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REVIEWARTICLE

RECENT TRENDS OF BONE REGENERATION IN DENTAL IMPLANTOLOGY: AN REVIEW ARTICLE

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ABSTRACT

Dental implant is an artificial tooth root that is placed into your jaw to hold a replacement of missing substitute. The use of dental implant for replacement of teeth has provided many treatment options for both patients and clinicians. As a result of recent advancements and newer implant designs, materials and techniques the use of dental implants has increased tremendously over the past decades and is expected to expand further more in the future. The patients present with bone deficiency represent clinical complexity and often requires additional biomaterials and surgical procedures in order to ensure successful treatment planning. This review outlines the various graft materials used in bone augmentation in order to achieve predictable long term prognosis of dental implants and on the recent advancement in the bone regeneration.

INTRODUCTION

Bone loss followed by extraction is a common physiological phenomenon. However this leads to alveolar resorption and subsequent formation of bone within the socket followed by osteoblastic differentiation and osteoprogenitor cells (Guglielmotti, 1985 and Sarala, 2018). The rehabilitation of missing teeth with dental implant prosthesis has tremendously increased in clinical practices. The quantity and quality of available bone on the recipient site attributes to the success of dental implants (Cullum, 2016). Certain factors like periodontal diseases lead to necessity of bone augmentation. If available bone is inadequate for implant placement in the desired locations 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 (Guglielmotti, 1985 and Cullum, 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.

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Classification of bone grafts based on material groups (Guglielmotti, 1985 and Niha Naveed, 2017)

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

Hyatt and Butler (Hyatt, 1957 and Kumar, 2016) have classified tissue grafts as follows:

- **Autograft:** Tissue taken from one operative site and grafted in another operative site within the same individual.

Table 1. Carranza (1999) classification of bone graft materials (Carranza, 1998)

Autogenous bone	Allograft	Xenograft	None bone graft materials	Alloplast	
Bone from intraoral site- Osseous coagulum Bone blend Intraoral cancellous bone marrow transplant Bone swaging	Bone from extraoral sites- Iliac crest Tibia	Freeze dried Decalcified freeze dried bone allograft	Calf bone Kiel bone Anorganic	Sclera Cartilage Plaster of paris Calcium phosphate apatite Tricalcium phosphate	Porous hydroxyapatite Non - porous hydroxyapatite HTR polymer Beta tricalcium phosphate Bio-active glass ceramics

- **Homograft/allograft:** Tissue taken from one operative site in one individual and grafted in the operative site in another individual of the same specie.
- **Heterograft/xenograft:** Tissue taken from one individual and grafted in the operative site of another individual of the different species.
- **Syngensio grafts:** Tissue graft removed from blood related relatives.
- **Orthotopic graft:** Tissue grafted into an anatomical site normally occupied by that tissue, for example, bone to bone and skin to skin.

Autogenous Bone Graft: Autologous or autogenous bone grafting involves utilizing bone obtained from same individual receiving the graft. Sources of bone include iliac crest, mandibular symphysis (chin area), anterior mandibular ramus (coronoid process), and bone removed during osteoplasty and osteectomy (Hiatt, 1973). Types of autograft include osseous coagulum (Robinson, 1969), bone blend (Diem, 1972), cancellous bone marrow transplant, and bone swaging (Ewen, 1965). An autogenous bone graft is the transplantation of bone from one site within the same person. One of the most complex challenges in implant density is the treatment of large bone defects or deficiencies. Successful regeneration requires the essential components of cells, scaffold and signaling molecules (Adell, 1981 and Friedlander, 1982). Autogenous bone graft is the only graft which is considered as the gold standard of bone regeneration as it possesses all of the following properties: osteoinduction, osteoconduction and osteogenesis. Disadvantage of autologous grafts is that additional surgical site is required, another potential location for postoperative pain and complications Additionally there are no immunogenic complications (Weingart, 2000).

Allogenic Bone Graft

Allogenic bone is non vital, osseous tissue harvested from one individual and transferred to another of the same species. The source is usually from a cadaver bone, which is subjected to a treatment sequence which renders its natural to immune reactions and help to avoid cross contamination of host diseases (Mellonig, 1981). The major drawback of this graft is that it exhibits a higher resorption rate and a large immunogenic response and less revascularization of the graft (Oklund, 1986 and Bohr, 1968). There are three types of bone allograft available: Fresh or fresh-frozen bone, FDBA and 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 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 (Urist, 2004).

