Review Article

Essentials in Periodontal Regeneration

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Abstract:
Various materials and techniques have been used in the treatment of periodontal disease to achieve regeneration of lost periodontal tissues including cementum, periodontal ligament (PDL) and alveolar bone. The composition, regenerative potential, application and therapeutic characteristics of several regenerative materials have been evaluated in the present study.

Key Words: Regeneration; Bone; Graft; Biomaterials

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INTRODUCTION

Progressive periodontitis can lead to tooth loss through the destruction of its attachment apparatus. When continued function necessitates additional periodontal support, optimal treatment should include not only periodontal infection control but also regeneration of the lost periodontium. Despite conclusive evidence that some regeneration may occur following regenerative procedures [1-2], complete regeneration is an unrealistic goal. Osseous grafting and guided tissue regeneration (GTR) are considered as two of the most successful methods for reestablishment of periodontal tissues [2-5]. However, other treatment modalities have also shown promise in terms of improving clinical conditions and demonstrating significant bone fill.

Periodontal regeneration is defined as reestablishment of the lost supporting tissues including alveolar bone, cementum, and PDL.

New connective tissue attachment is described as formation of new cementum with inserting collagen fibers in association with a root surface that has been deprived of its PDL [6].

Bone fill is the clinical restoration of bone tissue in a previously treated periodontal defect.

Guided cell repopulation or guided tissue regeneration (GTR) are procedures designed to manipulate the cells that are involved in wound healing which finally lead to regeneration [6].

Regenerative Surgical Techniques (Flap Procedures)

Regenerative periodontics can be divided into two major categories: non-graft-associated new attachment and graft-associated new attachment. A number of techniques have combined both procedures. These methods can be performed with and without flaps, but in most cases exposure of the area is preferable [7].

In non-graft associated regenerative procedures, reconstruction of periodontal tissues without using grafts is possible only in meticulously treated three wall defects (intrabony defects) and in periodontal and endodontal abscesses [7].

Bone formation has been reported in angular defects treated by surgical access procedures. Remodeling of two and three wall angular bone defects following a modified Wildman flap requires careful curettage of the bone defect and proper root debridement [8-9].

"*Modified flap operation*" is basically an access flap for proper root debridement. Bone regeneration in intrabony defects is considered as one of the major advantages of this technique [10].

"Coronally positioned flaps" have been used in the treatment of mandibular class II furcation defects. In this technique the flap margin is positioned away from the furcation and remains in that location during the early stages of healing [11].

Previous studies have shown vertical and horizontal bone fill in class II mandibular furcation defects [11].

In Graft associated regenerative procedures, graft materials are used in conjunction with flap procedures to stimulate periodontal regeneration. These materials can be classified into four types: autogenous, allogenic, xenogenic and alloplastic [12].

Autogenous bone grafts, Extra oral

Autogenous iliac cancellous bone and marrow have been shown to possess a high degree of osteogenic potential. Numerous case reports have demonstrated successful bone fill after application of these materials in furcations, dehiscences, and intraosseous defects of various morphologies [13-15]. Iliac grafts can be used as either fresh or frozen. Root resorption has been reported as a complication of fresh grafting techniques [15-16], which has led to the limited use of these materials in clinical practice.

Autogenous bone grafts, intra oral

Intraoral cancellous bone and marrow grafts are usually obtained from the maxillary tuberosity or a healing extraction site and are used as cortical bone chips [12], osseous coagulum or bone blend type grafts [18]. Some authors have reported the presence of a long junctional epithelium between the regenerated alveolar bone and root surface [19,20]. Thus, the presence of clinical bone fill does not necessarily indicate periodontal regeneration.

Allogenic bone grafts

Several types of bone allografts exist such as iliac cancellous bone and marrow, freeze-dried bone allografts, and decalcified freeze-dried bone allografts. Frozen and radiation-sterilized iliac crest allografts have both been used in different studies. Freeze-drying has been shown to markedly reduce the antigenicity of allografts [21].

Intraosseous defects in juvenile periodontitis have been successfully treated with a combination of freeze-dried bone allografts and tetracycline [22,23]. According to Mellonig et al [24], bone demineralization in 0.6N HCl followed by freeze drying can significantly increase the osteogenic potential of allografts, assumably through bone morphogenic proteins (BMPs) [24,25].

A recent study has indicated that mineralized human cancellous allograft with or without collagen membrane, significantly improved bone fill in mandibular class II furcation defects [26].

