24 Bone Tissue Engineering Challenges in Craniofacial Reconstructive Surgeries

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24.1 An Overview of Craniofacial Defects

The craniofacial region has always been one of the most noticeable regions of the human body for physicians, surgeons, and engineers. This region consists of a wide variety of soft tissues as well as diverse bones, including frontal, occipital, parietal, and temporal bones (which form the cranium); the two jaws that are named maxilla and mandible; and other kinds like zygomatic, nasal, sphenoid, and ethmoid bones. It contains six various cavities that are cranial, orbital, nasal, oral or buccal, and middle and inner ear ones. Hence, not only is it directly pertinent to some critical functions including breathing, speaking, eating, seeing, hearing, etc., but it also plays an essential role in social relationships thus it is indubitably important to scrutinize different types of the defects and deformities of this region and discover the reasons why these appear.

Craniofacial deformities can be categorized into congenital, traumatic, and cancerous ones. According to The International Statistical Classification of Diseases and Related Health Problems (ICD-10) [1], congenital malformations and deformations are divided into several groups. The first one is craniosynostosis, that is, when some of the cranial sutures ossify before the brain has matured suitably. It brings about some alterations in the pattern of skull growth. For instance, scaphocephaly and oxycephaly can be mentioned. The second division is craniofacial dysostosis, which is defined as a disorder of bone development, such as Crouzon and Treacher Collins syndromes, as well as hypertelorism. Other deformities are classified into the third division. Examples are macrocephaly, platybasia, plagiocephaly, and saddle nose syndrome.

Cancer may lead to the devastation of both soft and hard tissues in the craniofacial region. Yet, traumatic injuries result in a great number of diverse craniofacial defects, including lacerations, blunt traumas, and burns. Vehicle accidents, chemicals, heat, electricity, assaults, and falls are some examples of such injuries [2]. Regarding the importance of the roles which the craniofacial region plays as well as the prevalence of its deformities, pondering over finding appropriate therapies has always been an interest of technicians, such as physicians, surgeons, and engineers. Although there have been grandiose notions for repairing the deformities of the craniofacial region, some have become pragmatic after passing standard tests. Some main methods of treatment are discussed in the next section.

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24.1.1 Available Therapies

Repairing the defects and deformities of the craniofacial region has always been a concern for specialists due to destructive impact thereof. No record is found from early Greek physicians, such as Hippocrates and Galen, with regard to craniofacial reconstruction. However, dating back to the Incan Empire, there is some evidence in which some valuable metals and gourds are reported to be utilized in order to repair craniofacial defects. The application of grafts, harvested tissues, in reconstruction surgeries was first published by Meekeren in 1668. He utilized canine bone to reconstruct a defect in the cranium of a Russian man. Afterward, in the late nineteenth century, further experiments resulted in more progress in craniofacial reconstruction surgeries. Moreover, the special circumstances provided by warfare in the twentieth century brought about a leap in reconstruction surgeries. The specialists, at that time, sought applicable metals and plastics to use for larger defects [3]. The advancement in reconstruction surgery methods applying distinctive grafts experienced an incremental trend with the passage of time. In this section, the main purpose is to discuss these methods and various grafts.

Bone defects can be of different sizes. They can be either as small as periodontal defects (in millimeters) or large, which are mainly traumatic or caused by surgical incisions or cranioplasty. The vivid similarity among most of the defects is the complicated 3D structure thereof. The main expectation of reconstruction surgeries is the restoration of the functionality that has been restrained as well as the appearance that need to be aesthetically reconstructed due to the severe dependency of social relationships on it [4]. All of the process must be pursued in a way that controls the morbidity of both donor and recipient sites [5].

There are three significant criteria to amend the functionality of any graft, namely osteoconductivity, osteoinductivity, and osteogenesis. Osteoconductive grafts are those whose surfaces permit the formation of new bone cells along themselves. However, osteoinductivity causes the supply of the factors that are required for bone-forming cells to be recruited to the graft site and differentiate. In addition, osteogenic grafts benefit from bone-forming cells that can be induced or inducible. Thus, they can commence with the bone formation as soon as they are transplanted [4]. An ideal graft is the one which meets all the aforementioned criteria. Provided that the graft lacks osteoconductivity, the incorporation process of it into the recipient site declines intensely. Besides, if the graft is not osteoconductive, it does not tend to recruit bone-forming cells, such as osteoblasts and osteoprogenitors, and the stem cells cannot be differentiated due to scarcity of the needed factors. The circumstances exacerbate when the graft does not contain induced and inducible cells or in other words when the graft is not osteogenic.

Degradability is one of the vital factors depending on the purpose for which the graft is implanted. The condition that the graft is to stimulate bone formation and has to degrade as fast as the new bone tissue forms. Otherwise, degradability is absolutely a demerit for the grafts intending to contour the normal appearance or have mechanical functions. In this case, calvarial and cortical bones can be applied [6].

The ideal graft is the one which is not only osteoconductive, osteoinductive, and osteogenic but also suitably porous with interconnected pores. Porosity provides larger contact surface between the graft and recipient site and the cells thereof. So the osteoblasts can penetrate into the graft and form new bone structure and, on the other hand, osteoclasts can have a wider connection with the graft's surface so that resorption is facilitated. These are key to the incorporation of the graft into the recipient site. Besides, blood vessels are also required for nutrition delivery to the cells and their recruitment.

