Osseous Grafting Part II: Xenografts and Alloplasts for Periodontal Regeneration - A Literature Review

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Abstract

Osseous grafting represents one mode of therapy to manage periodontal osseous defects. Materials for osseous grafting can be obtained from the same person (autografts), from a different person of the same species (allografts), from a different species (xenografts), or from synthetic materials (alloplasts). The two types of grafts most frequently used in periodontal therapy are autogenous grafts and allografts. Both types can be obtained either intraorally or extraorally. They may be cancellous bone, cortical bone, or combinations of these. There has been a recent increase in interest in using xenografts and alloplasts. Bone graft materials are generally evaluated based on their osteogenic, osteoinductive, or osteoconductive potential. Selection of graft material is based on operator preference, type and size of the defect, resorbability of graft material, cost and patient acceptance. In this review we discuss different types of xenografts and alloplasts, and the advantages and disadvantages of each type.

Key words: Osseous graft, periodontal regeneration, xenograft, alloplast.

Xenografts

A xenograft is tissue transferred between genetically dissimilar members of different species. It is osteoconductive, biocompatible and structurally similar to human bone. There are two sources of xenografts used for bone replacement in periodontics: bovine bone and natural coral (Aichelmann-Reidy and Yukna, 1998; Nasr *et al*., 1999).

Bovine-derived bone replacement graft

Commercially available bovine bone is processed to yield natural bone mineral minus the organic component. A purported advantage of this product as a bone substitute is that it is natural in that it can provide structural components similar to that of human bone, improving its osteoconductive capability compared to that of synthetically derived mineral (Aichelmann-Reidy and Yukna, 1998; Nasr *et al*., 1999). Inorganic bovine bone is a hydroxyapatite (HA) skeleton, which retains a highly porous structure similar to cancellous bone (Jarcho, 1981) after chemical or low heat extraction of the organic component. Historically, bovine xenografts have failed due to rejection (Melcher and Dent, 1962), probably because earlier materials used chemical detergent extraction that left residual protein and therefore produced adverse reactions and clinically unacceptable results (Emmings, 1974; Aichelmann-Reidy and Yukna, 1998; Nasr *et al*., 1999). Currently available bovine-derived hydroxyapatite is deproteinated but retains its natural microporous structure and supports cell-mediated resorption (Jarcho, 1981; Nasr *et al*., 1999), which becomes important if the product is to be replaced with new bone. Two products are currently available: Osteograf/N (CeraMed Dental, LLC, Lake-wood, CO) and Bio-Oss® (Oseohealth Co., Shirley, NY). Both have been reported to have good tissue acceptance with natural osteotrophic properties (Callan and Rohrer, 1993; Cohen *et al*., 1994). Histologically, no fibrous tissue or space between hydroxyapatite and newly formed bone was found (Callan and Rohrer, 1993).

Bovine-derived HA bone substitutes increase the available surface area that can act as an osteoconductive scaffold because of their porosity. This HA mineral content is comparable to that of bone, allowing it to become well vascularized and integrate with new host bone (Thaller *et al*., 1994; Chen *et al*., 1996). A statisti-

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cally significant gain of clinical attachment and reduction in probing depth has been demonstrated when bovine bone was compared to a non-graft control for the treatment of human vertical osseous defects. When compared to demineralized freeze-dried bone allograft (DFDBA), similar amounts of probing depth reduction, clinical attachment level gain, bone fill and defect resolution were obtained (Richardson *et al.*, 1999). Human histologic studies of bovine bone in infrabony defects demonstrated that substantial amounts of new bone, cementum and periodontal ligament could result (Camelo *et al.*, 1998; Mellonig, 2000).

PepGen P-15™ is bovine-derived hydroxyapatite that contains P-15, a synthetic short chain peptide of the 15 amino acid sequence of type I collagen that is uniquely involved in the binding of cells, particularly fibroblasts and osteoblasts. The combination of P-15 with bovine bone has been shown *in vitro* to enhance the attachment of cells (Seyedin, 1989; Bhatnagar *et al.*, 1997; Bhatnagar *et al.*, 1999) and to promote attachment of periodontal ligament fibroblasts to bovine bone (Bhatnagar *et al.*, 1999).