Xenografts

Xenogenic materials have also been used for grafting around periodontal defects. These grafting materials are also referred to as anorganic bone, probably because all cells and proteinaceous material are removed during processing. Consequently an inert absorbable bone scaffold is left behind upon which revascularization, osteoblast migration, and woven bone formation can take place [27].

Human histologic studies have reported signs of periodontal regeneration in teeth treated with bovine-derived xenografts [28,29].

Xenografts have shown superior results when used in combination with guided bone regeneration (GBR) methods around implants and in sinus lift and ridge augmentation procedures [30-32].

A recent study found that porcine bone-derived biomaterials can be successfully used in humans for maxillary sinus augmentation prior to implant placement [33].

Alloplasts

Alloplasts are synthetic, inorganic, biocompatible bone substitutes which promote bone healing. There are presently six types of alloplasitc materials used in clinical practice which are as follows: nonporous hydroxyapatite (nonresorbable), porous hydroxyapatite or replamineform (nonresorbable), hydroxyapatite cement, beta tricalcium phosphate (resorbable), HTR (a calcium layered polymer of polymethylmethacrylate and hydroxyethylmethacrylate, nonresobable) and bioactive glass.

Several studies have demonstrated superior results in defects grafted with nonporous [34] and porous hydroxyapatitie [35], HTR [36] and beta tricalcium phosphate [37] as compared to those treated without the use of grafts. While clinical findings appear promising, histologically the grafts tend to be encapsulated by connective tissue with minimal or no bone formation [32-38]. Microscopic studies have found limited new bone in proximity to the implanted materials [39].

There is histologic evidence suggesting that a limited amount of regeneration may occur following HTR grafts [40].

Poehling et al [41], indicated that MD05, consisting of β-TCP coated with recombinant human growth/differentiation factor-5 (rh GDF-5), achieved superior bone regeneration compared to conventional materials. It was concluded that MD05 may be a suitable new bone substitute for application in dental and maxillofacial surgeries.

Bioactive glass (BG) is made from calcium salts, phosphate, sodium salts, and silicon glass particles. This silicon layer stimulates the formation of a hydroxycarbonate-apatite layer onto which osteoblasts can proliferate and produce bone [42].

A recent animal study investigated the effects of bioactive glass within a titanium cap. New bone was found to be generated at an early stage following utilization of BG for bone augmentation [43].

Mengel et al [44] studied the long term effectiveness of a bioabsorbable membrane and a bioactive glass in the treatment of intrabony defects in patients with generalized aggressive periodontitis. The results indicated significant improvements in probing depth (PD) and clinical attachment level (CAL) after 5 years with both regenerative materials. Radiographically, the bioactive glass group revealed superior bone fill.

Guided Tissue Regeneration (GTR)

According to the 1996 World Workshop in Periodontics, "GTR techniques attempt to regenerate lost periodontal structures through differential tissue responses. Barriers are employed in the hope of excluding epithelium and gingival corium from the root surface in the belief that they interfere with regeneration". Cells that repopulate the root surface after periodontal surgery will determine the type of attachment that forms on the root surface during healing [45,46].

Barriers have the advantage of maintaining space between the defect and the epithelium and gingival connective tissue cells. This allows the regenerative cells to enter from the periodontal ligament and alveolar bone. Barriers can also help to stabilize the clot, leading to enhanced regeneration [46].

A recent study evaluated the stability of horizontal clinical attachment gain in class II furcations and showed it to be equal between non-resorbable (ePTFE) and resorbable (polyglactin 910) barriers after GTR therapy [47].

GTR techniques have recently been employed for the treatment of marginal tissue recession defects with promising clinical and histological results [48].

A clinical study also compared subepithelial connective tissur grafts (SCTG) and GTR using bioabsorbable membranes together with bone derived xenografts and failed to show a significant difference between the two methods [49].

Several factors should be considered in the development and selection of membrane materials such as, biocompatibility, patient handling, tissue integration, space production and the cell's capability to cause occlusion [50].

Membrane barrier materials could be categorized as nonresorbable membranes and resorbable materials and devices.

Nonresorbable Membranes: Early investigators used nonresorbable materials, like cellulose filters (Millipore filter) and expanded polytetrafluoroethylene (ePTFE, Gore-Tex Regenerative Material). These materials were selected because they allowed the passage of liquid and nutritional products through the barrier. However the small dimensions of the pores prevented cell passage [51].