In reconstruction surgeries, the applied grafts can be classified into groups based on their source. Autografts are those which are harvested from the patient's own body. Spongy and cortical bones, bone marrows, and vascularized bones are examples of tissues that can be autografted. Autografts benefit from osteogenic cells which

do not activate the immune system. However, surgeons encounter a higher level of morbidity at the donor site as well as a restrained amount of harvestable tissues [7]. Grafts that are harvested from a person who is genetically identical to the patient are called isografts. The merits and demerits of isografts are roughly the same as autografts due to the similarities in genetics.

The next group of grafts, allografts, are those that are harvested from another individual with different genetics from the patient. Allografts are mostly harvested from a cadaver and used as augmentation for autografts. Before being applied, these grafts are generally decellularized since there is a huge risk of transplant rejection by the immune system. Allografts are also treated in preoperational procedures for decreasing the chance of disease transfer from the cadaver to the patient [5, 6].The last category of grafts is pertinent to xenografts that are defined as those harvested from animals. They can be bovine or porcine, or only collagen from such animals [8].

Grafts can be applied for various purposes such as filling a defect, mechanical functions, or triggering bone formation. There might be no need for its incorporation into the recipient site in some cases whereas large defects' reconstruction requires an incorporated graft. In other words, the graft has to be remodeled. The graft should allow bone cells to proliferate on its surface, that is, in contact with the recipient site. Afterward, the graft ought to begin its degradation process in order to permit the new bone cells to form the former normal tissue gradually. Deficiency of blood vessels restrains the remodeling process enormously [4, 9–11]. Thus, provided that the surgeon faces a huge loss of both soft and hard tissue, it is recommended to apply vascularized grafts since they can supply sufficient blood for the remodeling process. In the case of only hard tissue defects, nonvascularized grafts might also be applicable due to the ability of the recipient site to supply blood.

The incorporation quality depends mainly on the applied graft, recipient tissue, and the interface between graft-tissue and physiological capacities. One of the most influential factors of the applied graft is its degree of porosity. A more porous graft has wider contact with the recipient tissue. In osteoconductive grafts, the large surface allows much more bone cells to migrate and proliferate on it as well as facilitates the degradation process by permitting more osteoclasts to be in contact with the graft. In addition, being porous results in more blood vessels' invasion into the graft so the matrix will be demineralized and its proteins will be released, such as bone morphogenic protein (BMP), which provides osteoinductivity [4, 5].

Cortical bones are not porous in comparison with trabecular bones. Blood vessels and recruited cells can merely attach to the outer surface of such bones. Therefore, the integration process is prolonged and often incomplete. The application of vascularized grafts, even when they contain cortical bones, will accelerate integration [6, 9].

Another main challenge is for the graft to remain fixed in its place, as any strain may result in the failure of the remodeling process. There is a broad range of fixators and alloplastic materials, such as titanium reconstruction plate, that not only keep the graft strongly in its place but also assist the contouring procedure. For instance, according to Kim and Donoff (1992), titanium reconstruction plates that were applied in a lateral mandible reconstructive surgery showed acceptably low failure rate [4, 5, 12].

Vascularity and viability are the most important criteria for an appropriate graft bed or recipient site. The applied graft is needs access to the viable bleeding bed. Redundant reaming or high temperature throughout surgery might cause necrosis in recipient site's cells. On the other hand, other factors such as prior radiotherapy might jeopardize the success rate of reconstructive surgery due to its impact on vascularity and fibrosis of the recipient tissue. Thus, vascularized grafts are highly preferred in the cases that have experienced radiotherapy before reconstructive surgery. In these cases, anastomosis of the blood vessels should also be done in order to increase the success rate. In addition, prior surgeries and chemotherapy may become hazardous, in particular, in cases where tissue has been radiated simultaneously [4, 5].

A broad range of diverse grafts has been applied in reconstruction surgeries. In some cases, the hard tissue has been harvested whereas others have tried both hard and soft tissue that was concurrently harvested as vascularized pedicles. For instance, in an experimental study, calvarium bone grafts were used for 222 patients with mainly posttraumatic or congenital deformities [13]. Other grafts that have been used were harvested from various parts of the body such as acromion and spine of scapula [14], rib [15], radius [16], iliac crest [17, 18], tibial plateau [19, 20], fibula [21, 22]. Some studies reported the usage of myocutaneous free flaps that supply muscle mass, epithelial tissue, and blood such as trapezius and pectoralis major myocutaneous flaps [14, 23]. In some cases, even the resected tissue was applied as a graft [24].

24.1.2 Tissue Engineering Approach

Reconstructive surgeries with the application of grafts, including autografts, allografts, etc., are the best existing treatments for deformities in the maxillofacial region. However, there are some inevitable complications in these surgeries such as the probability of donor site morbidity, restraints in harvesting suitable tissue regarding the quality and the quantity thereof, and the vivid drawbacks of alloplastic materials. To address these complications, biochemical and biomaterial engineering are tried to be combined with cell transplantation studies in order to achieve a fabricated tissue or organ that not only reconstructs the defect but also does not trigger immune response when transplanted. This field of research is named Tissue Engineering and defined as "a new approach applying the principles of biology and engineering to the development of functional substitutes for damaged tissue" by Langer and Vacanti in 1993 [25–27].

