridge height, and significantly increased width at 75%, 50%, and 25% of the extraction socket length. In addition, histological analysis showed no differences between the rhBMP-2-induced bone and native bone.

Bone morphogenetic proteins (i.e., rhBMP2) have been used for alveolar reconstruction, sinus augmentation, and tooth extraction socket healing [38–40]. However, despite several preclinical studies and clinical trials, a lack of consensus continues to exist concerning the clinical efficacy of rhBMP2 for larger defects in the maxillofacial region [42].

2.4 Platelet Rich Plasma (PRP) and Platelet Rich Fibrin (PRF)

Platelets contain high amounts of key growth factors [such as platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), and fibroblast growth factor (FGF)] which can stimulate cell proliferation, matrix remodeling, and angiogenesis and this stimulated its use in implantology [43, 44].

First-generation products such as PRP and plasma rich in growth factors (PRGF) are obtained by collecting peripheral blood and adding anticoagulants [45]. Second generation concentrates (such as PRF) were developed without the need of anticoagulants. The collected blood is immediately centrifuged to obtain a clot rich in platelets, fibrin, and leucocytes [43]. The presence of a fibrin network represents a potential innovation for regenerative purposes, since it acts as a scaffold for cell proliferation. Additionally, leucocytes release vascular endothelial growth factor (VEGF) and transforming growth factor (TGF), which improve chemotaxis and angiogenesis [45] that are fundamental for bone formation.

Platelet rich fibrin (PRF) was also suggested as sole graft material during simultaneous sinus floor elevation and implant placement [46]. The concomitant use of PRF and bone allografts significantly reduced bone resorption and accelerated bone healing during the initial stage of post-extraction alveolar healing [47]. However, a recent systematic review concluded that it remains unclear whether PRF can improve soft tissue healing [44]. Most commonly, PRP and PRF are used in conjunction or as adjuvant therapy for the treatment of alveolar defects.

2.5 Distraction Osteogenesis (DO)

Historically, distraction osteogenesis (DO) was initially performed using transcalcaneal metal pins as a method of correcting malformations caused by femoral fractures by Codivilla in 1905. It had not progressed until the revolutionary principles and devices proposed by Ilizarov in 1951. The principle is called the "Ilizarov effect" and involves stimulating tissue growth by applying tension to it [48, 49].

As a basic concept, undifferentiated mesenchymal cells in the bone fracture line are stimulated by pulling and elongating the young callus with an external force, which stimulates differentiation into osteogenic cells. In the maxillofacial region, Perrott et al. [50] applied it to produce widening of the mandible and soft tissue expansion in a syndromic patient and McCarthy [51] applied it to correct mandibular hypoplasia. In 1996, Chin and Toth used the technique for correction of traumatic bone defects. Distraction osteogenesis (DO) is considered an appropriate technique for correcting large soft and hard tissue defects [51, 52], eliminating the need of multiple bone grafts.

Distraction osteogenesis (DO) devices can be broadly divided into transcutaneous, implantable (bone borne), horizontal, and vertical. The current hurdle in DO is device size.

Treatment with DO devices consists in three parts. The first one (after implantation of the device) is commonly referred as the "latency period," ranges from 0 to 7 days, and no distraction force is applied to the tissues [53]. The second one, the rhythm of distraction in increments of 0.5–1 mm/day. After the desired bone distraction has being achieved, a fixation period in which the device is kept in place without activation is also recommended, and this varies between 8 and 12 weeks [54]. Efforts to reduce the latency period have been reported [55–58]. In addition, stable results in which no latency period was required before activation of the DO device have been demonstrated [59].

The greatest advantage of DO is that no bone harvesting is required, and soft tissue can be expanded and maintained with an adequate blood supply, since the periosteum of the distracted bone is maintained attached. Disadvantages of DO include patient discomfort to activate the device and inability to wear dentures [60]. Another problem is how to control the direction of the bone segment being distracted (transport disk) [61]. This can be done by slants and lingual ramps [59].

2.6 Bone Tissue Engineering (BTE)

Bioengineering of autologous bone is an exciting minimally invasive alternative to bone harvesting techniques [62–65]. Tissue engineering of bone requires the combination of three main elements: biocompatible scaffolds, growth factors, and osteoprogenitor stem cells [62–66]. This approach combined with recent advances in three-dimensional (3D) printing technologies may soon allow the generation of large, bioartificial bone grafts with custom, patient-specific architecture [62, 66, 67].