Cellulose filters: Nyman et al [52], applied cellulose filters in animals to prevent the gingival epithelium and connective tissue from contacting the curetted root surface. Histologic examination revealed regeneration of the alveolar bone and inserting periodontal ligament fibers between the new cementum and bone [52]. Several disadvantages have also been reported following the use of cellulose fibers, including exfoliation, premature removal, and the need for a second surgical procedure for their removal [46].

Expanded polytetrafluoroethylene membranes: The permeable structure of this membrane allows the ingrowth and attachment of the connective tissue leading to stabilization of the healing wound and inhibition of epithelial migration [53].

Considering the increased tent-like effect of titanium-reinforced ePTFE membranes, their application is especially suggested in space-deficient defects. The success rate of furcation defects treated with a combination of barriers and bone replacement grafts is superior to those treated with GTR alone [54].

It has been shown that the amount of bone regeneration is significantly greater following application of ePTFE membranes compared to resorbable membranes [55].

The main disadvantage of ePTFE membranes is that they require a second surgery for their removal. The main advantage is the retention of its functional characteristics throughout the healing process [56].

Resorbable Materials and Devices: Avoiding a second surgery is the main advantage of resorbable membranes. However, exposure of these materials or flap dehiscence leading to postoperative tissue management problems is considered as disadvantages of bioresorbable membranes [57].

Collagen membranes: Collagens are a group of extracellular matrix proteins with different characteristics and functions. They are natural components of the periodontal connective tissues with weak immunogenicity and possess hemostatic properties facilitating early wound stabilization and maturation. In addition collagens are adaptable and semipermeable and are absorbed naturally. They also act as chemoattractants for fibroblasts, and support cell proliferation and migration [58].

Polylactic acid: Polylactic acid membranes promote the formation of new attachment and bone in the treatment of intrabony- and class II furaction defects, gingival recessions and interproximal defects in humans [59].

Polyglycolic acid and polylacitc acid: Barriers made of polyglycolic acid and polylactic acid (Resolut, Gore Co., USA) consist of an occlusive film with a bonded, randomly oriented fiber matrix located on each surface. The film bonds the fibers and separates the soft tissue from the defect. Connective tissue can grow inward through the porous fiber matrix. The arrangement of the fibers also inhibits apical migration of the epithelium.

The fiber matrix is considered as the primary component which provides adequate strength for space-making during the initial phases of healing (2 to 4 weeks) [60].

Synthetic liquid polymer: The rigidity of these materials is adequate for handling and placement, yet their flexibility is enough to allow proper adaptation to the defect and therefore avoid suturing [61].

Polyglactin: Polyglactin membrane barriers are made of Vicryl (polyglactin 910) and demonstrate a resorption rate of 30 to 90 days.

Various studies have reported the mesh to provide an insufficient barrier due to the fragmentation of the material used in its construction [62].

Root Surface Biomodification

Demineralization of the root surface is often used in regenerative procedures. This technique has the ability to modify the root surface by "detoxifying the surface" [63] and exposing collagen fibrils in the cementum or dentin matrix [64]. Histologic evidence supports the fact that root surface demineralization can cause new connective tissue attachment and limited regeneration. However, significant clinical improvements have not been reported in this healing pattern [65].

Enamel Matrix Derivative (EMD)

EMDs are a group of enamel matrix proteins isolated from developing porcine teeth. Emdogain, a commercial enamel matrix derivative, is a purified acidic extract of developing embryonal enamel obtained from six-month-old piglets [66,67]. According to Venezia et al [68], propylene glycol alginate (PGA) was the most effective vehicle regarding precipitation of EMD on treated root surfaces. EMD has been shown to increase proliferation rate, metabolism and protein synthesis, cellular attachment rate, and mineral nodule formation of PDL cells. It also similarly influences cementoblasts and mature osteoblasts. In addition, EMD enhances PDL cell attachment [68]. EMD is considered as a safe product in the treatment of periodontal defects [68].

Heijl [70] demonstrated enhanced regeneration when EMD was used in conjunction with periodontal surgery. Recent studies suggest that root conditioning with EDTA gel does not affect the clinical or radiographic outcomes of intrabony defects treated with EMD [71]. Sculean et al [72] treated intrabony defects with open flap debridement (OFD) followed by root surface conditioning with EDTA and application of EMD (OFD+EDTA+EMD) in one group and OFD and application of EMD in the other group (OFD+EMD). Pocket depth reduction and CAL gain of the defects did not reveal a significant difference between the OFD+EDTA+EMD and OFD+EMD procedures [72].

