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Regenerative potential and healing dynamics of the periodontium: a critical-size supra-alveolar periodontal defect study

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Abstract

Objectives: The nature and characteristics of the newly formed periodontium obtained following regenerative procedures remain a matter of controversy. The objective of this study was to evaluate the regenerative potential of the periodontal attachment and healing dynamics as observed from the spatial distribution of newly formed cementum, periodontal ligament (PDL) and alveolar bone following optimal circumstances for wound healing/regeneration in a discriminating animal model.

Material and Methods: Critical-size, 6-mm, supra-alveolar, periodontal defects were surgically created in six young adult Beagle dogs. Space-providing ePTFE devices with 300-μm laser-drilled pores were implanted to support wound stability and space provision in one jaw quadrant/animal. Treatments were alternated between left and right jaw quadrants in subsequent animals. The gingival flaps were advanced to submerge the defect sites for primary intention healing. Histometric analysis followed an 8-week healing interval.

Results: Healing was uneventful in all animals. The histometric analysis showed that cementum regeneration (2.99 ± 0.22 mm) was significantly greater than PDL (2.54 ± 0.18 mm, $p = 0.03$) and bone regeneration (2.46 ± 0.26 mm, $p = 0.03$). The wound area showed significant positive non-linear effect on cementum ($\log \beta = 1.25$, $p < 0.001$), PDL ($\log \beta = 1.24$, $p < 0.001$) and new bone formation ($\log \beta = 1.36$, $p < 0.001$). A high degree of concordance and significant linear relationship was observed between cementum, PDL and bone regeneration indicating that their formation virtually occurred in parallel.

Conclusions: Cementum, PDL and alveolar bone virtually regenerate in parallel under optimal circumstances for periodontal wound healing/regeneration. Moreover, space provision positively influences the extent of periodontal regeneration.

Key words: bone; cementum; periodontal ligament; periodontal regeneration; tissue engineering

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Conflict of interest and source of funding statement

The authors declare they have no conflicts of interests.

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Ultimately, periodontal therapy aims to completely restore the periodontal attachment including cementum, periodontal ligament (PDL) and alveolar bone lost due to periodontal disease or trauma. It has been hypothesized that tissue elements sequestered within the PDL are critical to this process (Melcher 1976). Undeniably, experimental and clinical studies attempting to favour migration and proliferation of tissue elements from the PDL domicile have shown that periodontal regeneration is a biological and clinical reality (for review see Karring et al. 1993, Karring & Cortellini 1999). Moreover, experimental studies have provided ample biologic evidence delineating wound stability, space-provision and wound closure favouring primary intention healing as critical clinical elements for procedures aimed at predictably resulting in reconstruction/regeneration of the periodontal attachment (for review see Wikesjö & Selvig 1999, Polimeni et al. 2006). However, contrary to popular belief, tissue partition using occlusive barrier devices does not appear critical for regeneration of the periodontal attachment (Wikesjö et al. 2003b, c, d). Notably, implementation of current regenerative protocols including barrier devices, bone grafts and biologics in support of periodontal regeneration have demonstrated difficulties in clinical execution and/or limited efficacy in controlled clinical studies (Sanz et al. 2004, Nevins et al. 2005, Nygaard-Østby et al. 2008). Thus, development of efficacious clinical protocols facilitating wound stability, space-provision and conditions immediately favouring primary intention healing supporting the native potential for periodontal regeneration appears a necessity.

