How Predictable Are Periodontal Regenerative Procedures?

Ron Zohar, *DMD, PhD, FRCD(C);* ***Howard C. Tenenbaum,*** *DDS, PhD, Dip Perio, FRCD(C)*

Contact Author

Dr. Zohar
E-mail: *ron.zohar@utoronto.ca*

ABSTRACT

Periodontal regeneration has become one of the primary objectives of periodontal therapy. The resulting scientific endeavours have elucidated modes of periodontal wound healing, the growth of periodontal cells and their association with the surrounding matrix, and growth-promoting factors. The periodontal regeneration industry is producing better and more expensive devices, but the criteria for evaluating their success have not progressed to the same extent. Although clinical measurements of attachment level and probing depths, along with radiography, are good methods of evaluating tooth survival and prognosis, they do not indicate true biological regeneration. In addition, the regeneration industry may encourage the overuse of allografts and alloplasts which may serve as an impediment to simple wound healing. This review is a critical assessment of the clinical use of various regenerative tools, specifically bone replacements and membranes. The future of the regeneration industry may depend on the merging of various technologies and biological concepts, including the possible use of biological barriers, various bone and periodontal growth inducers, and artificial matrices that will attract or carry the cells necessary for regeneration.

MeSH Key Words: alveolar bone loss/surgery; bone regeneration; guided tissue regeneration, periodontal; membranes, artificial

Regeneration can be defined as the reproduction or re-formation of organs or tissues that have been lost or injured as a result of a wound or infection. In the periodontium, such regeneration involves the creation of new alveolar bone, cementum and ligament. In this context, regeneration is distinct from tissue repair and is characterized by replacement of the damaged tissues with something that may be inferior to the original tissue both structurally and functionally.[1] Thus, the ideal periodontal treatment should include recruitment of embryonic, pluripotential cells (i.e., periodontal progenitor cells) capable of differentiating into specialized cell types, which will form a functional syncytium connected by highly specialized and appropriately oriented collagen fibres (i.e., Sharpey's fibres). Periodontal regenerative therapy may also be performed in simpler cases in which only bone is missing (e.g., preprosthetic or preimplant augmentation). In such cases, differentiation of primarily (but not exclusively) bone lineage cells, the osteoblasts, is required to orchestrate new osteogenesis.

The most important question facing practitioners in the field of periodontics is whether predictable regeneration of the periodontium or bone in the oral cavity is even possible (**Figs. 1a** to **1d**). From this question stems an equally important issue, the degree of confidence with which the practitioner can tell the patient that missing bone or attachment apparatus around the teeth can be faithfully regenerated. Indeed, there is little empirical evidence to suggest that current regenerative treatments yield more predictable long-term reductions in tooth loss than conventional debridement therapies (both surgical and nonsurgical).

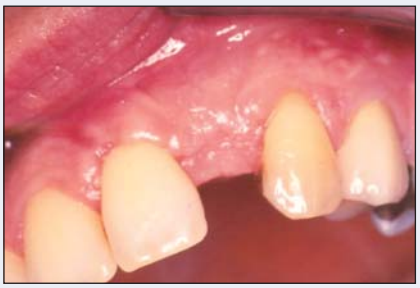

Figure 1a: A 22-year-old patient referred for implant therapy for missing upper lateral incisor (tooth 22). The ridge had been restored with demineralized, freeze-dried bone allograft (DFDBA) 2 years previously when the tooth was extracted.

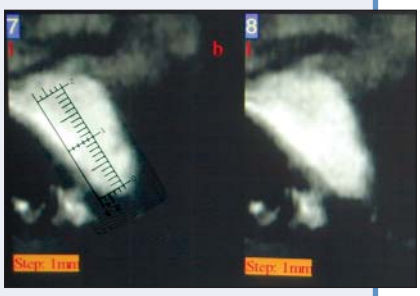

Figure 1b: Esthetic restoration of the missing lateral incisor was the patient's primary concern. Computed tomography imaging of the ridge was performed to ensure adequate buccopalatal bone width and height. The scan showed more than 15 mm of mineralized tissue height and more than 10 mm width at the middle of the ridge.

