

BONE GRAFTS AND BONE SUBSTITUTES

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Received: 02 Dec 2013 Revised and Accepted: 23 Dec 2013

ABSTRACT

Bone resorption is a natural phenomenon and can occur due to old age, loss of teeth, prolonged denture wear or as a result of systemic conditions. For the replacement of teeth by fabrication of prosthesis or the use of implants, a minimum amount of bone density is required. Bone grafting is a method by which bone-deficient areas are built up, with the use of different materials, such as autografts, allografts, alloplasts and xenografts. Over recent times, the use of frozen bone matrix formulations and synthetic ceramics has been used in greater frequency. This article discusses the use of human bone material (Allografts), synthetic materials (Alloplasts) and blood components as successful grafting materials. Their use has shown an effective amount of bone formation and proliferation in the defective sites and proves to be a beneficial choice in bringing back lost bone.

Keywords: Bone grafts, Bone substitutes, Allografts, Alloplasts.

INTRODUCTION

Defects in the alveolar ridge develop as a consequence of surgery, trauma, infection, or congenital malformations. The lack of intraosseous stimulation by periodontal ligament (PDL) fibers after tooth loss results in rapid resorption of alveolar bone as happens in pneumatization of maxillary sinus following tooth loss. [1] Nevertheless, due to increased frequency of localized or generalized bone defects of the alveolar ridge, as a result of atrophy, dental trauma, extractions or periodontal disease, reconstructive surgery is obligatory to regenerate such defects in order to have successful rehabilitation. [2] [3]

The goals of osseous replacement are maintenance of contour, elimination of dead space, and reduction of postoperative infection; thereby enhancing bone and soft tissue healing. Bone grafts are a therapeutic option to correct abnormal intermaxillary relations and to attain appropriate bone volume and morphology. [4] They are used as a scaffold to allow formation of bone and promote wound healing and act as a mineral reservoir which helps in new bone formation.

Bone grafting is a surgical procedure which entails replacement of missing bone with material from either patient's own body, an artificial or natural substitute. The rationale behind grafting is that bone grafting is possible because bone tissue has the ability to regenerate completely into the space which it has to develop. As natural bone grows, it generally replaces the graft material completely, resulting in a completely integrated region of new bone [1]. It is indicated in prosthodontic cases where requirement of minimal amount of bone is a prerequisite, such as implant placement and denture fabrication.

Classification of bone grafts

Several categories of bone graft and graft substitutes are available and include a variety of

materials, with different sources and origins. In spite of the availability of wide range of choices, autologous bone still remains the "gold standard" for stimulating bone repair and regeneration, but its availability may be limited and the procedure to harvest the material is associated with many complications. Bone-graft substitutes can either substitute autologous bone graft or expand an existing amount of autologous bone graft.

The Laurencin, Khan Y, El-Amin SF [5] classification of grafts and graft substitutes could be modified as follows: A. Harvested bone grafts and graft substitutes:

These include bone grafts, endogenous or exogenous, that are essential to provide support and enhance biologic repair of skeletal defects due to traumatic or non-traumatic origin. Additional surgery,

limited availability [2-4] and donor site morbidity often limit the use of endogenous bone substance, whereas allografts have been encountered with risk of disease transmission and immunogenicity. [6] Therefore, there is a growing need for synthesis of allograft bone substitutes.

B. Growth factor-based bone graft substitutes:

These are natural and recombinant growth factors used alone or in blend with other materials such as transforming growth factor-beta (TGF-beta), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and bone morphogenetic protein (BMP).

C. Cell-based bone graft substitutes:

These use cells to generate new tissue alone or are seeded onto a support matrix (e.g., mesenchymal stem cells).

D. Ceramic-based bone graft substitutes:

These include calcium phosphate, calcium sulfate, and bio glass used alone or in combination.

E. Polymer-based bone graft substitutes:

Degradable and nondegradable polymers are used alone or in combination with other materials (e.g., Cortoss [Orthovita, Inc, Malvern, Pa], open porosity polylactic acid polymer [OPLA], Immix [Osteobiologics, Inc, San Antonio, Tex]).

F. Miscellaneous:

Various unconventional marine biomaterials are also used as bone graft substitutes which include coral, chitosan, and sponge skeleton.

Allografts

These were developed as an alternative to autografts. Allografts are bone taken from one human for transplantation to another. These grafts, obtained from cadavers, are freeze-dried and treated for the prevention of disease transmission. They are available from commercial tissue banks. There are various types of allografts available, including freeze-dried bone allograft (FDBA) and demineralized freeze-dried bone allograft (DFDBA) [7]. FDBA, which is not demineralized, works primarily through osteoconduction, a process in which the graft by itself does not activate bone growth. It acts as a scaffold for the patient's own natural bone to grow onto and within the graft. Over time, the graft gets resorbed and replaced by bone. FDBA is still used today, but a large-scale research review showed that FDBA mixed with autogenous bone is more effective at increasing bone fill than FDBA alone [8].

