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RESEARCH ARTICLE

CONTEMPORANEOUS TRENDS AND RECENT ADVANCES IN BONE AUGMENTATION FOR DENTAL IMPLANT PLACEMENT

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ABSTRACT

The use of dental implants for the rehabilitation of missing teeth has broadened the treatment options for patients and clinicians equally. The use of dental implants has increased dramatically in the past two decades as a result of advancements in research in implant design, materials and techniques, and is expected to expand further in the future. However the clinical complexity of the patient who present with limited bone volume often requires additional biomaterials and surgical procedures to ensure successful implant treatment. This review outlines the various biomaterials used in augmenting bone deficiencies encountered, the different surgical techniques that are used in order to achieve a predictable long term success of dental implants with elaboration on the recent advancements and the future of bone regeneration.

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INTRODUCTION

The replacement of missing teeth with dental implant prostheses is a well-established clinical practice. Success of dental implants depends largely on the quality and quantity of available bone in the recipient site. If available bone is inadequate for implant placement in the desired recipient site for prosthetic support, then bone augmentation is considered. Several methods are available to augment the deficient ridge, including guided bone regeneration, block bone grafting, sinus/nasal floor bone grafting, interpositional grafting, ridge expansion, protected bone regeneration (titanium mesh), and distraction osteogenesis (Cullum and Deporter, 2016). The choice of a particular augmentation technique or graft material will depend on several factors, including the degree of atrophy, the morphology of the osseous defect, type of prosthesis, and clinician or patient preferences.

Classification of bone grafts:

Classification of bone grafts based on material groups: (Cullum and Deporter, 2016)

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a. Allograft-based bone graft involves allograft bone, used alone or in combination with other materials (e.g., Grafton, Ortho Blast).
b. Factor-based bone graft are natural and recombinant growth factors, used alone or in combination with other materials such as transforming growth factor-beta (TGF-beta), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF), and bone morphogeneic protein (BMP).
c. Cell-based bone grafts use cells to generate new tissue alone or are added onto a support matrix, for example, mesenchymal stem cells.
d. Ceramic-based bone graft substitutes include calcium phosphate, calcium sulphate, and bioglass used alone or in combination; for example, OsteoGraf, ProOsteon, OsteoSet.
e. Polymer-based bone graft uses degradable and nondegradable polymers alone or in combination with other materials, for example, open porosity polylactic acid polymer.

Rationale for bone grafting:

The biologic mechanisms that provide a rationale for bone grafting are osteoconduction, osteoinduction, and osteogenesis (Bedrossian *et al.,* 2006).

Osteoconduction

Occurs when bone graft material serves as a scaffold for new bone growth, which is perpetuated by the native bone. Osteoblasts from the margin of defect that is being grafted, utilize the bone graft material as a framework upon which to spread and generate new bone (Cullum and Deporter, 2016). In the very least, a bone graft material should be osteoconductive.

Osteoinduction

Involves stimulation of osteoprogenitor cells to differentiate into osteoblasts and then begins formation of new bone. The most widely studied type of osteoinductive cell mediators are BMPs (Bedrossian *et al.,* 2006). A bone graft material that is osteoconductive and osteoinductive will not only serve as a scaffold for currently existing osteoblasts but will also trigger formation of new osteoblasts, promoting faster integration of the graft.

Osteopromotion

Involves enhancement of osteoinduction without possession of osteoinductive properties. For example, enamel matrix derivative enhances the osteoinductive effect of demineralized freeze-dried bone allograft (DFDBA), but will not stimulate bone growth alone (Bedrossian *et al.,* 2006).

Osteogenesis

It occurs when vital osteoblasts originating from bone graft material contributes to the growth of new bone along with bone formation.

Types of grafts and Tissue Sources

Autograft

Autologous or autogenous bone grafting involves utilizing bone obtained from same individual receiving the graft. Bone can be harvested from nonessential bones, such as from iliac crest, mandibular symphysis (chin area), and anterior mandibular ramus (coronoid process). When a block grant will be performed, autogeneous bone is the most preferred because there is less risk of graft rejection as the graft is originated from the patient′s body (Stellingsma *et al.,* 2014). Autogenous bone has long been considered the gold standard of graft materials because of its superior biologic properties, including osteogenesis, osteoinduction, and osteoconduction. Disadvantage of autologous grafts is that additional surgical site is required, another potential location for postoperative pain and complications (Stellingsma *et al.,* 2014). All bones require blood supply in the transplanted site. Depending on where the transplant site is and size of the graft, an additional blood supply may be required. For these types of grafts, extraction of the part of the periosteum and accompanying blood vessels along with the donor bone is required. This kind of graft is known as a free flap graft.