The use of scaffolds plays a key role in BTE [68]. Different methods for producing porous scaffolds have been used, including solvent-casting, particulate-leaching, electrospinning, gas foaming, and phase separation [64]. However, several drawbacks are associated with the use of organic solvents, long fabrication periods, labor-intensive process, poor repeatability, irregularly shaped pores, insufficient interconnectivity of pores, and thin structures [64]. Many of these issues have been addressed with rapid prototyping technologies such as 3D printing. For these reasons, 3D-printed scaffolds made with functional biomaterials and appropriate structures have been widely developed for dental tissue regeneration [64, 68–70].

Three-dimensional printed scaffolds can be produced using rapid prototyping (RP) techniques, using data from medical images such as magnetic resonance imaging (MRI) and computed tomography (CT) of patients [71–73]. Briefly, the process from image acquisition to obtention of the final scaffold is as follows: patient with a bone defect will undergo a CT scan [obtention of digital imaging and communication in medicine (DICOM) files]; DICOM files will be imported into a medical image processing software; CT images will be segmented, and 3D virtual models generated; selection of the 3D printing technique and the selection of the materials; obtention of the 3D-printed bone scaffold; post processing and sterilization [73].

Different synthetic polymers have been widely used to fabricate bone scaffolds such as polylactic acid (PLA), polyglycolic acid (PGA), copolymers of PLA and PGA [poly(DL-lactic-co-glycolic acid) (PLGA)], and polycaprolactone (PCL). Synthetic calcium phosphates' (CP) chemical similarity to the natural bone mineral content allows to apply it successfully as bone substitutes among a variety of other materials (ceramics, bioglasses, polymers, and their combinations) [74–76]. Furthermore, composite scaffolds such as those made with PCL and β-TCP combine advantages of polymers and ceramics and have been used successfully to repair mandibular defects *in vivo* [63, 67, 77, 78]; synthetic biomaterials are not affected by the immunologic reactions that can be problematic for natural scaffolds [76].

The osteoprogenitor cells can be bone marrow stem cells (BMSCs), adipose stem cells (ASCs), dental pulp stem cells (DPSCs), or other stem cells that can initiate osteoblastic differentiation [66, 67, 79, 80]. These stem cells will then be seeded within scaffolds. The stem cell growth can be regulated by direct stimuli (i.e., growth factors) or environmental control (i.e., bioreactors) [62, 66, 67, 79, 80].

For a clinically relevant application, autologous bioengineered constructs should display deep cell penetration and angiogenesis. Vascularization is the key challenge in TE of bone [66, 81, 82]. This early process of angiogenesis is critical to sustain the grafted cells' viability. To achieve early angiogenesis, the implanted construct must contain proangiogenic factors (such as vascular endothelial growth factor secreted by osteoblastic cells) that will induce new vessel formation from the surrounding connective tissue envelope [66, 81, 82]. In addition, the construct must physically allow for such vessels to reach the interior of the scaffold before extensive extracellular matrix deposition has occurred [67, 83].

New bioactive synthetic biomaterials, in combination with the establishment of rigorous protocols for the translation of mesenchymal stem cells therapies and the use of growth factors that can guide cellular and molecular pathways to improve the healing mechanisms that will assist the maxillofacial restoration. Mimicking the complex 3D architecture and functional dynamics of maxillofacial bone tissue is a challenging proposal that generates the need for a customized and on-demand tissue replacement strategy to make patient specificity that could not be achieved to date.

3 Final Considerations

Maxillofacial reconstruction and rehabilitation pose significant challenges for the surgeons [66, 84]. As the technology advances and with the development of new approaches, the ability to develop and create detailed bioactive tissues will become more sophisticated [80]. Tissue engineering is a well-established field of research in the preclinical setting and a highly active field to develop products and devices following all principles of regenerative medicine [64, 65, 81, 85]. Surgeons should be aware of these advances, should be able to select appropriate techniques and materials based on current scientific knowledge, and should have the necessary skills for the reconstruction of maxillofacial bone defects.

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