

Chapter 11

Contemporary Clinical Directions in Regenerative Periodontics

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Introduction

Regeneration has been the focus of periodontal treatment over the past decade. Regeneration has been defined as the reproduction or reconstitution of a lost or injured part (Glossary of terms, AAP, 2003). Periodontal regeneration is the regeneration of the tooth's supporting structures including alveolar bone, periodontal ligament and cementum. (Glossary of terms, AAP, 2003) Researchers have been focusing on different ways to accomplish this using the following agents and procedures:

- 1 Growth and amelogenin-like factors.
- 2 Biomodification of root surfaces.
- 3 Bone substitutes from varying sources, autogenous, demineralized freeze dried bone allograft, freeze dried bone allograft, bovine-derived xenografts, alloplasts, etc.
- 4 Guided tissue regeneration for intrabony and furcation defects.
- 5 Guided tissue regeneration for root coverage.

Growth and amelogenin-like factors

A great deal of attention has been given to growth and amelogenin-like factors for periodontal regeneration. Growth factors are

natural biological mediators which have the ability to control vital events such as DNA synthesis, chemotaxis, cell differentiation and matrix synthesis, which are all involved in tissue repair (Anusaksathien *et al* 2002). The 2003 World Workshop lists the following as examples of growth factors used experimentally to treat periodontal disease:

- Platelet-derived growth factor (PDGF)
- Transforming growth factor- β (TGF- β)
- Basic fibroblast growth factor (FGF-2)
- Insulin-like growth factor (IGF-1)
- Bone morphogenic proteins (BMPs)
- Vascular endothelial growth factor (VEGF)
- Parathyroid hormone (PTH)

It is important to note that these growth factors are still under study and various stages of development and are not approved for human use at this time.

Enamel matrix derivative

Enamel matrix derivative (EMD) is derived from a developing porcine tooth germ. EMD is made up of 90% amelogenins, with the remaining 10% primarily proline-rich non-amelogenins, tuftelin, tuft protein, serum, ameloblastin, amelin, and salivary proteins (Brookes *et al* 1995). Current studies reveal that these proteins have been extraordinarily

well-conserved throughout evolution (Hammarstrom 1997) and maintain high homogeneity with human enamel proteins (Gestrelus *et al* 1997). Numerous clinical studies have reported improvement of periodontal parameters with the application of EMD to root surfaces in intrabony defects (Froum *et al* 2001, Heijl *et al* 1997, Zetterstrom *et al* 1997). In comparison with GTR and EMD, clinical trials have found comparable results with the use in intrabony defects (Pontoriero *et al* 1999, Sculean *et al* 1999) without one being superior to the other. EMD has also been found to be safe and has not shown any antibody response or other local or inflammatory occurrences (Zetterstrom *et al* 1997). Histologically, EMD has proven to show true periodontal regeneration consisting of cementum, periodontal ligament and alveolar bone aside from remarkably improving soft tissue measurements (Heiji 1997, Mellonig 1999, Yukna and Mellonig 2000). Current evidence supports the use of EMD in periodontal osseous defects to increase clinical attachment level and reduce probing depth, although long term benefits have yet to be established with further long term clinical trials (Giannobile and Somerman 2003)

Biomodification of root surfaces

Root surfaces act as a wound surface where periodontal regeneration can take place, thus it should provide an area suitable for cell attachment and fiber growth if regeneration is to be achieved. Many studies in the periodontal literature target citric acid, EDTA and tetracycline HCl as the media by which this is attained. Periodontal disease causes changes on the root surfaces of teeth, namely, collagen fiber loss (Selvig 1969), root surface contamination by bacteria and endotoxin (Adriens *et al* 1988, Aleo *et al* 1974), changes in the mineral density and composition of the

surface (Selvig *et al* 1977, Selvig *et al* 1962). Therefore, researchers seek to alter these changes caused by the disease on the root surface that can encourage regeneration. The mechanism by which these chemicals operate on the root surfaces is not well understood, but it has been hypothesized “that demineralizing agents act by exposing collagen fibers within the root matrix thereby facilitating attachment by other fibers in the periodontium and/or by decontaminating the root surface via elimination of endotoxin and bacteria, and/or by removal of the root debris allowing for the unobstructed attachment of regenerative cells to the root surface” (Mariotti 2003).