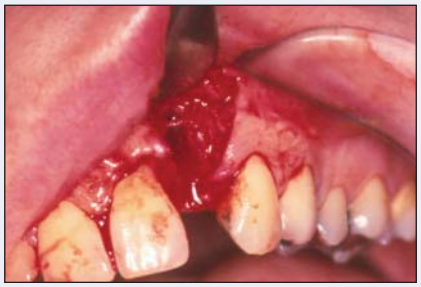

Figure 1c: Mucoperiosteal flap reflection of the ridge dislodged the mass of mineralized tissue, which left a large defect with no buccal bone. As such, the radiographic evidence of "regeneration" observed in this patient did not accurately portray the degree of treatment success.

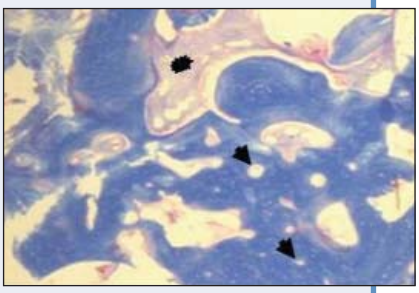

Figure 1d: Photomicrograph of mineralized tissue harvested from the augmented site one year after filling with DFDBA material (stained with Mallory's reagent). The mineralized particles reveal empty, acellular lacunae (black arrows), which are indicative of tissue death. Growth of connective tissue between bone particles (asterisk) was also observed. Original magnification ×40.

Periodontal Debridement

The removal of periodontal pathogenic bacteria, mineralized deposits on the root surface and infected cementum containing associated toxins is still one of the most predictable methods leading to stable periodontal healing, if not regeneration. This basic approach, whether achieved by nonsurgical disinfection during closed debridement (e.g., in periodontal pocket depths of up to 5 mm) or by surgical debridement,[2,3] can lead to the development of a stable attachment apparatus. Surgical debridement of intraosseous defects appears to lead predictably to an increase in periodontal attachment of about 2.5 mm, with variable amounts of bone filling.[4–6] The experience and surgical anatomic data reported by Prichard,[7] Polson and Heijl,[4] Becker and others,[6] and Ochsenbein,[8] among others, have served to explain and predict stable healing of the periodontium in clean, deep osseous defects with optimal osseous architecture, as well as revealing the factors that promote some degree of healing and regeneration.[9] However, where the loss of periodontal and bone connective tissues is excessive (e.g., cases of severe loss of horizontal alveolar bone), healing after debridement procedures is not followed by significant gains in new attachment. Given these limitations, experimental assessment of various bone grafting methods and other bone replacement materials has been undertaken.

Autogenous Grafts

The need for progenitors, blood supply and morphogens has encouraged the use of autogenous osteogenic tissue for grafting. For example, osseous coagulum bone blend[10] has been and still is used to achieve bone filling in periodontal and osseous defects. The rationale for the use of this mixture as well as blood and osteogenic cells is to supply progenitors and morphogens to the wound site and to promote stable clot formation. Histological analyses of tissues produced following these procedures have confirmed cementogenesis, osteogenesis and re-formation of functionally oriented ligament fibres, even on root surfaces covered with infected accretions.[11] Notably, even with autogenous grafts, the formation of functional periodontal fibres and new cementum is limited and generally occurs at the very base of the defect, where the conditions are apparently more conducive to regeneration (e.g., in the proximity of a vital periodontal ligament). Moreover, certain types of bone, such as fresh iliac marrow grafts, contain osteoclastic precursors that can promote root resorption and ankylosis.[12]

With the advent of the use of platelet-rich plasma (PRP) to promote regeneration of connective tissue,[13] the importance of a stable blood clot for successful periodontal regeneration has been recognized. In fact, it has been suggested that PRP, in conjunction with bone and periodontal regenerative therapy, may promote faster healing, which has led to the development of expensive chairside platelet-purifying centrifuges.[14] It has been claimed that the PRP generated by these units acts as a source of factors that accelerate and improve healing and regeneration

(e.g., transforming growth factor-beta 1[TGFβ1] and platelet-derived growth factors [PDGF]).[15] However, the notion that PRP increases levels of TGFβ1 and PDGF must be examined carefully. Given that these cytokines modulate and stimulate osteodifferentiation and osteogenesis by serving as chemoattractants and differentiation-stimulating factors for mesenchymal cells,[16] their clinical use should theoretically be beneficial, but this may not be the case in practice. Notably, these cytokines have been shown to have biphasic effects on mesenchymal cells both in vivo and in vitro. In this regard, TGFβ1 and PDGF can also *inhibit* osteogenic cell differentiation,[17,18] an effect that appears to depend on dose and mode of administration. Indeed, given the vagaries of and variations in the clinical methods for preparing PRP, as well as the limited understanding of the underlying mechanisms of its action, there may be little need for fresh platelet products or the expensive chairside machines used to prepare them.