Xenograft

It is the tissue removed from an animal donor and surgically transplanted to a human. A xenograft is most popularly known as bovine organic cancellous bone. It is mainly produced by subjecting bovine bone to a special purpose, which thereby removes its organic components and retains its organic structure. The product so formed contains biological apatite crystals (Kumar, 2016)¹. Long term studies have demonstrated that there is lack of osteogenic response when a xenograft is implanted into either hard or soft tissues (Heiple, 1967 and Lustmann, 1995). Xenografts have also a disadvantage of transmission of bovine or procure viruses or other infective agents.

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 (Kumar, 2016).

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 cellular activity. 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 (Engelke, 1997 and Hegedus, 1923).

Other growth factors apart from BMP include

- Platelet derived growth factor
- Transforming growth factor- β
- Insulin-like growth factor (I)
- Vascular endothelial growth factor
- Fibroblast growth factor

Graftless Approach: The introduction of CBCT 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 morbidities. Although patients may tend to prefer a minimally invasive approach, dentist should not disregard options that require bone grafting. In 'graftless' approach the treatment planning is done by avoiding the need for bone grafting. Reduced diameter or shorter implants maybe 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 (Bedrossian, 2006). As long as biomechanical support is not compromised, fewer implants may also be considered for a fixed prosthesis (4 to 6 versus 8 to 10) (Hyatt, 1957). The dentist may elect extraction of compromised teeth for full-arch implant placement instead of augmenting the atrophic maxillary or mandibular posterior ridges.

Tissue Engineering

Tissue engineering may be used to regenerate bone by combining cells from the body with growth factors and scaffold cells from the body with growth factors and scaffold biomaterials (Kraigler 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. Recombinant growth factors are genetically engineered versions produced in the laboratory that are identical in structure and action to the naturally occurring cytokines. 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 morphogenetic 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 intraosseous defects (Gallucci, 2016; Boyne et al., 2005 and Fiorellini, 2005). Infuse Bone Graft has FDA approval for the repair of extraction socket defects and sinus bone grafting. The use of these recombinant growth factors for ridge-augmentation procedures is considered an "off label" application. 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 and Faundez, 2016).

Maxillary Sinus Lift (Lateral Approach): One of the most challenging situations in implant dentistry is the deficiency of the bone in the posterior maxillary region. Resorption of alveolar process due to loss of posterior maxillary teeth causes expansion of sinus cavity into alveolar process. This in turn results in the lack of quantity and quality of bone for implant placement. In this technique bone augmentation is done following a sinus floor elevation with involves elevating the schneiderian membrane from the maxillary sinus floor. Maxillary sinus grafting may also be combined with nasal inlay grafting if the bone volume in the sub nasal area for placement of implants also needs to be increased.

Maxillary Sinus Elevation (Trans Alveolar Approach): Maxillary sinus elevation using trans alveolar approach can be recommended in sites with adequate alveolar crest width, initial height of 5mm and flat sinus floor anatomy. This method is considered to be less invasive which involves gentle fracturing by moving the sinus floor and usually performed with the help of osteomers.

Split-Ridge/ Ridge-Expansion Technique: Split ridge/ridge expansion technique refers to the creation of a linear groove in the middle of the ridge with rotary burs or a piezosurgery device and deepening this groove with an osteotome chisel. The lingual or palatal cortical bone is used as a guide and careful tapping with a mallet will advance the chisel into the cancellous part of the bone. It is indicated in utrophic edentulous ridge (Lustmann, 1995 and Engelke, 1997).

Vertical Distraction Osteogenesis: This technique is mainly used to increase the height of alveolar ridge. In this technique there is creation of new bone along with adjacent soft tissue after gradual and controlled displacement of a bone fragment obtained by surgical osteotomy.

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^[30]. Another promising technique for growth factor delivery is the application of gene therapy. 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^[30]. 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 (Dimitriou, 2011 and Yamada, 2014). Custom titanium meshes have been developed to protect and contain growth factor-enhanced grafts. At present, allogeneic and xenograft block bone grafts may be milled to custom fit an atrophic ridge (Casap, 2013 and Schlee, 2013). In the future, custom-made resorbable scaffolds will routinely be fabricated using 3-dimensional printers (Dimitriou, 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^[35]. 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 (Dimitriou, 2011). 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, 2011 and Bhumiratana, 2012). The use of biologic agents on dental implant surfaces may be another alternative for encouraging bone formation in deficient sites.

Conclusion

One of the major challenges in implant dentistry is the treatment of large bone defects or deficiencies. Although four categories of grafts are present, autografted is the only one considered to be of gold standard due to its osteoinductivity, osteoconductivity and osteogenicity. Traditional approaches are abandoned nowadays by the clinicians as new and less innovative procedures provide better results. Various bone regenerative materials in the form of gels, particle and scaffolds have also been designed with the help of nanotechnology and engineering and have opened up a new horizon for bone regeneration. The clinicians should however take into account 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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