Although many studies have shown some connective tissue attachment to cementum after application of these demineralizing agents (Cole *et al* 1980) the results are not universal (Stahl *et al* 1983). No clinical significance with its utilization has been shown to prove its claim. Further clinical studies have been suggested to fully establish its supposed objective (Mariotti 2003).

Bone replacement grafts

Bone replacement grafts (BRG) have been used as a therapeutic measure to treat periodontal osseous defects. A wide variety of BRGs are available and have been categorized into 4 main types:

- 1 Autogenous.
- 2 Allografts.
- 3 Hetero-Xenografts.
- 4 Alloplastic materials.

Autogenous grafts

Autogenous grafts are usually obtained from the maxillary tuberosity, healing extraction sites, edentulous spaces of the jaw, mandibular retromolar area or osseous coagulum from bone while osteoplasty or osseous resection are being

performed at surgical sites (Mann 1964, Ellegard *et al* 1971, Hiatt 1973). Studies have shown 1.2 mm probing bone gain in areas grafted with intraoral autogenous bone compared to 0.8 mm in non grafted controls (Renvert *et al* 1985). Superior fill compared to open flap debridement has been successfully shown with use of bone blend or osseous coagulum (Froum *et al* 1975). Autogenous grafts have been the material of choice provided it is available and patients are informed of the advantages and disadvantages.

Allografts

The most extensively studied allograft is demineralized freeze dried bone allograft (DFDBA). Results from animal studies have indicated that demineralization of a cortical bone allograft improves its osteogenic potential by exposing bone inductive proteins referred to as bone morphogenic proteins (BMP) which induces host cells to differentiate into osteoblasts (Urist *et al* 1970, Harakas 1984, Mellonig *et al* 1981). A controlled study has shown a mean bone fill of 2.6 mm (65% bone defect fill) in grafted sites treated with DFDBA versus 1.3 mm (30% bone defect fill) in non grafted sites (Mellonig 1984). Histologically, when DFBA is placed into intrabony defects a new attachment apparatus forms, including new bone, cementum, and periodontal ligament while open flap debridement has shown only periodontal repair characterized by formation of a long junctional epithelium (Bowers *et al* 1989, Bowers *et al* 1991).

Freeze dried bone allograft (FDBA) has been studied less but also has shown some possible clinical efficacy in osseous defects (Barnett *et al* 1989, Mellonig 1991). More controlled studies of the clinical benefits are needed to show its efficacy in achieving good consistent results. Attention has been given to this graft for the potential to act as a scaffold-

base carrier for biologically active molecules because of its clinical characteristic as a good space maintainer (Rosen *et al* 2002). In fact DFDBA and FDBA have been used as a carrier for biologically active molecules and further studies are recommended to determine its potential as scaffold-based carriers for growth and amelogenin like factors (Reynolds *et al* 2003).

Xenografts

The most common xenograft is a natural bone mineral of bovine origin. This is a highly purified osteoconductive mineral structure that is made from natural bone in a multistage purification process under strict safety standards. Bovine porous bone mineral closely mimics human cancellous bone as compared to other allografts or synthetic hydroxyapatite materials when assessing parameters such as inner surface area, porosity, crystalline size and calcium-to-phosphorous ratio (Valdre *et al* 1995). A few studies have documented the ability of this xenograft to enhance bone formation in situations such as those around implants (Berglundh 1997), critical sized osseous defects (Schmitt *et al* 1997) and sinus elevations (Valentini *et al* 1997). Although there are some histologic studies demonstrating new attachment formation after its use (Camelo *et al* 1998, Camelo *et al* 2001), further investigation should be done to investigate the predictability of their outcome. Randomized clinical trials that confer clinical outcome data and uncontrolled human histologic studies are still to be performed in order to verify its ability to produce true periodontal regeneration (Reynolds *et al* 2003). Furthermore, limited but well-substantiated evidence also shows that xenogenic bone mineral matrix and bovine collagen/mineralized bovine bone matrix exhibits the ability to produce regeneration in intrabony defects (Camelo *et al* 1998, Nevins