Researchers have extensively argued the nature and characteristics of the newly formed periodontium obtained following regenerative procedures. Using occlusive barrier devices applied to a canine through-and-through furcation defect model, Araujo et al. (1996, 1997) observed a gradual maturation of the regenerating periodontal tissues. However, cementum maturation/thickness and the ratio of PDL collagen/vascular elements did not approach that of the pristine periodontium within a 5-month healing interval. Two longer-term studies, also implementing occlusive barrier devices in support of periodontal wound healing/regeneration, investigated the quality and quantity of the regenerated periodontal attachment using induced buccal dehiscence (observation interval: 6 weeks, 6 months and 2 years) and intra-bony (observation interval: 6 months and 2 years) periodontal defects in non-human primates (Graziani et al. 2005, Laurell et al. 2006). They reported a time-dependent maturation of the periodontal attachment; the histometric analysis revealing a de novo formed periodontal attachment not significantly different from the pristine periodontium within the 2-year healing interval. Notably, in these defect models tissue resources within the PDL circumscribing the defects contribute to observed regenerative outcomes and thus the results may not necessarily indicate the regenerative potential of the discrete components of the periodontal attachment.

Other previous studies (Polimeni et al. 2004a, b, c, d, 2005) have elucidated a relationship between space provision and the regenerative potential and healing dynamics of the alveolar bone in periodontal and peri-implant alveolar settings using discriminating canine supra-alveolar defect models (Wikesjö & Nilvéus 1991, Wikesjö et al. 1994, 2006). The regenerative potential of the cementum and the PDL has not been presented in such discriminating models that uniquely allow a linear evaluation of the regenerative potential of tissue resources sequestered within the PDL in an apical–coronal dimension. The objective of this study was to evaluate the regenerative potential of the periodontal attachment and healing dynamics as observed from the spatial distribution of newly formed cementum, PDL and alveolar bone following optimal circumstances for wound healing/regeneration in a discriminating animal model.

Material and Methods

Animals

The surgical and animal technical protocol has been described (Wikesjö et al. 2003c, d). In brief, six young adult male Beagle dogs obtained from a USDA approved dealer were used. Animal selection, management and experimental protocol were approved by the Animal Care and Use Committee, W.L. Gore & Associates Inc., Flagstaff, AZ, USA. The animals had access to standard laboratory diet and water until the beginning of the study. Oral prophylaxis was performed within 2 weeks before experimental surgeries.

GTR devices

Space-providing porous expanded polytetrafluoroethylene (ePTFE) devices (Reinforced GORE-TEX®, W.L. Gore & Associates Inc.) were used. The porous devices exhibiting laser-etched 300-μm pores at 0.8 mm (centre to centre) intervals to allow penetration of tissue resources from the gingival connective tissue and were reinforced with a laminated polypropylene mesh.

Surgical procedures

Food was withheld the night before surgery. The animals were pre-medicated with atropine (0.02 mg/kg IM), buprenorphine (0.04 mg/kg IM) and flunixin meglumine (0.1 mg/kg IV). A prophylactic antibiotic (cefazolin; 22 mg/kg IV) was administered. General anaesthesia was induced with diazepam (0.2 mg/kg IV) and ketamine (6 mg/kg IV). An endotracheal tube was placed and the animals were maintained on isoflurane gas (1–2%) in 100% oxygen using positive pressure ventilation. An IV line was placed and the animals received a slow constant rate infusion of lactated Ringer's solution (10–20 ml/kg/h) to maintain hydration while anaesthetized. Routine dental infiltration anaesthesia with epinephrine was used at the surgical sites.

Critical-size, 6-mm, supra-alveolar, periodontal defects were created around the third and fourth mandibular premolar teeth in right and left jaw quadrants in each animal (Wikesjö et al. 1994). The crowns of the teeth were reduced to approximately 2 mm coronal to the cemento–enamel junction and exposed pulpal tissues were sealed (Cavit®, ESPE, Seefeld/Oberbayern, Germany). Porous ePTFE devices were implanted in one jaw quadrant/animal. Treatments were alternated between left and right jaw quadrants in subsequent animals. To ensure an adequate blood clot underneath the ePTFE device, autologous blood was drawn using an IV-catheter and aspirated blood was expelled underneath the device. The ePTFE device was fixed to the reduced alveolar bone with medical grade stainless steel tacks (FRIOS® Augmentation System, Friadent, Mannheim, Germany). Periostea were fenestrated at the base of the mucogingival flaps to allow tension-free flap apposition. The flaps were advanced and the margins adapted and sutured (GORE-TEX™ Suture CV5, W.L. Gore & Associates Inc.) 3–4 mm coronal to the ePTFE device.