Tissue engineering consists of three main strategies that are based on the materials utilized for treatment. Isolated cells or substitutes thereof can be used for improving the functionality of the tissue. There are some substances that can result in tissue formation induction. This strategy relied on the application of these materials. Engineered constructs, called scaffolds, can be utilized and implanted into a defect and lead to the reconstruction of the lost or deformed tissue [28].

24.1.3 Scaffolds

Three-dimensional structures, scaffolds are the main part of tissue-engineered constructs. Tissue engineering scaffold should benefit from some criteria such as biocompatibility in order to have an appropriate function when implanted. For preventing immune rejection, scaffolds must be biocompatible. In some cases, scaffolds are designed for a temporary function. So, they should degrade when their mission is completed. These scaffolds are supposed to be biocompatible in both implantation and degradation time. In other words, the products of their degradation must be nontoxic and safe, as well as themselves. Also, the degradation rate is important and has to be measured and well adjusted.

Since scaffolds are implanted to function as the extracellular matrix of the tissue, they should have suitable mechanical properties. In fact, the preferred scaffolds are those which mimic the native tissue properties. Similar to grafts, scaffolds should be adequately porous and penetrable. The size of pores and their interconnectivity are really important for cell and blood vessel invasion. The cells' diameter is the determinant of pore size. Suitable surface properties are vital as well in order to achieve cell attachment [29].

When a scaffold is to be designed, the first and foremost step is the selection of suitable materials. The materials should be biocompatible and biodegradable and have suitable mechanical and surface properties. A broad range of materials have been introduced with the potential of being used as scaffolds. They can be classified into four groups, namely, polymers, ceramics, metals, and composites [29–31].

24.1.3.1 Polymers

Polymers can be a golden choice for tissue engineering scaffolds due to their high ability to be designed in a way to address the needs. For this,

their composition and structure can be altered [1, 32]. Polymers are divided into two groups of natural and synthetic ones, and each has its pros and cons. Natural polymers are derived from either plants or animal sources similar to the nature of human body, so they are less likely to be rejected by the immune system. Due to their origin, they have variations that may cause an inaccuracy in their engineering and functionality. Their major demerit to some extent are their weak mechanical properties [29, 33].

Collagen can be named as one of the major natural polymers that have been used as tissue engineering scaffolds. Although 28 different types of collagen are known, the collagen type 1 is found the most in human body tissues like bones, tendons and ligaments [34, 35]. Collagen is used because it is not only profuse but biocompatible. In addition, it has the ability to be highly porous and easily processed. Also, it is a hydrophilic and absorbable material having low antigenicity [36, 37]. In addition, some other natural polymers have been used as scaffolds and have shown good performance such as chitosan and hyaluronic acid [38, 39].

Synthetic polymers are aimed to meet the deficiencies in natural ones. They do not have variations and their degradation is always the same, on any patient. This similarity is due to chemical hydrolysis of synthetic polymers rather than an enzymatic one [29]. Some synthetic polymers that have been used for tissue engineering scaffolds are poly lactic acid, polyglycolic acid, and polycaprolactone [40–44].

In a study, the scaffolds made of poly-DL-lactic-co-glycolic acid (PLGA) by solvent-casting particulate-leaching technique were used for repairing defects in porcine mandible. The scaffolds were accompanied by porcine mesenchymal stem cells derived from ilium. The results were satisfactory and PLGA scaffolds could cause bone regeneration at the implantation site [40]. PLGA scaffolds were used in a rabbit mandible with pore sizes of 100–250 μm and resulted in adequate bone formation [41].

Polycaprolactone was used in a dog's mandible in order to reconstruct the mandibular defect [42]. It was also implanted into the anterior mandible of a 71-year-old woman and the results illustrated new bone formation and higher bone volume in comparison with controls [43]. In another study, polylactic acid was used as a scaffold for a defect of critical size. The results were satisfactory, and the PLA scaffold could play a role in bone formation due to its proper mechanical properties and suitably low degradation rate [44].

24.1.3.2 Ceramics

Ceramics can be used widely as bone tissue engineering scaffolds due to their great biocompatibility and bioactivity [29]. Ceramics are highly osteoconductive [45] and osteoinductive [46–48]. Unlike the polymers that are mostly ductile, ceramics are stiff and brittle materials. They are usually used in combination with polymers [29] in order to obtain better characteristics.

There are a broad range of ceramics that have been used as tissue engineering scaffolds, such as hydroxyapatite [49, 50], bioglass [51], titanium oxide [52], and zirconia [53]. For instance, among ceramics, bioactive glasses are not only osteoconductive and bioactive [49, 54–57] but are also able to deliver cells [58]. Furthermore, their degradation can be controlled [59–61]. Bioactive glasses or bioglasses can be fabricated porously with suitable shape and pore size by replication technique [62–64]. In a study, a new sintering method was tested and bioglasses could achieve appropriate mechanical strength as well [51].