Haghighati et al [73] compared the clinical efficacy of SCTGs and coronally advanced flaps (CAFs) along with EMD application in the treatment of gingival recession. Both procedures demonstrated improvement in the studied clinical parameters, however a significant difference was not observed between the two groups. Therefore CAF+EMD may also be successfully used in the treatment of gingival recession.

Recent studies have indicated that topical application of EMD can be beneficial in increasing the effects of CAF in terms of root coverage; gain in clinical attachment and also in increasing the apico-coronal dimension of the keratinized tissue [74]. Hence, EMD may be considered as a valuable, long-term effecttive treatment alternative to achieve root coverage [75].

In the treatment of intrabony periodontal defects, the use of bovine porous bone mineral (BPBM) has been suggested to augment the effect of EMD when compared with application of only EMD or OFD [76]. Moreover, addition of a membrane to EMD+BPBM may enhance these results [77].

EMD and platelet derived growth factor-BB (PDGF-BB) have both been applied alone and in combination for the treatment of periodontal defects. Their combination has been shown to produce greater proliferative and wound-healing effects on PDL cells than when each of them are used individually [78].

Demineralized freeze-dried bone allograft (DFDBA) together with EMD was found to demonstrate osteoinductive activity [79]. The combination of EMD with natural bone mineral and with β-TCP resulted in significant PD reduction and CAL gain, 1 year after surgery in both combinations; but a significant difference was not observed between the two groups [80].

A recent study evaluated the effect of Autogenous Cortical Bone Particulate (ACBP) in conjunction with EMD in the treatment of periodontal intraosseous defects. The results indicated that both EMD and EMD+ACBP treatments significantly improved the clinical and radiographic parameters [81].

Acellular Dermal Matrix Allograft (ADMA)

Acellular human cadaver skin is a relatively new type of bioresorbable grafting material that has been obtained from tissue inks (Alloderm). One of the major advantages of ADMA is that it's basically an immunologically inert avascular connective tissue. This is due to the fact that most of the targets of rejection response have been eliminated during the initial deepithelialization and decellularization processes [46].

In periodontal surgery, the use of ADMA has been recommended in the management of ridge deformities [82] and also in increasing keratinized tissue around teeth and dental implants [83].

A recent study compared the clinical efficacy of ADMA and SCTG in the treatment of recession defects. Based on this investigation the mean changes of all clinical parameters were not significantly different between the two study groups. Accordingly, ADMA may also be utilized in the treatment of shallow to moderate gingival recessions depending on the patients' ability to afford this procedure [84].

Shin et al [85] compared root coverage using ADMA with and without EMD in the treatment of localized recessions. Based on their findings the use of EMD in conjunction with ADM significantly affected the increase of keratinized tissue, but not the probing attachment level or percentage of surface coverage [85].

CONCLUSION

A variety of materials and techniques are used for periodontal regeneration. Autogenous and allogenic bone grafts have resulted in substantial bone fill. There is sufficient clinical and histologic evidence of bone fill and periodontal regeneration to recommend their application in daily practice. Guided tissue regeneration can be advantageous as a regenerative procedure particularly in gingival recessions, 3-wall intrabony and class II mandibular furcation defects. Regenerative wound healing is regarded as an ideal outcome in treatment of periodontal defects. Therefore a considerable number of products have been developed for GTR and new materials are being manufactured by investigators throughout the world.

Flap management techniques have enhanced wound stability during early healing and have produced substantial bone fill in mandibular class II furcations. However they were less effective in the treatment of mandibular class III furcation defects.

Alloplastic materials function primarily as biocompatible space fillers and can be used for regenerative therapy similar to osseous grafts and GTR procedures.

Root surface biomodification to promote new attachment has shown favorable results that are not reliably reproducible in humans. Hence the value of this procedure in clinical practice remains limited.

Emdogain seems to be a safe and promising product for the treatment of intrabony periodontal defects. The use of EMD in periodontal regenerative treatment has been evaluated in several clinical trials revealing an advantage to the use of this material in the treatment of periodontal intrabony defects.

Several factors can determine the outcome of periodontal treatment; these include the anatomic and biological characteristics of the defect, the clinician's experience and surgical skills, environmental factors such as smoking, and the patient's behavior like complying with postoperative instructions for oral hygiene.

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