Allografts

Allograft is derived from humans. The difference is that allograft is harvested from an individual other than the one receiving the graft. Allograft bone is taken from cadavers that have donated their bone so that it can be used for living people who are in need of it; it is typically sourced from a bone bank.

There are three types of bone allograft available (Krekmanov *et al.,* 2000):

- Fresh or fresh-frozen bone
- FDBA
- DFDBA

The use of allografts for bone repair often requires sterilization and deactivation of proteins normally found in healthy bone. Contained in the extracellular matrix of bone tissue are the full cocktail of bone growth factors, proteins, and other bioactive materials necessary for osteoinduction and successful bone healing; the desired factors and proteins are removed from the mineralized tissue by using a demineralizing agent such as hydrochloric acid. The mineral content of the bone is degraded, and the osteoinductive agents remain in a demineralized bone matrix (DBM).

Synthetic variants

Flexible hydrogel-hydroxyapatite (HA) composite which has a mineral to organic matrix ratio, approximating that of human bone. Artificial bone can be created from ceramics such as calcium phosphates (e.g., HA and tricalcium phosphate), bioglass, and calcium sulphate are biologically active depending on solubility in physiological environment (Gallucci *et al.,* 2016). These materials combine with growth factors, ions such as strontium or mixed with bone marrow aspirate to increase biological activity. The presence of elements such as strontium can result in higher bone mineral density (BMD) and enhanced osteoblast proliferation.

Xenograft

Xenografts are bone grafts from a species other than human, such as bovine or porcine derivatives are used as a calcified matrix.

Alloplastic grafts

Alloplastic grafts may be made from hydroxyapatite, a naturally occurring mineral (main mineral component of bone), made from bioactive glass. Hydroxyapatite is a synthetic bone graft, which is the most used now due to its osteoconduction, hardness, and acceptability by bone. Some synthetic bone grafts are made of calcium carbonate, which start to decrease in usage because it is completely resorbable in short time and makes breaking of the bone easier. Finally used is the tricalcium phosphate in combination with hydroxyapatite and thus giving effect of both, osteoconduction and resorbability.

Growth factors

Growth factors enhanced grafts are produced using recombinant DNA technology. They consist of either human growth factors or morphogens (BMPs in conjunction with a carrier medium, such as collagen).The factors and proteins that exist in bone are responsible for regulating cellularactivity. Growth factors bind to receptors on cell surfaces and stimulate intracellular environment to act. Generally, this activity translates to a protein kinase that induces a series of events

resulting in transcription of messenger ribonucleic acid (mRNA) and ultimately into the formation of a protein to be used intracellularly or extracellularly. The combination and simultaneous activity of many factors results in controlled production and resorption of bone. These factors, residing in extracellular matrix of bone, include TGF-beta, insulin like growth factors I and II, PDGF, FGF, and BMPs (Aghaloo *et al.,* 2016; Misch, 2010). Cell-based bone graft substitutes: Stem cells are cultured in the presence of various additives such as dexamethasone, ascorbic acid, and β-glycerophosphate to direct the undifferentiated cell towards osteoblast lineage.The addition of TGF-beta and BMP-2, BMP-4, and BMP-7 to the culture media can also influence the stem cells towards osteogenic lineage. Mesenchymal stem cells have also been seeded onto bioactive ceramics conditioned to induce differentiation to osteoblasts.

Ceramic-based bone graft substitutes

Majority of bone grafts available involve ceramics, either alone or in combination with another material (e.g., calcium sulfate, bioactive glass, and calcium phosphate). The use of ceramics, like calcium phosphates is calcium hydroxyapatite which is osteoconductive and osteointegrative; and in some cases, osteoinductive. They require high temperatures for scaffold formation and have brittle properties.