Hydroxyapatite (HAp) can be another example of widely used ceramics. Hydroxyapatite is used not only for tissue engineering scaffolds but also as a coating for implants and fillers. All of these applications are due to its high biocompatibility, even with soft tissues, low degradation rate, and proper osteoinductivity and osteoconductivity [28]. HAp is chemically kind of similar to the inorganic component of the bone matrix, so it can form strong chemical bonds with the recipient tissue [65]. HAp does not benefit from suitable mechanical strength. In a study, it has been shown that if HAp is used in nanoscale, the mechanical strength thereof rises [28].

Generally, the materials have to be selected properly in order to achieve suitable characteristics. However, there are some methods of fabrication that confer specific features to the scaffold such as porosity. These methods consist of firing powder and firing slurry [66]. Replication technique is an example [51]. The scaffolds that are fabricated via replication technique are suitably porous. For having a scaffold with desired characteristics, not only is it vital to choose a proper material but also by the use of some techniques, the characteristics of the chosen material can be manipulated as desired .

24.1.4 Cells

Embryonic stem cells (ESCs) are pluripotent stem cells which can be found in the inner cell mass inside the blastocyst. These stem cells have the potential to recreate every organ of the human body. For this, ESCs have to be divided into the groups of cells with the potential to work more specifically, called multipotent stem cells. Mesenchymal stem cells (MSCs) are derivatives of ESCs and play an important role in forming the craniofacial structure by differentiating to various forming cells, such as chondroblasts, osteoblasts, etc. [67]. Mesenchymal stem cells can be easily harvested, isolated, and proliferated. In addition, in freezing, they do not lose their osteogenic potential [5]. MSCs might be the best choice for tissue engineering approach.

Generally, stem cells' division is slightly different from other mature cells. Stem cells need to be constantly available inside the human body. Whenever they differentiate, they produce a cell with characteristics identical to their own. These identical stem cells remain inside various tissues and will be recruited and used whenever required [67]. So, although there are some available sources of MSCs inside the human body, the presence of these cells in a scaffold seems to be beneficial. For instance, for stem cell recruitment, there is a need for blood supply in the defect site while in some cases, in particular in large defects, blood supply shortage is clear.

MSCs have been embedded in various kinds of scaffolds, such as adipose [68–73]. In a study, MSCs that were derived from adipose tissue were embedded in apatite-coated PLGA scaffolds and implanted into a large defect in calvarium. The results were satisfactory and MSCs could induce bone formation [73]. In some studies, MSCs were seeded in an injectable hydrogel, such as the composite of oligo (poly(ethylene glycol) fumarate) (OPF) and gelatin microparticles [74] or sodium alginate hydrogels [75]. Radiation therapy affects reconstruction adversely. It not only endangers vascularization but also makes an incremental change in apoptosis of the embedded cells [76, 77].

In order to induce chondro- or osteogenesis by stem cells that are embedded in a biocompatible and biodegradable scaffold, growth factors need to be added [67].

24.1.5 Growth Factors

There are various growth factors used concomitantly with scaffolds and cells in order to induce tissue formation. Some of them are discussed here, including platelet-derived, insulin-like transforming growth factors, as well as bone morphogenic protein and platelet-rich plasma.

Platelet-derived growth factor (PDGF) is known to affect bone formation by amending the proliferation of both osteoblasts and osteoclasts [78, 79]. It improved bone formation when an absorbable scaffold containing it was implanted into a rat calvarial defect [80], and new attachment and bone defect filling were observed when implanted in monkeys [81].

Insulin-like growth factor (IGF) is one of the growth factors that seem to be effective on general growth of body skeleton [82]. Its systemic application for a critical-size defect in rats that were under radiation prior to reconstruction improved bone formation [83]. IGF has been mostly applied in combination with PDGF [84–86], and in a study, it was illustrated that these growth factors can lead to a dose-dependent improvement in bone formation when applied concomitantly [87].

Transforming growth factor beta (TGFβ) is one of the most prevalent and multipurpose cytokines that generally have an influence on various tissue formations [88]. There are 30 proteins included in the TGFβ superfamily, such as activin, bone morphogenic proteins, and TGFβs themselves [82]. These growth factors have been applied in various studies, albeit with somewhat vague results. Yet, it has been shown that the effectiveness of TGFβs is largely dependent on their carrier and its degradation pace [89]. For instance, $TGF\beta_1$ could not affect bone formation in the rabbit calvarial defects when it was administered freely; however, it vividly resulted in bone regeneration when embedded in a gelatin capsule [90].

Bone morphogenic protein (BMP), as is clear from its name, plays a role in the morphogenesis of bones, specifically three types: BMP2, BMP4, and BMP7. These three types have been shown to induce dose-dependent ectopic and orthotopic bone formation [91, 92]. Recombinant human bone morphogenic type 2 has been used for an elderly female patient in a polycaprolactone carrier and shown to induce de novo bone formation [43]. Some other studies, in particular animal studies, have tested the BMP [93–97].

Platelet-rich plasma (PRP) is a source of platelets produced by blood centrifuging. It benefits from a high amount of thrombocytes containing several prepacked growth factors, such as PDGF, TGFβ, IGF, and VEGF (vascular endothelial growth factor) [82, 97, 98]. In some studies, the application of PRP has led to more bone volume and bone regeneration [42, 43].