A multi-center re-entry clinical study in humans demonstrated that the use of the P-15 synthetic cell binding peptide combined with inorganic bovine-derived hydroxyapatite yields better clinical results than either DFDBA or open debridement in the treatment of human periodontal defects (Yukna *et al.*, 1998; Yukna *et al.*, 2000; Radhakrishnan and Anusuya, 2004; Vastardis *et al.*, 2005; Bhongade and Tiwari, 2007).

Coralline calcium carbonate

Bicoral (Inoteb, Saint Gonnery, France) is calcium carbonate obtained from natural coral and is composed primarily of aragonite (> 98% calcium carbonate). It is biocompatible and resorbable with a pore size of 100 to 200 μm, similar to the porosity of spongy bone (Guillemin *et al.*, 1987; Aichelmann-Reidy and Yukna, 1998; Nasr *et al.*, 1999). Its porosity provides a large surface area for resorption and replacement by bone (Yukna, 1994a). It does not require surface transformation into a carbonate phase, as do other bone substitutes, to initiate bone formation (Guillemin *et al.*, 1987); hence, it should more rapidly initiate bone formation (Aichelmann-Reidy and Yukna, 1998; Nasr *et al.*, 1999). It has a high osteoconductivity potential because no fibrous encapsulation has been reported. When compared to other bone substitutes, coralline calcium carbonate produces comparable results. Significant gain in clinical attachment level, reduction of probing depth, and defect fill have been reported (Mora and Ouhayoun, 1995; Kim *et al.*, 1996; Gao *et al.*, 1997).

Porous hydroxyapatite (Interpore 200, Irvine, CA) is obtained by the hydrothermal conversion of the calcium carbonate exoskeleton of natural coral into calcium phosphate hydroxyapatite. It has a pore size of 190 to 200 μm, which allows bone ingrowth (West and Brustein, 1985; Minegishi *et al.*, 1988) into the pores and within the lesion itself (Kenney *et al.*, 1986; Aichelmann-Reidy and Yukna, 1998; Nasr *et al.*, 1999). Clinical defect fill, probing depth reduction and attachment gain have been reported (Kenney *et al.*, 1985). Histologically, new attachment was not achieved in humans (Kenney *et al.*, 1986).

Alloplasts

Alloplasts are synthetic graft materials. A number of synthetic or inorganic graft materials are available for use in the treatment of intrabony lesions. Recent reviews (Yukna, 1993; Rosen *et al.*, 2000) of available histological evidence (Froum *et al.*, 1982; Sapkos, 1986; 1986; Carranza *et al.*, 1987; Stahl and Froum, 1987; Stahl *et al.*, 1990; Stahl and Froum, 1991) indicate that synthetic grafts act almost exclusively as biological fillers, with scant bone fill and very limited connective tissue regeneration.

Hydroxyapatite

Hydroxyapatite, $Ca_{10}(PO4)_6(OH)_2$, is the primary mineral component of bone. Synthetic hydroxyapatites have been marketed in a variety of forms, primarily as a porous non-resorbable form, a dense or solid non-resorbable form, and a porous, resorbable, non-ceramic form. Processing of the basic calcium phosphate mixture dictates which of the listed properties it will possess. Hydroxyapatite resorbability is determined by the temperature at which it is processed. Resorbability is desired if the graft is eventually to be replaced by the host bone (Aichelmann-Reidy and Yukna, 1998; Nasr *et al.*, 1999).

When prepared at high temperature (sintered), hydroxyapatite is non-resorbable, nonporous and dense, and has a larger crystal size (Klein *et al.*, 1983). Dense hydroxyapatite grafts are osteophilic and osteoconductive, and act primarily as inert biocompatible fillers. They have produced greater clinical defect fill than flap debridement alone in the treatment of intrabony defects (Rabalais *et al.*, 1981; Meffert *et al.*, 1985). Histologically, new attachment was not achieved (Froum *et al.*, 1982). They yield similar defect fill as other bone replacement grafts and the clinical improvement is more stable than with debridement alone (Yukna *et al.*, 1989; Aichelmann-Reidy and Yukna, 1998; Nasr *et al.*, 1999).

Porous hydroxyapatite (Interpore 200, Irvine, CA) is obtained by the hydrothermal conversion of the calcium carbonate exoskeleton of natural coral into calcium phosphate hydroxyapatite (see coralline calcium carbonate).