The maxillary first, second and third premolar teeth were surgically extracted, and the maxillary fourth premolars were reduced in height and exposed pulpal tissues sealed (Cavit®, ESPE) to prevent potential trauma from the maxillary teeth to the mandibular experimental sites. A surgeon (U.M.E.W.) extensively familiar with the experimental model performed all surgical procedures.

Post-surgery protocol

The animals were fed a soft dog food diet. Buprenorphine (0.04 mg/kg IV, IM, or SQ every 5 h) was used for analgesia the first few days. A broad-spectrum antibiotic (enrofloxacin; 2.5 mg/kg, IM, bid) was used for infection control for 14 days. Plaque control was maintained by twice daily topical application of chlorhexidine (Chlorhexidine Gluconate 20%, Xttrium Laboratories Inc., Chicago, IL, USA; 40 ml of a 2% solution) until suture removal and thereafter once daily until the completion of study. Sutures were removed under sedation at approximately 10 days. The animals were anaesthetized and euthanized at 8 weeks when the experimental teeth including surrounding soft and hard tissues were removed en bloc. ePTFE devices were not removed during the healing interval.

Histological processing and evaluation

The tissue blocks were fixed in 10% buffered formalin for 3–5 days, decalcified in 5% formic acid for 8–10 weeks, trimmed, dehydrated and embedded in paraffin. Serial sections (7 μm) were produced in a buccal–lingual plane throughout the mesial–distal extension of the teeth. Every 14th section was stained with hematoxylin for observations at 100 μm intervals.

The most central stained section of each root of the third and fourth premolar teeth was identified by the size of the root canal. This section was subjected to histometric analysis (Koo et al. 2004). Analysis was performed using incandescent and polarized light microscopy (BX 60, Olympus America Inc., Melville, NY, USA), a microscope digital camera system (DP10, Olympus America Inc.) and a PC-based image analysis system (Image-Pro Plus™, Media Cybernetic, Silver Spring, MD, USA) by one experienced, calibrated (intra-class correlation coefficient = 0.984) examiner (G.P.). The following measurements were recorded for the buccal and the lingual tooth surfaces for each section:

- *Cementum regeneration*: distance between the apical extension of the root planing and the coronal extension of newly formed cementum on the planed root.
- *PDL regeneration*: distance between the apical extension of the root planing and the coronal extension of PDL fibres attached to the planed root.
- *Bone regeneration*: distance between the apical extension of the root planing and the coronal extension of alveolar bone regeneration along the planed root.
- *Wound area*: area circumscribed by the planed root surface, the ePTFE device and the base of the defect at the level of the apical extension of the root planing.

Data analysis

Generalized estimating equations were used to perform the present analysis. Measurements at tooth level were used and estimates were adjusted for clustering of teeth into animals using a robust variance estimator. The analysis suggested a non-linear relationship between wound area and periodontal regeneration, thus a log transformation was used for wound area data. The relationship between bone height and cementum and PDL regeneration was deemed linear. Wald tests were used for multiple comparisons and the level of significance was set at 5%. All analysis was performed using a computer-based statistical software (Stata 7.0 for Windows, Stata Corporation, College Station, TX, USA).

Results

Clinical observations

Clinical healing was generally uneventful. All but one porous ePTFE device remained submerged throughout the 8-week healing interval. This device showed a small exposure at approximately 5 weeks. The wound dehiscence displayed a limited local inflammatory reaction and was maintained as such throughout the healing interval.