24.2 Conclusions

The craniofacial region of the human body plays many vital roles in our lives; therefore, the defects in this site have to be considered as those of critical nature to be reconstructed. Implanting autologous grafts was a gold standard due to not triggering immune rejection, etc., yet, nowadays, the tissue engineering approach seems to be much better since it does not result in donor site morbidity nor does it have the problem of lack of suitable source in terms of quality and quantity. Tissue engineering approach is to implant or inject a biomaterial called scaffold that benefits from some criteria such as biocompatibility, biodegradability, porosity, etc., in combination with cells and some inducing factors in order to enhance the capability of the body to reconstruct the defect. Although a lot of work and experimental studies have been carried out in this regard, there is a broad range of studies that remain and hoped to be done for finding the best cure for these kinds of problems.

References

1. International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)-WHO Version for 2016 http://apps.who.int/classifications/icd10/browse/2016/en#/Q75 Accessed 3/15/18.
2. Wolford LM. Craniofacial deformities. 2017 http://www.drlarrywolford.com/craniofacial-deformities. Accessed 3/16/18.
3. Sanan A, Haines S. Repairing holes in the head: a history of cranioplasty. Neurosurgery. 1997;40(3):588–603.
4. Elsalanty M, Genecov D. Bone grafts in craniofacial surgery. Craniomaxillofac Trauma Reconstr. 2009;2(03):125–34.
5. Smith BT, Shum J, Wong M, Mikos AG, Young S. Bone tissue engineering challenges in oral & maxillofacial surgery. Adv Exp Med Biol. 2015;881:57–78.
6. Bauer T, Muschler G. Bone graft materials. Clin Orthopaed Relat Res. 2000;371:10–27.
7. Khan S, Cammisa F, Sandhu H, Diwan A, Girardi F, Lane J. The biology of bone grafting. J Am Acad Orthopaed Surg. 2005;13(1):77–86.
8. Laurencin CT, El-Amin SF. Xenotransplantation in orthopedic surgery. J Am Acad Orthop Surg. 2008;16:4–8.
9. Dell P, Burchardt H, Glowczewskie F. A roentgenographic, biomechanical, and histological evaluation of vascularized and non-vascularized segmental fibular canine autografts. J Bone Joint Surg. 1985;67(1):105–12.
10. Goldberg V, Stevenson S. Natural history of autografts and allografts. Clin Orthopaed Relat Res. 1987;(225):7–16.
11. Stevenson S, Li X, Davy D, Klein L, Goldberg V. Critical biological determinants of incorporation of non-vascularized cortical bone grafts. Quantification of a complex process and structure. J Bone Joint Surg. 1997;79(1):1–16.
12. Kim MR, Donoff RB. Critical analysis of mandibular reconstruction using AO reconstruction plates. J Oral Maxillofac Surg. 1992;50:1152–7.