et al 2003). New studies have shown that bovine bone in combination with EMD has promising results, however the predictability of such outcome still needs to be investigated (Zuchelli 2003).

Alloplasts

Alloplasts are various inorganic synthetic graft materials. Two groups of alloplasts are available (Garrett 1996):

- 1 Absorbable: Plaster of paris, calcium carbonate, absorbable ceramics such as tricalcium phosphate and absorbable hydroxyapatite.
- 2 Non-absorbable: Dense hydroxyapatite, bioglass, calcium coated polymer consisting of polymethacrylate and hydroxyethylmethacrylate.

Reviews of these materials have generally shown that their use leads to considerable improvements in probing depth and clinical attachment levels, increase in bone level, reduce crestal bone as compared to open flap debridement procedures in intrabony defects (Reynolds *et al* 2003). Histologically they act almost exclusively as biologic fillers inducing little bone fill and very limited, if any, periodontal regeneration (Yukna 1993, Yukna 1994.) The Glossary of Terms by the American Academy of Periodontology (2001) defines bone fill as the “clinical restoration of bone tissue in a treated periodontal defect”. This term does not address the presence or absence of periodontal regeneration or new connective tissue attachment. Thus evidence shows that alloplastic grafts produce periodontal repair rather than regeneration (Reynolds *et al* 2003).

Guided tissue regeneration for intrabony and furcation defects

For many years GTR has been shown to regenerate periodontal tissues lost as a result of periodontal disease. The procedure allows

progenitor cells residing in the periodontal ligament to form a new connective tissue attachment. When other cell populations are blocked from the healing area, then the cells in the periodontal ligament (PDL) can repopulate the root surface and thereby produce regeneration of cementum, PDL and bone. A landmark study (Gottlow *et al* 1984) strongly suggested that when the epithelial and gingival connective tissue cells are excluded from the healing area with the use of a physical barrier membrane, the periodontal ligament cells are allowed to repopulate the previously diseased root surface and thus produce regeneration.

Since its discovery, many physical barriers (absorbable and non-resorbable) have been used in different configurations to fit the periodontal defects in need of regeneration. The most common non resorbable membrane is from GORE-TEX and made of expanded polytetrafluorethylene (e-PTFE) designed for periodontal regeneration. Because this type of membrane does not resorb, even after healing, it requires a second procedure to remove it. Thus, researchers have developed resorbable membranes in order to eliminate the need for second stage surgery. The most common of these bioresorbable membranes are polylactic acid, polyglycolic acid and collagen membranes. Similar satisfactory results can be expected with bioabsorbable materials as with non-bioabsorbable materials (Hugoson *et al* 1995, Cortellini *et al* 1996).

Based on the systemic review in 2003 by Murphy and Gunsolley, the following conclusions regarding GTR can be made:

- 1 GTR procedures demonstrated a greater gain in clinical attachment level (CAL) and reduced probing depths as compared to open flap debridement when used for intrabony defects. Barrier types (resorbable versus non-resorbable membrane types) did not differ significantly when meta analyses among the studies were carried out.