Non-Autogenous Bone Replacements

The need for sufficient graft material, as well as the complications associated with second-site surgery (used to obtain autogenous bone), led to the development of allograft and alloplastic graft materials (**Figs. 2a** and **2b**). Prior discoveries by Urist[19] showed that demineralized lyophilized bone matrix (DMB) induces *ectopic* osteogenesis, which indicates that DMB should be useful for osteogenic sites requiring augmentation and regeneration. The rationale is that DMB is enriched with morphogens capable of inducing *de novo* formation of mineralized connective tissues.[9,19] Implantation of DMB into periodontal or bone defects can lead to increases in clinical attachment levels and increased bone filling.[20,21] In this regard, the use of freeze-dried bone allografts (FDBA) or demineralized FDBA has led to the filling of periodontal defects

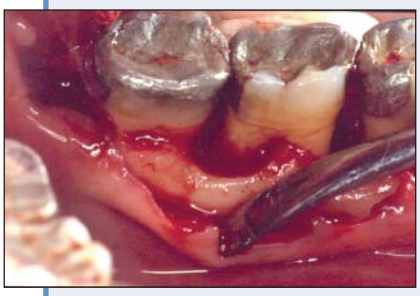

Figure 2a: Alloplastic grafting. Post-debridement image of the posterior lower sextant shows extensive bone resorption with reverse architecture and deep intrabony defects. Conservative resective surgery would have resulted in exposure of the furcation of the first and second molars and would have worsened the prognosis.

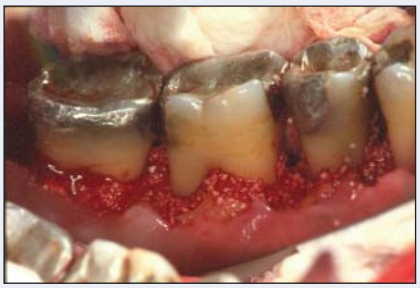

Figure 2b: The defects were filled with hydroxyapatite filler (an alloplast) to replace the missing bone and perhaps the periodontal ligament as well. It was anticipated that the alloplast would also provide support for the gingival tissues.

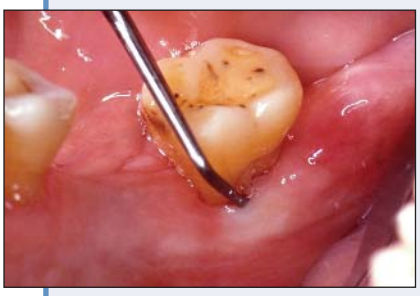

Figure 3a: Mandibular second molar with deep lingual probing depth and normal vitality.

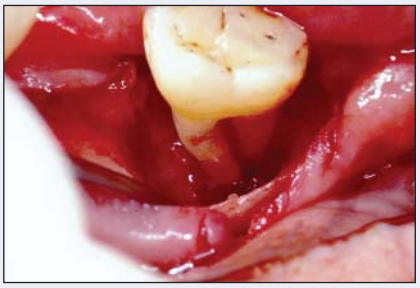

Figure 3b: Surgical exposure revealed a wide, deep circumferential defect surrounded by sound osseous walls. A resorbable membrane was adapted and secured without bone replacement or filler.

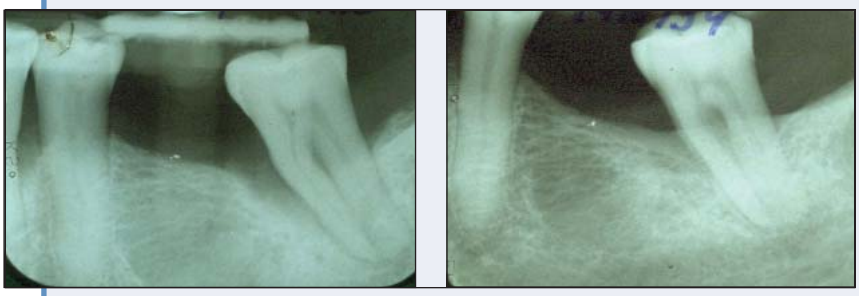

Figure 3c: Radiographs of the mandibular second molar during surgery (left panel) and one year later, during re-entry (right panel). The defect appeared quite wide and extended to the apex. It was filled with radiopaque material with a density similar to that of the surrounding tissue, which was suggestive of new bone.