- Calcium sulfate is also known as plaster of Paris. It is biocompatible, bioactive, and resorbable after 30-60 days. Significant loss of its mechanical properties occurs upon its degradation; therefore, it is a questionable choice for load-bearing applications:
- OsteoSet is a tablet used for defect packing. It is degraded in approximately 60 days.
- Allomatrix is Osteoset combined with DBM, forms a putty or injectable paste. OsteoSet is a calcium sulfate tablet used for bone defect sites, whereas allomatrix is a combination of calcium sulfate and DBM that forms an injectable paste or fable putty.

Bioactive glass (bioglass) is a biologically active silicate-based glass, (Misch *et al.,* 2012) having high modulus and brittle nature; it has been used in combination with polymethylmethacrylate to form bioactive bone cement and with metal implants as a coating to form a calcium-deficient carbonated calcium phosphate layer which facilitates the chemical bonding of implants to the surrounding bone. Different types of calcium phosphates are tricalcium phosphate, synthetic hydroxyapatite, and coralline hydroxyapatite; available in pastes, putties, solid matrices, and granules. Such calcium phosphates products include Bio-Oss and OsteoGraft. Both products use hydroxyapatite, either as a particulate (Bio-Oss) or as blocks and particulates (OsteoGraft). Pro-Osteon is a unique product based on sea coral, which is converted from calcium carbonate to calcium hydroxyapatite. The advantage of this material is that the structure of coral, which is similar to that of trabecular bone.

Polymer-based bone graft substitutes

This can be divided into natural polymers and synthetic polymers. Subclassified into degradable and non degradable types. Polymer-based bone graft substitutes include the following:

- Healos is a natural polymer-based product, a polymer-ceramic composite consisting of collagen fibers coated with hydroxyapatite and indicated for spinal fusions.
- Cortoss is an injectable resin-based product with applications for load-bearing sites.

Degradable synthetic polymers, like natural polymers are resorbed by the body. The benefit of having the implant resorbed by the body is that, the body is able to heal itself completely without remaining foreign bodies.

The Graftless Approach

A recent trend is toward minimally invasive surgical procedures to reduce complications, decrease discomfort, and facilitate faster recovery. One way to accomplish this is by treatment planning to avoid the need for bone grafting or choosing a "graftless" approach. Reduced-diameter or shorter implants may be utilized when minimal available bone volume is present. Today, with short implants, bone grafting the atrophic edentulous mandible is rarely needed. In the atrophic maxilla, tilted implants or zygomatic implants can be used to avoid the maxillary sinus, eliminating the need for sinus bone grafting. As long as biomechanical support is not compromised, fewer implants may also be considered for a fixed prosthesis (Krekmanov *et al.,* 2000; Gallucci *et al.,* 2016; Aghaloo *et al.,* 2016; Misch, 2011; Boyan *et al.,* 2006; Chiapasco *et al.,* 2009). The dentist may prefer extraction of compromised teeth for full-arch implant placement instead of augmenting the atrophic maxillary or mandibular posterior ridges. The introduction of cone-beam computed tomography to the dental office has been integral to this minimally invasive trend. The ability to more accurately diagnose available bone and visualize anatomy enables the clinician to manage cases with marginal conditions. It also permits the use of computer-guided surgery with a flapless approach to further decrease morbidity. Although patients may tend to prefer a minimally invasive approach, dentists should not disregard options that require bone grafting solely on this basis.

Tissue Engineering

The developing field of tissue engineering offers a strategy to replace the need for harvesting bone from the patient. Tissue engineering may be used to regenerate bone by combining cells from the body with growth factors and scaffold biomaterials (Kaigler *et al.,* 2012). This combination of cells, signaling molecules, and scaffold is often referred to as the tissue engineering triad. Growth factors are naturally occurring signaling proteins that can recruit cells and stimulate cell proliferation and differentiation. For many years, surgeons have used autologous blood-derived growth factors to enhance wound healing (Transparency Market Research, 2015; Kaigler *et al.,* 2012). The platelets contain several growth factors, including platelet-derived growth factor, transforming growth factor beta, and vascular endothelial growth factor[13]. Various types of platelet concentrates have been developed, such as platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and plasma rich in growth factors (PRGF). Their production methods are diverse, and as such, cellular and cytokine compositions vary. No consensus is available regarding the preference or biologic superiority of one type of blood borne product. The rationale for using platelet concentrates in bone augmentation is acceleration of graft revascularization, improved soft tissue healing, and enhanced bone formation