- 2 GTR procedures demonstrated gains in vertical probing attachment level (VPAL) and horizontal probing attachment level (HOPA) with reductions in vertical probing depth as compared to open flap debridement when used for furcation defects. Barrier types seemed to affect the heterogeneity of the data as VPAL was only enhanced with the use of e-PTFE and polymeric barriers.
- 3 For furcation defects, there seems to be better regenerative outcome when augmentation material was used with barrier membranes than without. For intrabony defects, however, there was no advantage in the use of augmentation materials with barrier membranes.
- 4 Recession of the gingival margin increased when physical barriers were used in intrabony defects. Whether it was a resorbable or a non resorbable membrane that was used in intrabony defects, no difference between the two were noticed when compared.
- 5 In furcation defects, the use of coronally positioned flaps in an effort to fully cover the barrier membranes was associated with better clinical outcomes.
- 6 In the treatment of intrabony defects, intensive post operative care can lead to shallower probing depths.

Guided tissue regeneration for root coverage procedures

Indications for root coverage procedures are for esthetics, hypersensitivity, prevention of further recession defects and correction of anatomic deficiencies that may affect tissue health such as frenum pull. In the past, different procedures to perform root coverage involved autogenous soft tissue grafting and/or repositioning of flaps to cover denuded root surfaces and gain attached gingiva. Recently,

allogenic tissue grafts have been introduced in order to eliminate the use of the palate as a second surgical site. Moreover, GTR procedures with barrier membranes and GTR procedures using EMD have been introduced to cover recession defects.

When comparing connective tissue (CT) grafts with GTR or allogenic grafts, studies have shown that CT grafts provided a greater gain in root coverage than the GTR procedures (Jepsen *et al* 1998, Zuchelli *et al* 1998). For gains in width of keratinized tissue, studies have shown that CT grafts had greater gain in keratinized tissue than the GTR or allogenic graft procedures (Novaes *et al* 2001, Wang *et al* 2001, Aichelmann-Reidy *et al* 2001, Borghetti *et al* 1999). Therefore, it has been shown through meta analysis from the systemic review (Oates *et al* 2003) that autogenous connective tissue grafts offer significantly more advantages than GTR with bioabsorbable barriers in terms of root coverage and width of keratinized tissue. Moreover, with use of allogenic dermal tissue grafts, limited studies support their advantages over CT grafts. A more recent study reported on short term and long term comparison of root coverage with an acellular dermal matrix and a subepithelial connective tissue graft. Long term results (four years) showed that subepithelial grafts remained more stable with time than those treated with acellular dermal matrix. There were also smaller probing depth reductions and less increase in keratinized tissue with the acellular dermal matrix than the subepithelial connective tissue graft (Harris 2004).

Future investigations

Future investigations are still needed to investigate the long term stability of the different ways to regenerate lost periodontium due to periodontal disease. It is of major interest for all clinicians to have predictable and successful results each time a technique is

performed. It is therefore imperative for future investigations to give specific indications as far as choice of material for a particular defect, location of defect in combination with patient factors (oral hygiene habits, smoking, susceptibility, etc.) are concerned so that clinicians have a better guide to the ultimate goal of regeneration.