Another form of synthetic hydroxyapatite is a resorbable, particulate material processed at a low temperature (OsteoGen, Impladent, Holliswood, NY;

OsteoGraf LD, GeraMed Dental, LLC, Lakewood, CO). This resorbable form is a non-sintered precipitate with particles measuring 300 to 400 μm. Its reported advantage is the slow resorption rate, allowing it to act as a mineral reservoir as well as a scaffold for bone replacement (Wagner, 1989; Ricci *et al.*, 1992; Aichelmann-Reidy and Yukna, 1998; Nasr *et al.*, 1999).

Tricalcium phosphate

Tricalcium phosphate is a porous form of calcium phosphate: the most commonly used form is β-tricalcium phosphate. The beta refers to the particular orientation of the tricalcium phosphate crystal. β-tricalcium phosphate was one of the earliest calcium phosphate compounds to be applied as a bone graft substitute (Shima *et al.*, 1979). With this material, it is possible to induce osteoconduction of bone into the defect followed by the resorption of the β-tricalcium phosphate scaffold so that no biomaterial is permanently left within the reconstruction site. Unfortunately, the replacement of β-tricalcium phosphate by bone does not occur in a 1:1 ratio; that is, less bone volume is produced in comparison with the volume of tricalcium phosphate absorbed. This bone volume also varies according to the site of application and local conditions within the defect (Costantino and Friedman, 1994).

Tricalcium phosphate as a bone substitute has gained clinical acceptance, but the results are not always predictable. In a direct comparison with allograft, the allograft appears to outperform tricalcium phosphate (Strub *et al.*, 1979). The tricalcium phosphate particles generally become encapsulated by fibrous connective tissue and do not stimulate bone growth (Baldock *et al.*, 1985; Amler, 1987); however, some bone deposition has been reported with tricalcium phosphate graft (Strub *et al.*, 1979; Baldock *et al.*, 1985; Bowers *et al.*, 1986; Stahl and Froum, 1986; Amler, 1987).

The incorporation of platelet-derived growth factor-BB (PDGF-BB) with β-tricalcium phosphate was approved by the FDA in 2004. This combination proved to enhance the osteogenic properties of this alloplast both *in vitro* and *in vivo* (Bateman *et al.*, 2005).

GEM-21S™ is a completely synthetic grafting system for bone and periodontal regeneration launched in 2005. This system is composed of a purified platelet-derived growth factor-BB (PDGF-BB) and β-tricalcium phosphate matrix.

In one of the largest prospective, randomized, triple-blinded and controlled pivotal clinical trials reported to date aimed to evaluate the safety and effectiveness of purified recombinant human platelet-derived growth factor (rhPDGF-BB) mixed with a synthetic β-tricalcium phosphate (β-TCP) matrix for the treatment of advanced periodontal osseous defects at six months of healing. The study demonstrated that the use of rhPDGF-BB was safe and effective in the treatment of periodontal osseous defects. Treatment with rhPDGF-BB stimulated a significant increase in the rate of clinical attachment level gain, reduced gingival recession at three months post-surgery, and improved bone fill, as compared to a β-TCP bone substitute alone at six months (Nevins *et al.*, 2005). This combination seems to be promising; however, more studies are needed with longer periods of follow-up to evaluate the stability of the results.

Calcium sulfate (plaster of Paris)

Calcium sulfate has a 100-year history in orthopedic literature as a safe bone substitute. It resorbs within 33 days (Bell, 1964). This material had been used as a bioabsorbable barrier for guided tissue regeneration in periodontal defects. Controlled trials show similar clinical outcomes when this material used as a barrier compared with other barriers (Sottosanti, 1993a,b; Orsini *et al.*, 2001) In the last few years several authors reported cases of clinical attachment gain and bone fill in the treatment of periodontal and endodontic lesions with calcium sulfate alone or with other filling materials (Anson, 1996; Pecora *et al.*, 1997; Andreana, 1998; Kim *et al.*, 1998). More controlled trials are needed about the use of this material as a bone substitute for periodontal regeneration. Due to the quick resorption of this material, it is advisable to mix it with other types of bone graft when used to fill large defects.