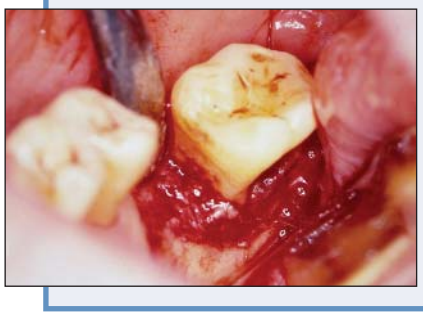

Figure 3d: Re-entry procedure showed that the defect was filled with mineralized connective tissue consistent with bone regeneration.

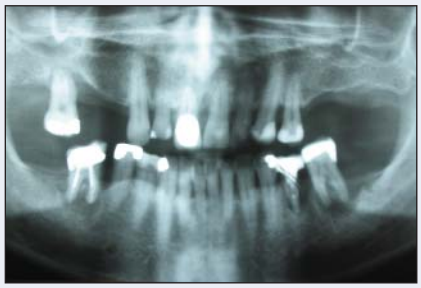

Figure 4a: Implant candidate. The panoramic radiograph shows 3 foci of extensive bone destruction and combined periodontal–endodontic lesions (teeth 17, 36, 35 and 46). The teeth were extracted and the defects debrided to remove residual inflammatory and granulation tissue. Surgical manipulation was performed to protect the healing sockets.

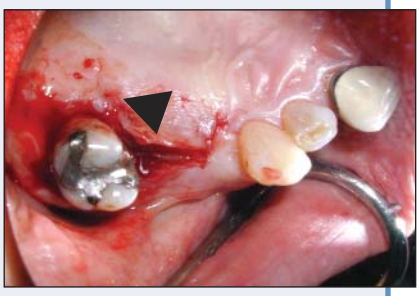

Figure 4b: Tooth 17 exhibited loss of bone approximating the sinus floor. A split-thickness flap of the palatal tissue is visible (arrow).

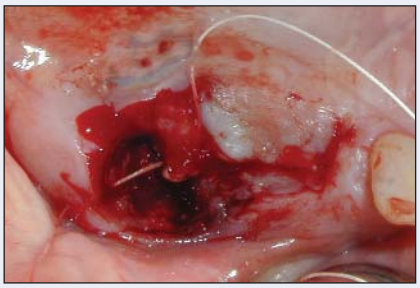

Figure 4c: The underlying connective tissue, still connected to its blood supply, was rotated and sutured to cover the socket and protect the sinus and the extraction socket.

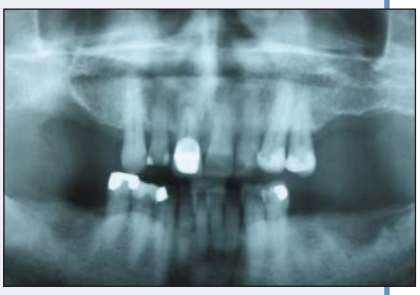

Figure 4d: Panoramic radiograph taken at the time of implant placement, 6 months later, shows normal healing, which allowed placement of endosseous implants at least 4 mm in diameter and 12 mm in length.

with mineralized bone-like material.[22] Although regeneration may or may not take place with this type of grafting, some reports have described the development of new cementum, oriented periodontal fibres and 1.2 mm of new periodontal attachment.[20,22–24] This gain in attachment may be independent of the grafted material and may be more the result of removal of etiological factors. Notably, FDBA and demineralized FDBA produce variable healing results over time, which may be related to tissue bank processing, possible antigenicity or even the source of the bone.[23] In some cases defect filling induced by FDBA or demineralized FDBA was no better than that induced by other agents thought to be inferior, such as alloplastic materials.[25] Moreover, bone allografts have been shown to persist as foreign and dead mineralized particles at the grafted site (**Figs. 1c** and **1d**),[26] which might interfere with normal healing of bone. Other case reports have documented lack of resorption of such allograft materials; hence, along with the other caveats mentioned above, the value of these materials for periodontal or bone regeneration remains questionable. This variability in actual bone formation might be explained by the small quantity of bone morphogenetic proteins (BMPs) that are present in bone, especially the adult cortical bone used by bone banks, given that, in previous studies, embryonic bone has been more osteoinductive than bone derived from adult donors.[27] In view of the very low and unpredictable quantities of BMPs in adult human bone graft preparations, successful clinical results have been attributed to other noncollagenous proteins in allograft preparations that might be osteostimulative. Therefore, although bone allografting can be considered safe and may improve probing depth and radiopacity, its biological effectiveness is still in question.