(Marx, 2001). However, scientific evidence is insufficient to support that platelet concentrates significantly improve grafting outcomes when used with bone substitutes (Plachokova *et al.,* 2008; Lemos *et al.,* 2016). The fibrin within the plasma creates a gel consistency, improving the placement and containment of the graft. The amplification of soft-tissue healing over the graft site and improved graft handling properties may justify routine use of platelet concentrates. Recombinant growth factors are genetically engineered versions produced in the laboratory that are identical in structure and action to the naturally occurring cytokines (Wozney, 2008). Commercially available growth factors for clinical use in dentistry include recombinant platelet-derived growth factor (rhPDGF-BB) (Gem 21S®, Osteohealth, osteohealth.com) and recombinant bone morphogentic protein 2 (rhBMP-2) (Infuse® Bone Graft, Medtronic, medtronic.com). Gem 21S has been approved by the Food and Drug Administration (FDA) for the treatment of moderate to severe periodontal intra osseous defect (McGuire *et al.,* 2009). Infuse Bone Graft has FDA approval for the repair of extraction socket defects and sinus bone grafting (Boyne *et al.,* 2015; Fiorellini *et al.,* 2015). The use of these recombinant growth factors for ridge-augmentation procedures is considered an "off label" application (Misch *et al.,* 2015). Although the off-label designation does not prevent clinicians from considering their use for bone augmentation, dental teams should inform patients of this status, any alternative treatment options, and possible risks. Any adverse affects must also be well documented. Infuse Bone Graft has been the subject of some media attention regarding its off-label usage, high cost, and adverse events in spinal applications (Woo, 2012; Faundez *et al.,* 2016). Platelet-derived growth factor (PDGF) is chemotactic for osteoblasts, cement oblasts, and periodontal ligament cells. It is also a potent mitogen that enhances cell proliferation and the induction of angiogenesis (Kaigler *et al.,* 2016).

Although PDGF is a mitogen that does not actually induce bone formation, it may augment bone regeneration by improving the conditions for osseous regeneration. Findings from animal studies using mandibular defects have shown an increase in bone formation and defect repair (Simion *et al.,* 2009; Herford and Cicciu, 2012). To date, the only human studies on rhPDGF-BB for bone augmentation are clinical case reports using the growth factor in combination with bone substitutes (Nevins *et al.,* 2012 & 2014). A clinician should not assume that adding a growth factor, such as rhPDGF-BB, would necessarily improve augmentation outcomes (Amorfini *et al.,* 2014; Geurs *et al.,* 2014). So far, evidence does not support routine use in sinus lift procedures and socket healing or lateral/vertical augmentations of the alveolar crest (Schliephake, 2015). A possible strategy for using rhPDGF-BB in bone augmentation may be to enhance wound healing and flap closure over the grafted site. Wound dehiscence is one of the most common complications with bone-augmentation procedures (Misch, 2015). The growth factor can be applied to a collagen sponge and placed under the flaps during closure. Results from animal studies have shown decreased dehiscence of titanium mesh grafts with this technique (Herford *et al.,* 2012). Bone morphogenetic proteins (BMPs) are naturally occurring osteoinductive growth factors found in bone. These cytokines are chemotactic for mesenchymal stem cells and induce their proliferation and differentiation into osteoblasts. In extraction sockets with significant buccal wall defects, rhBMP-2 has been shown to be effective in enhancing bone formation for implant placement (Boyan *et al.,* 2006; Misch, 2010). Studies have also found rhBMP-2 is applicable to maxillary sinus floor augmentation (Boyne *et al.,* 2005). However, many surgeons have questioned the use of a more costly product when other less expensive bone substitutes have been shown to be as effective (Kelly *et al.,* 2016). Although the absorbable collagen sponge (ACS) has been found to be an optimal carrier for the rhBMP-2 molecule, it has poor scaffolding properties to resist flap compression (Wozney *et al.,* 2008). When horizontal or vertical bone augmentation is needed, titanium mesh has been used as a method to provide space maintenance and protection of the rhBMP-2/ACS graft (Marx *et al.,* 2013; Misch, 2011; De freitas *et al.,* 2013; Misch *et al.,* 2015). The addition of an osteoconductive matrix to the rhBMP-2/ACS complex, such as particulate allograft, has also been suggested as a strategy to provide additional scaffolding and matrix for cellular migration (Marx *et al.,* 2013; Misch, 2011; De freitas *et al.,* 2013; Misch *et al.,* 2015). This also decreases the material cost as less BMP is needed. Outcomes of rhBMP-2 bone grafts with titanium mesh in lateral and vertical augmentations have been comparable to autografts (Marx *et al.,* 2013; De freitas *et al.,* 2013). The benefits for using a growth factor are significant, as there is no bone graft harvest and associated morbidity. The surgery may be performed in an office environment under sedation and local anesthesia instead of in an operating room under general anesthesia. Also, surgical time may be less. The disadvantages of the use of rhBMP-2 compared to autograft include greater postoperative edema, longer graft healing times, softer initial bone quality, and higher materials costs (Marx *et al.,* 2013; Misch *et al.,* 2015).