13. Ilankovan V, Jackson I. Experience in the use of calvarial bone grafts in orbital reconstruction. Br J Oral Maxillofac Surg. 1992;30(2):92–6.
14. Demergasso F, Piazza M. Trapezius myocutaneous flap in reconstructive surgery for head and neck cancer: An original technique. Am J Surg. 1979;138(4):533–6.
15. Taggard D, Menezes A. Successful use of rib grafts for cranioplasty in children. Pediatr Neurosurg. 2001;34(3):149–55.
16. Schwartz M, Cohen J, Meltzer T, Wheatley M, McMenomey S, Horgan M, Kellogg J, Delashaw J. Use of the radial forearm microvascular free-flap graft for cranial base reconstruction. J Neurosurg. 1999;90(4):651–5.
17. McClintock HG, Dingman RO. The repair of cranial defects with iliac bone. Surgery. 1951;30(6):955–63.
18. David D, Tan E, Katsaros J, Sheen R. Mandibular reconstruction with vascularized iliac crest. Plast Reconstr Surg. 1988;82(5):792–801.
19. Hughes C, Revington P. The proximal tibia donor site in cleft alveolar bone grafting: experience of 75 consecutive cases. J Craniomaxillofac Surg. 2002;30(1):12–6.
20. Tessier P, Kawamoto H, Matthews D, Posnick J, Raulo Y, Tulasne J, Wolfe S. Taking tibial grafts in the diaphysis and upper epiphysis--tools and techniques: IV. A 650-case experience in maxillofacial and craniofacial surgery. Plast Reconstr Surg. 2005;116(5 Suppl):47S–53S.
21. Tideman H. Fibula free flap: A new method of mandible reconstruction. Int J Oral Maxillofac Surg. 1990;19(1):61.
22. Schusterman M, Reece G, Miller M, Harris S, Urken M. The osteocutaneous free fibula flap. Plast Reconstr Surg. 1992;90(5):794–6.
23. Ariyan S. The pectoralis major myocutaneous flap a versatile flap for reconstruction in the head and neck. Plast Reconstr Surg. 1979;63(1):73–81.
24. Rossi G, Arrigoni G. Reimplantation of the mandibular condyle in cases of intraoral resection and reconstruction of the mandible. J Maxillofac Surg. 1979;7:1–5.
25. Schimming RM, Schmelzeisen R. Tissue-engineered bone for maxillary sinus augmentation. J Oral Maxillofac Surg. 2004;62(6):724–9.
26. Payne K, Balasundaram I, Deb S, Di Silvio L, Fan K. Tissue engineering technology and its possible applications in oral and maxillofacial surgery. Br J Oral Maxillofac Surg. 2014;52(1):7–15.
27. Langer R, Vacanti JP. Tissue engineering. Science. 1993;260(80):920–6.
28. Zhou H, Lee J. Nanoscale hydroxyapatite particles for bone tissue engineering. Acta Biomater. 2011;7(7):2769–81.
29. Yang S, Leong K, Du Z, Chua C. The design of scaffolds for use in tissue engineering. Part I. traditional factors. Tissue Eng. 2001;7(6):679–89.
30. Cohen S, Baño M, Cima L, Allcock H, Vacanti J, Vacanti C, Langer R. Design of synthetic polymeric structures for cell transplantation and tissue engineering. Clin Mater. 1993;13(1–4):3–10.
31. Whang K, Healy K, Elenz D, Nam E, Tsai D, Thomas C, Nuber G, Glorieux F, Travers R, Sprague S. Engineering bone regeneration with bioabsorbable scaffolds with novel microarchitecture. Tissue Eng. 1999;5(1):35–51.
32. Liu X, Ma P. Polymeric scaffolds for bone tissue engineering. Ann Biomed Eng. 2004;32(3):477–86.
33. Ferreira AM, Gentile P, Chiono V, Ciardelli G. Collagen for bone tissue engineering. Acta Biomater. 2012;7(6):3191–200.
34. Gelse K. Collagens—structure, function, and biosynthesis. Adv Drug Deliv Rev. 2003;55(12):1531–46.
35. Brodsky B, Eikenberry EF. Characterization of fibrous forms of collagen. In: Leon W, Cunningham DWF, editors. Methods in enzymology. NewYork: Academic Press; 1982. p. 127–74.
36. Glowacki J, Mizuno S. Collagen scaffolds for tissue engineering. Biopolymers. 2008;89(5):338–44.
37. Miyata T, Taira T, Noishiki Y. Collagen engineering for biomaterial use. Clin Mater. 1992;9(3–4):139–48.
38. Solchaga L, Yoo J, Lundberg M, Dennis J, Huibregtse B, Goldberg V, Caplan A. Hyaluronan-based polymers in the treatment of osteochondral defects. J Orthopaed Res. 2000;18(5):773–80.
39. Di Martino A, Sittinger M, Risbud M. Chitosan: a versatile biopolymer for orthopaedic tissue-engineering. Biomaterials. 2005;26(30):5983–90.
40. Abukawa H, Shin M, Williams W, Vacanti J, Kaban L, Troulis M. Reconstruction of mandibular defects with autologous tissue-engineered bone. J Oral Maxillofac Surg. 2004;62(5):601–6.
41. Ren T, Ren J, Jia X, Pan K. The bone formation in vitro and mandibular defect repair using PLGA porous scaffolds. J Biomed Mater Res Part A. 2005;74A(4):562–9.
42. Rai B, Ho K, Lei Y, Si-Hoe K, Jeremy Teo C, Yacob K, Chen F, Ng F, Teoh S. Polycaprolactone-20% tricalcium phosphate scaffolds in combination with platelet-rich plasma for the treatment of critical-sized defects of the mandible: A Pilot Study. J Oral Maxillofac Surg. 2007;65(11):2195–205.
43. Schuckert K, Jopp S, Teoh S. Mandibular defect reconstruction using three-dimensional polycaprolactone scaffold in combination with platelet-rich plasma and recombinant human bone morphogenetic protein-2: de novosynthesis of bone in a single case. Tissue Eng Part A. 2009;15(3):493–9.
44. Schliephake H, Weich H, Dullin C, Gruber R, Frahse S. Mandibular bone repair by implantation of rhBMP-2 in a slow release carrier of polylactic acid—an experimental study in rats. Biomaterials. 2008;29(1):103–10.
45. Holmes RE. Osteoconduction in hydroxyapatite-based materials. In: Brighton CT, Friedlaender G, Lane JM, editors. Bone formation and repair. Rosemont: American Academy of Orthopedic Surgeons; 1994. p. 355–65.