Guided Tissue Regeneration and Cell Exclusion Techniques

The rationale for the use of guided tissue regeneration (GTR) was first described in 1976 by Melcher, who suggested that differences in the behaviour and characteristics of attachment cells lead to *repair* of the periodontium by epithelium instead of *regeneration* with periodontal progenitor cells.[28] Interestingly, earlier studies had suggested that exclusion of the oral epithelium could lead to improvements in periodontal healing after surgery.[29,30] This concept led to the development of epithelial exclusion methods, which apparently led in turn to more predictable filling of intraosseous defects around periodontally diseased teeth.[7,26] To further refine this approach, surgical sites were sometimes covered with autogenous barriers such as free gingival grafts, which would provide more primary closure and may also assist in cell exclusion. The principles of selective cell repopulation, ultimately termed GTR, were developed further by Nyman and his colleagues.[31] By using selective approximation of periodontal instead of gingival tissue, new connective tissue attachment can form on previously diseased roots. The use of membrane filters also fulfilled the principles of tissue exclusion; when placed properly within a surgical wound, these membranes induced new cementum formation with oriented periodontal fibres.[32]

The development of various barrier-based treatment modalities and techniques and a wide range of nonresorbable

and resorbable membranes gave rise to the acceptance of another tissue regenerative approach focused solely on bone regeneration: guided bone regeneration. This method allows for migration of osteoprogenitor cells within the area protected by the barrier, in the absence of infection. As noted above, however, newly regenerated tissues created by GTR methods often occur at the base of the periodontal defect, an area that may be more prone to true regeneration than the more coronal aspects of the defect. Regenerative procedures can be complemented by the addition of osteogenic inducers[9,16,33] (e.g. BMP or enamel matrix proteins), which are not discussed here. Notably, even in the absence of such osteogenic inducers, cell exclusion and space-making approaches to the treatment of periodontal defects seem to lead to more favourable healing (**Figs. 3a** to **3d**).

Conclusions

Given the many unknowns outlined here, it is important to understand the various limitations in the assessment of periodontal regeneration, such as confirming the formation of bone rather than ectopically mineralized fibrous tissues, as well as the re-formation of the attachment apparatus after therapy. The predictability of regeneration is affected by anatomic factors, as outlined at the outset of this article, and by host systemic factors (e.g., smoking, chronic diseases). These issues, although important, are beyond the scope of this paper. Moreover, as stated above, even with the "best" regenerative treatments available, it is probably appropriate to overcome the clinical impulse to fill or regenerate every defect, so that simpler approaches to controlling disease, which have greater evidence for long-term success can be used (**Figs. 4a** to **4d**).

As our understanding of stem cells, matrix and morphogens increases, there is hope that their contribution to regeneration will eventually lead to combined therapy based on sound scientific principles.

THE AUTHORS

Acknowledgements: *The authors' studies were funded by the Rosenstadt fund, faculty of dentistry, University of Toronto and by grant MOP-457134 from the Canadian Institutes of Health Research.*

Dr. Zohar *is an assistant professor in the departments of periodontology and biomaterials at the faculty of dentistry, University of Toronto, Ontario.*

Dr. Tenenbaum *is associate dean of diagnostic and biological sciences and professor of periodontology at the faculty of dentistry, University of Toronto, Ontario.*

Correspondence to: *Dr. Ron Zohar, Biomaterials and Periodontal Department, Faculty of Dentistry, University of Toronto, 124 Edward St., Toronto, ON M5G 1G6. E-mail: ron.zohar@utoronto.ca.*

The authors have no declared financial interests in any company manufacturing the types of products mentioned in this article.

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