The Future of Bone Regeneration:

Presently in dentistry, the main focus in tissue engineering has been on using growth factors. However, there are limitations to using one recombinant growth factor in a supraphysiologic dose at the time of surgery for early release in wound healing. Improvements may be attained by a combination of growth factors that are released at times that mimic the normal cascade of bone formation (Dimitriou *et al.,* 2011). Another promising technique for growth factor delivery is the application of gene therapy (Caplan, 2000). Genetic material is transferred into the genome of the target cells, causing them to produce a functional protein, such as BMP, at physiologic amounts and timelines. Research is ongoing to develop biodegradable scaffolds that maintain space, allow vascular ingrowth, and promote cell adhesion (Dimitriou *et al.,* 2011). Dentistry is at the forefront for integrating radiographic imaging with CAD/CAM technology for fabricating custom devices. A CBCT scan of the jaw can be obtained for virtual planning of the reconstruction using software. It can also be used to produce a stereolithographic model of the jaw for reconstructive planning or creating made-to-order matrices (Yamada *et al.,* 2014; Chow *et al.,* 2007). Custom titanium meshes have been developed to protect and contain growth factor-enhanced grafts (Casap *et al.,* 2013). At present, allogeneic and xenograft block bone grafts may be milled to custom fit an atrophic ridge (Schlee and Rothamel, 2013). In the future, custom-made resorbable scaffolds will routinely be fabricated using 3-dimensional printers (Dimitriou *et al.,* 2011). The printed porous scaffold may then be seeded with osteoblasts or mesenchymal stem cells. Mesenchymal stem cells from bone marrow, adipose tissue, and cryopreserved umbilical cord blood have shown the ability to form new bone

tissue (Bhumiratana *et al.,* 2012). Bone-marrow aspirate from the iliac crest may be centrifuged to produce a concentrate of mesenchymal stem cells for mixture with bone substitutes or seeding of a porous matrix. In vitro cultural expansion can further generate a larger number of progenitor cells[38]. Another strategy for customized bone reconstruction is to infuse a porous biodegradable scaffold with osteoinductive growth factors that recruit host cells and guide bone ingrowth (Dimitriou *et al.,* 2011; Bhumiratana *et al.,* 2012). The use of biologic agents on dental implant surfaces may be another alternative for encouraging bone formation in deficient sites.

Conclusion

We practice implant dentistry at a time when numerous ways are available to help us treat cases with bone deficiencies. No single clinical technique or biomaterial is optimum for every augmentation procedure. However, clinicians may be tempted to abandon traditional approaches for new and less complicated procedures that may not provide comparable results. Surgeons should consider the advantages and disadvantages of each alternative in a given clinical situation and select the material with lowest overall cost and morbidity and the highest likelihood of success (Rogers and Greene, 2012). Clinicians will need to weigh the higher costs of newer tissue engineering techniques against the benefits of simplified surgery, enhanced biologic response, and potential for reduced morbidity.

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