46. Heughebaert M, LeGeros R, Gineste M, Guilhem A, Bonel G. Physicochemical characterization of deposits associated with HA ceramics implanted in nonosseous sites. J Biomed Mater Res. 1988;22(S14):257–68.
47. Zhang X, Zhou P, Zhang J, Chen W, Wu C. A study of HA ceramics and its osteogenesis. In: Ravaglioli A, Krahewsky A, editors. Bioceramics and the human body. London: Elsevier Applied Science; 1991. p. 408–16.
48. Yuan HP, Kurashina K, de Bruijn JD, Li Y, de Groot K, Zhang X. A preliminary study on osteoinduction of two kinds of calcium phosphate ceramics. Biomaterials. 1999;20:1799–806.
49. Oonishi H, Kutrshitani S, Yasukawa E, Iwaki H, Hench LL, Wilson J, Tsuji E, Sugihara T. Particulate bioglass compared with hydroxyapatite as a bone graft substitute. Clin Orthop Relat Res. 1997;334:316–25.
50. Li S, De Wijn J, Layrolle P, De Groot K. Synthesis of macroporous hydroxyapatite scaffolds for bone tissue engineering. J Biomed Mater Res. 2002;61(1):109–20.
51. Chen Q, Thompson I, Boccaccini A. 45S5 Bioglass®-derived glass–ceramic scaffolds for bone tissue engineering. Biomaterials. 2006;27(11):2414–25.
52. Gerhardt L, Jell G, Boccaccini A. Titanium dioxide (TiO_2) nanoparticles filled poly(d, l lactid acid) (PDLLA) matrix composites for bone tissue engineering. J Mater Sci Mater Med. 2007;18(7):1287–98.
53. Chen Q, Boccaccini A, Zhang H, Wang D, Edirisinghe M. Improved mechanical reliability of bone tissue engineering (zirconia) scaffolds by electrospraying. J Am Ceramic Soc. 2006;89(5):1534–9.
54. Wilson J, Pigot GH, Schoen FJ, Hench LL. Toxicology and biocompatibility of bioglass. J Biomed Mater Res. 1981;15:805–11.
55. Hench LL, Splinter RJ, Allen WC. Bonding mechanisms at the interface of ceramic prosthetic materials. J Biomed Mater Res Symp. 1971;2(part 1):117–41.
56. Hench LL, Paschall HA. Direct chemical bond of bioactive glass–ceramic materials to bone and muscle. J Biomed Mater Res Symp. 1973;4:25–42.
57. Hench LL, Paschall HA. Histochemical response at a biomaterial's interface. J Biomed Mater Res Symp. 1974;5(Part 1):49–64.
58. Gatti AM, Valdre G, Andersson OH. Analysis of the in vivo reactions of a bioactive glass in soft and hard tissue. Biomaterials. 1994;15:208–12.
59. Clark AE, Hench LL. Calcium phosphate formation on sol–gel derived bioactive glasses. J Biomed Mater Res. 1994;28:693–8.
60. Hench LL. Sol–gel materials for bioceramic applications. Curr Opin Solid State Mater Sci. 1997;2:604–10.
61. Hench LL, Wilson J. Surface-active biomaterials. Science. 1984;226:630–6.
62. Schwartzalder K, Somers AV. Method of making a porous shape of sintered refractory ceramic articles. United States Patent no. 3090094, 1963.
63. Cowin SC. Bone mechanics. Boca Raton, FL: CTC Press; 1989. p. 1–4.
64. Gibson LJ, Ashby MF. Cellular solids: structure and properties. 2nd ed. Oxford: Pergamon; 1999. p. 429–52.
65. Tonino A, Thèrin M, Doyle C. Hydroxyapatite-coated femoral stems. J Bone Joint Surg. 1999;81(1):148–54.
66. Gauthier O, Bouler J, Aguado E, Pilet P, Daculsi G. Macroporous biphasic calcium phosphate ceramics: influence of macropore diameter and macroporosity percentage on bone ingrowth. Biomaterials. 1998;19(1-3):133–9.
67. Mao J, Giannobile W, Helms J, Hollister S, Krebsbach P, Longaker M, Shi S. Craniofacial tissue engineering by stem cells. J Dent Res. 2006;85(11):966–79.
68. Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, Benhaim P, Lorenz HP, Hedrick MH. Multilineage cells from human adipose tissue: implications for cell based therapies. Tissue Eng. 2001;7:211–28.
69. Zuk PA, Zhu M, Ashjian P, De Ugarte DA, Huang JI, Mizuno H, Alfonso ZC, Fraser JK, Benhaim P, Hedrick MH. Human adipose tissue is a source of multipotent stem cells. Mol Biol Cell. 2002;13:4279–95.
70. De Ugarte DA, Morizono K, Elbarbary A, Alfonso Z, Zuk PA, Zhu M, Dragoo JL, Ashjian P, Thomas B, Benhaim P, Chen I, Fraser J, Hedrick MH. Comparison of multi-lineage cells from human adipose tissue and bone marrow. Cells Tissues Organs. 2003;174:101–9.
71. Gimble JM, Guilak F. Differentiation potential of adipose derived adult stem (ADAS) cells. Curr Top Dev Biol. 2003;58:137–60.
72. Hicok KC, Du Laney TV, Zhou YS, Halvorsen YD, Hitt DC, Cooper LF, Gimble JM. Human adipose-derived adult stem cells produce osteoid in vivo. Tissue Eng. 2004;10:371–80.
73. Cowan CM, Shi YY, Aalami OO, Chou YF, Mari C, Thomas R, Quarto N, Contag CH, Wu B, Longaker MT. Adipose-derived adult stromal cells heal critical-size mouse calvarial defects. Nat Biotechnol. 2004;22:560–7.
74. Park H, Temenoff JS, Tabata Y, Caplan AI, Mikos AG. Injectable biodegradable hydrogel composites for rabbit marrow mesenchymal stem cell and growth factor delivery for cartilage tissue engineering. Biomaterials. 2007;28:3217–27.
75. Shang Q, Wang Z, Liu W, Shi Y, Cui L, Cao Y. Tissue-engineered bone repair of sheep cranial defects with autologous bone marrow stromal cells. J Craniofac Surg. 2001;12:586–93.
76. Okunieff P, Mester M, Wang J, Maddox T, Gong X, Tang D, Coffee M, Ding I. In vivo radioprotective effects of angiogenic growth factors on the small bowel of C3H mice. Radiat Res. 1998;150:204–11.
77. Okunieff P, Wang X, Rubin P, Finkelstein JN, Constine LS, Ding I. Radiation-induced changes in bone perfusion and angiogenesis. Int J Radiat Oncol Biol Phys. 1998;42:885–9.
78. Hock JM, Cannalis E. Platelet-derived growth factor enhances bone cell replication but not differentiated function of osteoblasts. Endocrinology. 1994;134:1423–8.