DFDBA provides more bone fill than FDBA. The healing of DFDBA grafts is still a topic of study. Some authors contend that they heal by osteoinduction which is a process that involves pluripotential cells

from the surrounding bone over which the graft is placed. These cells are recruited, and further differentiated into bone-forming cells. Over time, the allograft is resorbed by the natural bone, and this whole regenerative process is thought to be induced by bone morphogenic protein (BMP) and other growth factors released from the allograft [9].

Fate of Graft

Reynolds and Bowers (1996) showed that this the only graft which, if more residual particles remain post grafting, results in significantly greater amounts of new attachment.

Antigenicity of FDDBA

Quattlebaum 1988 – concluded that the FDDBA has markedly reduced antigenicity stating that the freeze drying procedure may spatially distort the three dimensional presentation of the HLA antigens on FDDBA affecting immune recognition. [10]

Synthetic bone substitutes: [11]

As the name suggests these grafts have their origin from materials outside of the human body. The usage of these materials avoid the problems of finding suitable bone from within the body and the infective risks associated with the use of human cadaver materials or other animal tissue. Types of synthetic bone substitute available are:

- a) Hydroxyapatite
- b) Ceramics (other than hydroxyapatite)
 1. Tricalcium phosphate.
 2. Bioactive glasses.
 3. Calcium sulphate.
- c) Polymers
 1. Combinations of polyglycolic acid (PGA) and polylactic acid (PLA)
 2. HTR polymer (composite of polymethylmethacrylate and polyhydroxyethylmethacrylate)
 3. Bioresorbable fixation materials
- d) GIC derived bone substitutes.

Hydroxyapatite

Hydroxyapatite is an alloplastic material. A biocompatible ceramic produced through a high-temperature reaction and is highly crystalline form of calcium phosphate. Hence, its composition is similar to that of cortical bone [12]. The nominal composition of this mixture is $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ with a calcium-to-phosphate atomic ratio of 1:67. The most unique property of this material is its chemical similarity with the mineralized phase of bone. It is an osteoconductive material and shows high biocompatibility. [13] Hydroxyapatite has been established to be an excellent carrier of osteoinductive growth factors and osteogenic cell populations, which greatly add to their utility as bioactive delivery vehicles in the future [14] [15].

Ceramics

Ceramics are synthetic scaffolds which are made from minerals such as calcium phosphate. Tricalcium phosphate (TCP) has been used in dentistry for two decades as synthetic bone void fillers in orthopaedic and dental applications. It is bio absorbable and biocompatible. The chemical composition and crystallinity of the material are similar to those of the mineral phase of bone. The nominal composition of TCP is $\text{Ca}_3(\text{PO}_4)_2$. It exists in either α or β -crystalline forms [15] [16].

Tricalcium phosphate ceramic has a stoichiometry similar to amorphous bone precursors, whereas hydroxyapatite has a stoichiometry similar to bone mineral. Ceramics do not have any natural existence, but they are capable of inducing a biologic response similar to that of bone. Cutright et al found 95 per cent

absorption of tricalcium phosphate ceramic implants in rat tibias 48 days postoperatively with extensive bone growth and marrow reformation [17].

Bioactive glasses

Bioactive glasses are hard, (non-porous) materials consisting of, phosphorus, calcium, and

silicon-dioxide. By mixing different proportions of sodium oxide, calcium oxide, and silicon dioxide, all type of forms can be produced ranging from soluble to non-resorbable. They possess both osteointegrative and osteoconductive properties. A very strong bond between bioactive glass and bone eventually forms by means of hydroxyapatite crystals similar to that of bone and bonding occurs without an intervening fibrous connective tissue interface [18] [19]. When compared to calcium phosphate preparations, such as ceramic-HA they have greater mechanical strength. Bioactive glass blocks do not yield to drilling and shaping, and they may fracture in the process. As a consequence they are found to be difficult to fix to the skeleton. They are successfully used as a bone graft expander. This material has been extensively used for filling bone defects [20] alone and in combination with autogenous and allogenic cancellous bone graft [21]. The porosity in the material provides a scaffold on which newly-formed bone can be deposited by vascular in growth and osteoblast differentiation. The porosity of bio glass is also advantageous due to its ability for resorption and the bioactivity of the material [22]. The biocompatibility of the glass has been verified by the absence of any adverse cellular reactions [23].

Bioactive glasses have been clinically used for tympanoplastic reconstruction [24], as filling material in benign tumor surgery [25], for reconstruction of defects in facial bones [26], for treatment of periodontal bone defects [27], in obliteration of frontal sinuses [28] [29], in repairing orbital floor fractures [30], and for reconstruction of the iliac crest defect after bone graft harvesting [31].

“Bioactive-ceramics”, is a new variation, which has significantly better mechanical properties than bioactive glass. However, both are relatively brittle and prone to fracture with cyclic loading. Two methods have been engaged to improve the fracture toughness of bioactive glasses and bioactive ceramics i). Incorporation of stainless steel fibres into bio glass increases bending strength and ii). Incorporation of ceramic particles (zirconia) into apatite-wollastonite (A/W) glass ceramic, increases bending strength and toughness [32].