References

- Adriens PA, Edwards CA, DeBoever JA, Loesche WJ. Ultrastructural observations of bacterial invasion of cementum and radicular dentin of periodontally diseased human teeth. *J Periodontol* 1988;59:493-503.
- Aichelmann-Reidy ME, Yukna RA, Evans GH, Nasr HF, Mayer ET. Clinical evaluation of acellular allograft dermis for the treatment of human gingival recession. *J Periodontol* 2001;72:998-1005.
- Aleo JJ, DeRenzis FA, Farber PA, Varboncoeur AP. The presence and biological activity of cementum-bound endotoxin. *J Periodontol* 1974;45:672-675.
- American Academy of Periodontology. Glossary of periodontal terms, 4th ed. Chicago: The American Academy of Periodontology, 2001. pp4.
- American Academy of Periodontology. Periodontal regeneration (Position paper). Chicago: The American Academy of Periodontology, 1993.
- Anusaksathien O, Giannobile WV. Growth factor delivery to re-engineer periodontal tissues. *Current Pharm Biotech* 2002;3:129-139.
- Barnett JD, Mellonig JT, Gray JL, Towle JH. Comparison of freeze dried bone allograft and porous hydroxylapatite in human periodontal defects. *J Periodontol* 1989;60:231-237
- Berglundh T, Lindhe J. Healing around implants placed in bone defects treated with Bio-Oss. *Clin Oral Impl Res* 1997;8:117-124.
- Borghetti A, Glise JM, Monnet-Corti V, Dejou J. Comparative clinical study of a bioabsorbable membrane and connective tissue graft in the treatment of human gingival recession defects. *J Periodontol* 1999;70:123-130.
- Bowers GM, Chadroff B, Carnevale R, Mellonig J, Corio R, Emerson J, Stevens M, Romberg E. Histologic evaluation of new attachment apparatus formation in humans. Part I. *J Periodontol* 1989;60:664-674.
- Bowers GM, Chadroff B, Carnevale R, Mellonig J, Corio R, Emerson J, Stevens M, Romberg E. Histologic evaluation of new attachment apparatus formation in humans. Part III. *J Periodontol* 1989;60:683-693.
- Bowers G, Felton F, Middleton C, Glynn D, Sharp S, Mellonig J, Corio R, Emerson J, Park S, Suzuki J, et al. Histologic comparison of regeneration in human intrabony defects when osteogenin is combined with demineralized freeze-dried bone allograft and with purified bovine collagen. *J Periodontol* 1991;62:690-702.
- Brookes SJ, Robinson C, Kirkham J, Bonass WA. Biochemistry and molecular biology of amelogenin proteins of developing dental enamel. *Arch Oral Biol* 1995;40:1-14.
- Camelo M, Nevins ML, Schenk RK, Simion M, Rasperini G, Lynch SE, Nevins M. Clinical, radiographic and histologic evaluation of human periodontal defects treated with bio-oss and Bio-Guide. *Int J Periodont Rest Dent* 1998;18:321-331
- Camelo M, Nevins ML, Lynch SE, Schenk RK, Simion M, Nevins M. Periodontal regeneration with an autogenous bone-Bio-Oss composite graft and a Bio-Guide membrane. *Int J Periodont Rest Dent* 2001;21:109-119
- Cole RT, Crigger M, Bogle G, Egelberg J, Selvig KA. Connective tissue regeneration to periodontally diseased teeth. A histological study. *J Periodont Res* 1980;15:1-9.
- Cortellini P, Pini Prato G, Tonetti M. Periodontal regeneration of human intrabony defects with bioresorbable membranes. A controlled clinical trial. *J Periodontol* 1996;67:217-223.
- Ellegard B, Loe H. New attachment of periodontal tissues after treatment of intrabony lesions. *J Periodontol* 1971;41:648-652.
- Froum S, Thaler R, Scoop IW, Stahl SS. Oseous autografts: I. Clinical responses to bone blend or hip marrow grafts. *J Periodontol* 1975;46:515-521.
- Froum SJ, Weinberg MA, Rosenberg E, Tarnow D. A comparative study utilizing open flap