Histological observations

Regeneration of periodontal structures included formation of woven and lamellar bone with evidence of fibrovascular tissue within the marrow spaces (Figs 1 and 2). Cementum formation, generally cellular, intrinsic/extrinsic fibre cementum, paralleled the level of the newly formed bone. Notably, a functionally oriented PDL with inserting fibres was present at all sites (Figs 1 and 2). In sites exhibiting evidence of compression of the space-providing device to the root surface, bone and cementum formation appeared limited. Undermining root resorption was observed in one site.

Histometric analysis

The results of the histometric analysis are shown in Tables 1–3 and Figs 3 and 4. Cementum regeneration was significantly greater than PDL ($p = 0.03$) and alveolar bone ($p = 0.03$) regeneration, whereas no significant differences were observed between PDL and alveolar bone regeneration ($p = 0.34$) (Table 1). The same trend was observed for the percent defect fill in height by the periodontal tissues. The wound area in a buccal–lingual plane provided by the porous ePTFE device averaged

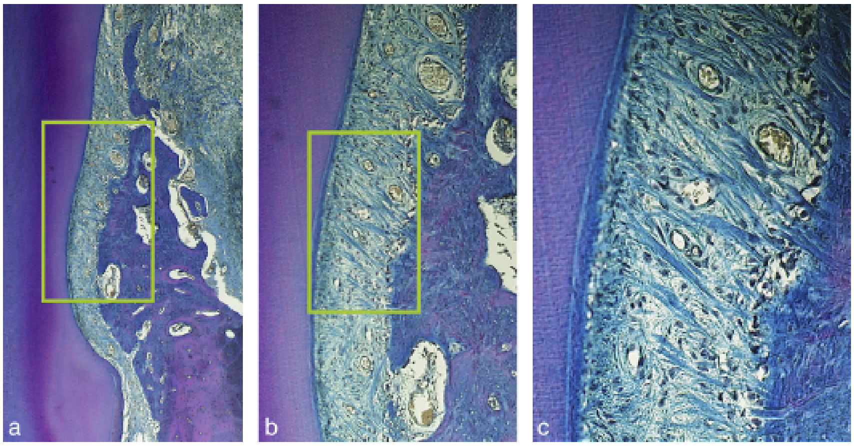

Fig. 1. Photomicrographs of supra-alveolar periodontal defect implanted with the space-providing, porous expanded polytetrafluoroethylene (ePTFE) device. Overview and higher magnifications of the apical aspect of the defect showing regeneration of cementum and a functionally oriented periodontal ligament (PDL) paralleled by new bone formation.

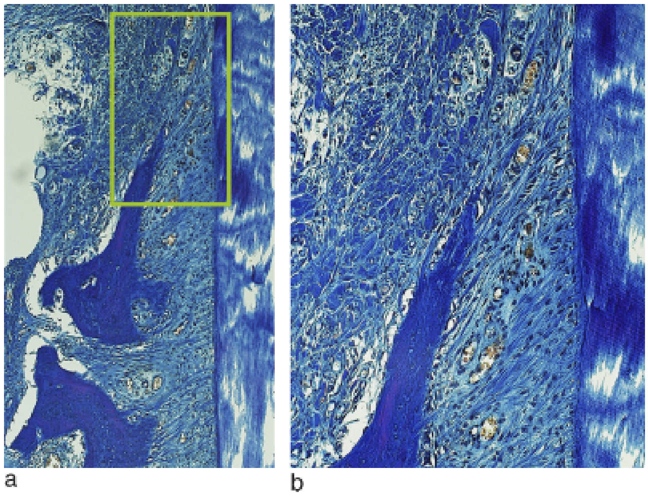

Fig. 2. Photomicrographs of supra-alveolar periodontal defect implanted with the space-providing, porous expanded polytetrafluoroethylene (ePTFE) device. Overview and higher magnifications of the coronal aspect of the defect showing regeneration of cementum and a functionally oriented periodontal ligament (PDL) paralleled by new bone formation.