Polymers

These are large organic macromolecules composed of a regular pattern of many monomers. Cellulose, collagen, agarose, chitin or hyaluronan form the members of natural polymeric materials or so-called biological polymers. Natural polymers such as collagen have been used for bone tissue engineering purposes [33]. The most commonly used bioresorbable materials are polymers of monocarboxylic acid derivatives. Different types of natural and synthetic polymers, such as poly-lactic acid (PLA), poly-glycolic acid (PGA), polyurethane (PU), and polycaprolactone (PCL), are also used as tissue scaffolds [34].

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 completely heal itself without remaining foreign bodies. Recently these materials have been joined by polyhydroxykanoates (PHA) which are linear polyesters of microbiological origin.

Local tissue responses to polymers depend on the biocompatibility of the polymer and its degradative by-products [35]. At present, two polymers are commercially available as a bone substitution material, first a PLA granulate (TruGraft™, Osteobiologics, San Antonio, U.S.A.) and second NovoSorb™ (PolyNovo Biomaterials, Port Melbourne, Australia).

The poly (α -hydroxy acid) polymers such as PLA, polyglycolide (PLG) and their copolymers PLGA are the widely used as synthetic polymers to deliver BMPs [36].

In addition polymers which are used as BMP delivery systems include polyanhydrides, polypropylene fumarate, polyethylene glycol-PLA as well as polyphosphate.

Glass ionomers

"Glass ionomer cements" were first used in restorative dentistry. Ionomeric cement consists of calcium/aluminium/fluorosilicate glass powder mixed with polycarboxylic acid which results in a porous cement paste. The paste takes 5 minutes to harden after which it is insoluble in water. After 24 hours it has a compressive strength and modulus of elasticity which is comparable to that of cortical bone. It is biocompatible and osseointegrates in a similar ways as bioactive glasses. Its porous structure aids osteoconduction and further ingrowth of bone. They may be added along with antibiotics and high molecular weight proteins for slow release action [37].

Recent advances

Bone morphogenic protein (bmp)

BMP's are members of the family of transforming growth factors. 15 different bmp's have been identified all having different degrees of cellular activity, including cartilage or bone inducing properties. Two recombinant proteins are available at present- recombinant human bone morphogenic protein (rhBMP-2) and (rhBMP-7). Two rhBMP associated carrier systems have received approval from the US Food and Drug Administration.

1). Osteogenic protein-1 (OP-1) consists of rhBMP-7 and bovine collagen (Stryker Biotech Hopkinton, Massachusetts)

2).InFuse System (Medtronic Sofamor Danek Warsaw, Indiana) consists of rhBMP-2 on an absorbable bovine type I collagen sponge carrier.

BMP product is packaged as a lyophilized powder in a sterile vial which can be reconstituted with sterile water and applied to the carrier [38].

Platelet rich plasma (prp)

PRP is a source of platelet derived growth factor (PDGF) and transforming growth factor beta (TGF- β) that is obtained by sequestering and concentrating platelets by a process of gradient density centrifugation.

Platelet derived growth factor (PDGF)

PDGF, a glycoprotein has a molecular weight of approximately 30kd. It was first described in the alpha granules of platelets, but can also be synthesized and secreted by cells like macrophages and endothelium. There are approximately 0.06ng of PDGF per one million platelets, a fact that emphasizes this molecule's great potency [39]. Its mechanism is to activate cell membrane receptors on target cells, which results in the development of high-energy phosphate bonds on internal cytoplasmic signal proteins which then activate the signal proteins which initiate a specific activity within the target cell. The most specific activities of PDGF are mitogenesis, angiogenesis and macrophage activation.

TGF- β

The term transforming growth factor beta is applicable to the superfamily of growth and differentiating factors. Bone morphogenic protein (BMP) is a member of this family and contains at least 13 BMPs. TGF- β 1 and TGF- β 2 are proteins that have molecular weight of approximately 25kd. Like PDGF, they are synthesized and found in macrophages as well as in other cell types. When released by platelet degranulation or actively secreted by macrophages, they act as paracrine growth factors and affect cells such as fibroblasts, marrow stem cells and preosteoblasts. Each of these target cells has the ability to synthesize and secrete its own TGF- β proteins. TGF- β therefore represents a mechanism for sustaining a long term healing process and even develops into a bone remodeling factor. The most important functions are chemotaxis and mitogenesis of osteoblast precursors. They also have the ability to stimulate osteoblast deposition of the collagen matrix of wound healing and bone. In

addition TGF- β inhibits osteoclast formation thus favoring bone formation over resorption [40].

CONCLUSION

The extensive need for bone grafts has introduced a number of different possible materials that can be used. A large amount of research has been, and is continuously being done to provide a variety of options that substitute as grafts. With the successful use of Allografts and Alloplasts in recent years, it is only a matter of time before their limitations can be overcome. They have the potential of becoming the material of choice in cases of all bony deficiencies.

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