- debridement with and without enamel matrix derivative in the treatment of periodontal intrabony defects: A 12-month re-entry study. *J Periodontol* 2001;72:25-34.
- Garrett S. Periodontal regeneration around natural teeth. *Ann Periodontol* 1996;1:621-666.
- Gestrelus S, Andersson C, Johansson AC, Persson E, Brodin A, Rydhag L, Hammarstrom L. Formulation of enamel matrix derivative for surface coating. Kinetics and cell colonization. *J Clin Periodontol* 1997;24:678-684.
- Giannobile WV, Somerman MJ. Growth and amelogenin-like factors in periodontal wound healing. A systematic review. *Ann Periodontol* 2003;8:193-203.
- Gottlow J, Numan S, Karring T, Lindhe J. New attachment formation as the result of controlled tissue regeneration. *J Clin Periodontol* 1984;11:494-503.
- Hammarstrom L. Enamel matrix, cementum development and regeneration. *J Clin Periodontol* 1997;24:658-668
- Harakas N. Demineralized bone matrix induced osteogenesis. *Clin Orthop* 1984;188:239-251.
- Harris, RJ. A short term and long term comparison of root coverage with an acellular dermal matrix and a subepithelial graft. *J Periodontol* 2004;75:734-743.
- Heijl L, Heden G, Svardstrom G, Ostgren A. Enamel matrix derivative (EMDOGAIN) in the treatment of intrabony periodontal defects. *J Clin Periodontol* 1997;24:705-714.
- Hiatt WH, Schallhorn RG. Intraoral transplants of cancellous bone and marrow in periodontal lesions. *J Periodontol* 1973;44:194-208.
- Hugoson A, Ravald N, Fornell J, Johard G, Teiwik A, Gottlow J. Treatment of class II furcation involvements in humans with bioresorbable and nonresorbable guided tissue regeneration barriers. A randomized multicenter study. *J Periodontol* 1995;66:624-634.
- Jepsen K, Heinz B, Halben JH, Jepsen S. Treatment of gingival recessions with titanium reinforced barrier membranes versus connective tissue grafts. *J Periodontol* 1998;69:383-391.
- Mann W. Autogenous transplant in the treatment of an infrabony pocket. *Periodontics* 1964;2:205-208.
- Mariotti A., Efficacy of chemical root surface modifiers in the treatment of periodontal disease. A systematic review. *Ann Periodontol* 2003;8:205-226.
- Mellonig J, Bowers G, Baily R. Comparison of bone graft materials. I. New bone formation with autografts and allografts determined by strontium-85. *J Periodontol* 1981;52:291-296.
- Mellonig JT. Decalcified freeze-dried bone allograft as an implant material in human periodontal defects. *Int J Periodont Rest Dent* 1984;4:41-55.
- Mellonig JT. Freeze dried bone allografts in periodontal reconstructive surgery. *Dent Clin North Am* 1991;35:505-520.
- Mellonig JT. Enamel matrix derivative for periodontal reconstructive surgery: Technique and clinical histologic case report. *Int J Periodont Rest Dent* 1999;19:9-19.
- Murphy KG, Gunsolley JC. Guided tissue regeneration for the treatment of periodontal intrabony and furcation defects. A systematic review. *Ann Periodontol* 2003;8:266-300.
- Nevins ML, Camelo M, Lynch SE, Schenk RK, Nevins M. Evaluation of periodontal regeneration following grafting intrabony defects with bio-oss collagen: A human histologic report. *Int J Periodont Rest Dent* 2003;23:9-17
- Novaes AB Jr, Grisi DC, Molina GO, Souza SLS, Taba M Jr, Grisi MFM. Comparative 6-month clinical study of a subepithelial connective tissue graft and acellular dermal matrix graft for the treatment of gingival recession. *J Periodontol* 2001;72:1477-1484.
- Oates TW, Robinson M, Gunsolley JC. Surgical therapies for the treatment of gingival recession. A systematic review. *Ann Periodontol* 2003;8:303-320.
- Pontoriero R, Wennstrom J, Lindhe J. The uses of barrier membranes and enamel matrix proteins in the treatment of angular bone defects. A prospective controlled clinical study. *J Clin Periodontol* 1999;26:833-840.
- Renvert S, Garrett S, Schallhorn RG, Egelberg J. Healing after treatment of periodontal intraosseous defects. III. Effect of osseous grafting and citric acid conditioning. *J Clin Periodontol* 1985;12:441-445.
- Rosen PS, Reynolds MA. A retrospective case