79. Schliephake H, Bertram H, Lindenmaier W, Rohde M, Mayer H, Planck H. In-vitro engineering of human bone marrow derived mesenchymal stem cells (MSC) for tissue engineered growth of bone. Int J Oral Maxillofac Surg. 1999;28(Suppl 1):107–8.
80. Chung CP, Kim DK, Park YJ, Nam KH, Lee SJ. Biological effects of drug loaded biodegradable membranes for guided bone regeneration. J Periodontal Res. 1997;32:172–5.
81. Rutherford RB, Ryan ME, Kennedy JE, Tucker MM, Charette MF. Platelet-derived growth factor and dexamethasone combined with a collagen matrix induce regeneration of the periodontium in monkeys. J Clin Periodontol. 1993;20:537–44.
82. Schliephake H. Bone growth factors in maxillofacial skeletal reconstruction. Int J Oral Maxillofac Surg. 2002;31(5):469–84.
83. Thaller SR, Salzhauer MA, Rubinstein AJ, Thion A, Tesluk H. Effect of insulin-like growth factor type I on critical size calvarial bone defects in irradiated rats. J Craniofac Surg. 1998;9:138–41.
84. Stefani CM, Machado MA, Sallum EA, Toledo S, Nocti HJR. Platelet derived growth factor/insulin-like growth factor-1 combination and bone regeneration around implants placed into extraction sockets: a histometric study in dogs. Implant Dent. 2000;9:126–31.
85. Nacti FHJ, Stefani CM, Machado MA, Sallum EA, Toledo S, Sallum AW. Histometric evaluation of bone regeneration around immediate implants partially in contact with bone: a pilot study in dogs. Implant Dent. 2000;9:321–8.
86. Lynch SE, Buser D, Hernandez RA, Weber HP, Stich H, Fox CH, Williams RC. Effects of the platelet-derived growth factor/insulin-like growth factor-I combination on bone regeneration around dental implants. Results of a pilot study in beagle dogs. J Periodontol. 1991;62:710–6.
87. Howell TH, Fiorellini JP, Paquette DW, Ofenbacher S, Giannobile WV, Lynch SE. A phase I/II trial to evaluate a combination of recombinant human platelet-derived growth factor-BB and recombinant human insulin-like growth factor-I in patients with periodontal disease. J Periodontal Res. 1997;68:1168–93.
88. Gao J, Symons AL, Bartold PM. Expression of transforming growth factor-beta 1 (TGF-beta 1) in the developing periodontium of rats. J Dent Res. 1998;77:1708–16.
89. Yamamoto M, Tabata Y, Hing L, Miyamoto S, Hashimoto N, Ikada Y. Bone regeneration by transforming growth factor-beta 1 released from a biodegradable hydrogel. J Control Release. 2000;64:133–42.
90. Hong L, Tabata Y, Niyamoto S, Yamada K, Aoyoma I, Tamura M, Hashimoto N, Ikada Y. Promoted bone healing at a rabbit skull gap between autologous bone fragment and the surrounding intact bone with biodegradable microspheres containing transforming growth factor-beta 1. Tissue Eng. 2000;6:331–40.
91. Sandhu HS, Kanim LE, Kabo JM, Toth JM, Zeegen EN, Liu D, Delemarter RB, Dawson EG. Effective doses of recombinant human bone morphogenetic protein-2 in experimental spinal fusion. Spine. 1996;21:2115–22.
92. Riley EH, Lane JM, Urist MR, Lyons KM, Lieberman JR. Bone morphogenetic protein-2: biology and applications. Clin Orthop. 1996;324:39–46.
93. Higuchi T, Kinoshita A, Takahashi K, Oda S, Ishikawa I. Bone regeneration by recombinant human bone morphogenetic protein-2 in rat mandibular defects. an experimental model of defect filling. J Periodontol. 1999;70:1026–31.
94. Gerhart TN, Kirker-Head CA, Kriz MJ, Holtrop ME, Hennig GE, Hipp J, Schelling SH. Healing of segmental femoral defects in sheep using recombinant human bone morphogenetic protein. Clin Orthop. 1993;293:317–23.
95. Cook SD, Baffes GC, Wolfe MW, Sampath TK, Rueger DC. Recombinant human bone morphogenetic protein-7 induces healing in a canine long-bone segmental defect model. Clin Orthop. 1994;301:302–11.
96. Bostrom M, Lane JM, Tomin E, Browne M, Berberian W, Turek T, Smith J, Woszeny J, Schildhauer T. Use of bone morphogenetic protein-2 in the rabbit ulnar nonunion model. Clin Orthop. 1996;327:272–82.
97. Tozum TF, Demiralp B. Platelet-rich plasma: a promising innovation in dentistry. J Can Dent Assoc. 2003;69:664.
98. Ramay H, Zhang M. Biphasic calcium phosphate nanocomposite porous scaffolds for load-bearing bone tissue engineering. Biomaterials. 2004;25(21):5171–80.