Bioactive glass

Bioactive glass is a hard, solid, transparent material composed of sodium oxide, calcium oxide, phosphorus pentoxide, and silicon dioxide, with silicate as the primary component. The actual mechanism that allows bone to bond with bioactive glass is interesting and complex (Costantino and Friedman, 1994). The bone bonding depends on a reactive microenvironment that forms at the surface of bioactive glass implants after implantation. This microenvironment exists within a layer of silica-rich gel that forms on the material when bioactive glass is exposed to a physiologic aqueous solution. Within this gel layer, the calcium and phosphate composing the implant nucleate to form crystals of hydroxyapatite. The hydroxyapatite agglomerations provide a means of incorporating collagen, mucopolysaccharides, and glycoproteins within the surface-active layer attached to the implant. The resulting composite organic-inorganic interface is responsible for the mechanically and chemically strong bond between bioactive glass and bone. Bioactive glass is not replaced by bone, but a strong molecular bond does form between its surface and bone without an intervening layer of fibrous tissue. The use of silicate in bioactive glass results in an implant with significantly greater mechanical strength as compared with calcium phosphate preparations such

as ceramic hydroxyapatite (Costantino and Friedman, 1994). Treatment of intraosseous defects by means of bioactive glass resulted in an improvement of the bony lesion when compared to the open flap debridement (OFD) procedure. The mean difference in clinical attachment level gain between bioactive glass and OFD was 1.04 mm in one systematic review (Trombelli *et al.*, 2002; Trombelli, 2005), and 1.05 mm (SD 1.89) in the other (Reynolds *et al.*, 2003; Trombelli, 2005). Meta-analysis also showed that bioactive glass resulted in significantly greater probing depth reduction than the OFD procedure (Reynolds *et al.*, 2003).

There are two forms of bioactive glass currently available: PerioGlas® and Biogran™. PerioGlas® has a particle size ranging from 90 to 710 μm, which facilitates manageability and packing into osseous defects. In surgically created defects in nonhuman primates, 68% defect repair was achieved as new attachment (Fetner *et al.*, 1994). Fetner *et al.* (1994) showed that PerioGlas® produced significantly greater bone and cementum repair in animals compared to tricalcium phosphate, hydroxyapatite and unimplanted control. Observations of the material suggest good manageability, haemostatic properties, and the possibility that PerioGlas® is not only osteoconductive but may also act as a barrier retarding epithelial downgrowth (Aichelmann-Reidy and Yukna, 1998; Nasr *et al.*, 1999).

Biogran™ has a narrower range of particle sizes in the purportedly critical 300 to 355 μm size range. Schepers *et al.* (1991) have demonstrated that Biogran™ can be used successfully in the treatment of human oral osseous defects.

Hard tissue replacement

Hard tissue replacement (HTR) polymer is a porous biomaterial composed of polymethylmethacrylate (PMMA) coated with polyhydroxyethylmethacrylate (PHEMA) and calcium hydroxide. Even though it is primarily composed of carbon-based polymeric materials, its coating of calcium hydroxide enhances and promotes its bioactivity with bone (Amler and LeGeros, 1990). In contrast to the PMMA component of this implant, which is affected very little by the presence of water, the PHEMA coating absorbs some two-thirds of its weight in water, resulting in a gel. Coating the PMMA with PHEMA and calcium hydroxide results in a very hydrophilic material with calcium ions at its surface, which makes it bioactive with adjacent bone (Costantino and Friedman, 1994). Its hydrophilicity enhances clotting, and its negative particle surface charge allows adherence to bone. Favorable clinical results have been achieved with HTR in the treatment of intrabony and furcation defects (Yukna, 1990, 1994b). However, improved clinical results with this bone replacement graft have not always been achieved (Shahmiri *et al.*, 1992). Histologically, new bone growth has been found deposited on HTR particles, but no new attachment has been reported (Stahl *et al.*, 1990; Yukna and Greer, 1992; Froum, 1996).

Conclusion

This review indicates that reconstructive procedures using xenografts and alloplasts support comparable clinical outcomes to other bone grafting materials. It should be considered, however, that similar improvements in clinical parameters do not necessarily imply similar wound healing processes on a histological level. The effect of graft biomaterials on the formation of a new attachment apparatus, including bone, cementum and periodontal ligament, rather than periodontal repair, is still a matter of debate. The addition of autograft or growth factors to xenografts and alloplasts seems to enhance the regenerative potential of these materials. Due to limited information on long-term outcome, it is unclear whether stability of periodontal support and tooth survival are affected by application of grafting procedures.

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