- series comparing the use of demineralized freeze-dried bone allograft and freeze-dried bone allograft combined with enamel matrix derivative for the treatment of advanced osseous lesions. *J Periodontol* 2002;73:942-949.
- Reynolds MA, Aichelman-Reidy ME, Branch-Mays GL, Gunsolley JC. The efficacy of bone replacement grafts in the treatment of periodontal osseous defects. A systematic review. *Ann Periodontol* 2003;8:227-264.
- Schmitt JM, Buch DC, Joh Sp, Lynch SE, Hollinger JO. Comparison of porous bovine mineral and biologically active glass in critical-sized defects. *J Periodontol* 1997;68:1043-1053.
- Sculean A, Donos N, Miliauskaitė A, Arweiler N, Brex M. Treatment of intrabony defects with enamel matrix proteins or bioabsorbable membranes. A 4 year follow up split-mouth study. *J Periodontol* 2001;72:1695-1701.
- Selvig KA. Biological changes at the tooth saliva interface in periodontal disease. *J Dent Res* 1969;48:846-855
- Selvig KA, Zander HA. Chemical analysis and microradiograph of cementum and dentin from periodontally diseased human teeth. *J Periodontol* 1962;33:303-310.
- Selvig KA, Hals D. Periodontally diseased cementum studied by correlated microradiography, electron probe analysis and electron microscopy. *J Periodont Res* 1977;12:419-429.
- Stahl SS, Froum SJ, Kushner L. Healing responses of human teeth following the use of debridement grafting and citric acid root conditioning. II. Clinical and histologic observations: One year post surgery. *J Periodontol* 1983;54:325-338.
- Urist MR, Strates B. Bone formation in implants of partially and wholly demineralized bone matrix. *Clin Orthop* 1970;71:271-278.
- Valdre G, Mongiorgi R, Ferrieri P, Corvo G, Cattaneo B, Tartaro G. Scanning Electron microscopy and microanalysis applied to the study of biomaterials for dental use (in Italian). *Minerva Stomatologica* 1995;44:55-68.
- Valentini P, Abensur D. Maxillary sinus floor elevation for implant placement with demineralized freeze-dried bone and bovine bone (Bio-Oss): A clinical study of 20 patients. *Int J Periodont Rest Dent* 1997;17:233-241.
- Wang HL, Bunyaratavej P, Labadie M, Shyr Y, MacNeil RL. Comparison of 2 clinical techniques for treatment of gingival recession. *J Periodontol* 2001;72:1301-1311.
- Yukna RA. Synthetic bone grafts in periodontics. *Periodontol* 2000 1993;1:92-99.
- Yukna RA. Synthetic grafts and regeneration. IN: Polson AM. Periodontal Regeneration. Current Status and Directions. Chicago: Quintessence Publishing Company Inc, 1994. pp103-112.
- Yukna RA, Mellonig JT. Histologic evaluation of periodontal healing in humans following reconstructive therapy with enamel matrix derivative. A 10-case series. *J Periodontol* 2000;71:752-759.
- Zetterstrom O, Andersson C, Eriksson L, Fredriksson A, Friskopp J, Heden G, Jansson B, Lundgren T, Nilveus R, Olsson A, Renvert S, Salonen L, Sjoström L, Winell A, Ostgren A, Gestrelus S. Clinical safety of enamel matrix derivative (EMDOGAIN) in the treatment of periodontal defects. *J Clin Periodontol* 1997;24:697-704.
- Zuchelli G, Clauser C, De Sanctis M, Calandriello M. Mucogingival versus guided tissue regeneration procedures in the treatment of deep recession type defects. *J Periodontol* 1998;69:138-145.
- Zuchelli G, Amore C, Montebugnoli L, De Sanctis M. Enamel matrix proteins and bovine porous bone mineral in the treatment of intrabony defects: A comparative controlled clinical trial. *J Periodontol* 2003;74:1725-1735.