Table 1. Mean (±SE) periodontal tissue regeneration and wound area

	Mean linear regeneration*	SE	% Defect regeneration*	SE
Cementum regeneration (mm)	2.99A	0.22	57.67A	2.94
PDL regeneration (mm)	2.54B	0.18	49.99B	2.58
Bone regeneration (mm)	2.46B	0.26	48.05B	2.90

*Estimates followed by the same capital letters did not differ statistically.
PDL, periodontal ligament.

Table 2. Effect of wound area (log transformed) on periodontal tissue regeneration

	$\log \beta$	SE	p
Cementum regeneration	1.25	0.18	<0.001
PDL regeneration	1.24	0.18	<0.001
Bone regeneration	1.36	0.22	<0.001

Table 3. Effect of bone height on cementum and periodontal ligament (PDL) regeneration

	β	SE	p
Cementum regeneration	0.97	0.10	<0.001
PDL regeneration	0.85	0.04	<0.001

$5.27 \pm 0.41\,mm^2$ ranging between 1.26 and $12.66\,mm^2$.

Regeneration of the periodontal attachment followed a non-linear order with increasing wound area (Fig. 3). For small wound areas, regeneration of the periodontal attachment increased progressively with increasing wound area. Only small additional gains were observed with increasing wound area for larger defects. In contrast, a linear relationship was observed between the regenerated cementum and PDL, and that of the alveolar bone (Fig. 4). In this regard, a high degree of concordance was observed among the three periodontal tissues indicating that cementum, PDL and bone regenerated in parallel. A higher concordance was observed between PDL and bone regeneration ($CCC_{PDL-bone} = 0.95 \pm 0.02$, $p<0.001$) than the concordance between these parameters with new cementum ($CCC_{PDL-cementum} = 0.79 \pm 0.05$, $p<0.001$ and $CCC_{bone-cementum} = 0.76 \pm 0.06$, $p<0.001$).

Wound area had a significant effect on the regeneration of all three periodontal tissues (Table 2). Wound area had a similar effect on regeneration of the cementum, PDL and alveolar bone as appreciated by the magnitude of the β coefficients. Bone regeneration was significantly associated with regeneration of the cementum and the PDL (Table 3). Bone regeneration had a slightly greater influence on regeneration of the cementum than that of the PDL.

Discussion

The objective of this study was to evaluate the regenerative potential of the periodontal attachment and healing dynamics as observed from the spatial distribution of the cementum, PDL and alveolar bone under optimal conditions for wound healing/regeneration using a discriminating canine, supra-alveolar, periodontal defect model. In order to assure optimal healing circumstances (for review see Wikesjö & Selvig 1999, Polimeni et al. 2006), a porous ePTFE device provided wound stability and space provision, and the gingival flaps were advanced to submerge the defect sites for primary intention healing. Healing was uneventful in all animals following the 8-week healing interval. Cementum, PDL and alveolar bone regeneration occurred in parallel with a slightly greater regeneration of cementum. The wound area provided by the ePTFE device similarly affected cementum, PDL and bone formation.

In this study, within 8 weeks, regeneration of the periodontal structures included cementum formation reaching or exceeding the level of newly formed bone, a functionally oriented PDL present at all sites, and bone formation characterized by woven and lamellar bone with evidence of fibrovascular tissue in the marrow spaces. In sites exhibiting evidence of compression of the ePTFE device to the root surface, in other words space provision was compromised, cementum, PDL, and bone formation appeared limited. These observations corroborate current understanding of periodontal wound healing/regeneration (Polimeni et al. 2006). Briefly, a number of studies utilizing a variety of experimental models indicate discrete biological phases of periodontal wound healing/regeneration and maturation. Clot formation, i.e. absorption/adhesion of blood elements onto the root surface, represents the very first phase of periodontal wound healing/regeneration, blood elements randomly being imposed onto the root surface during surgery and wound closure. A root surface-adhering fibrin clot develops within minutes of wound closure. Within hours one may observe the early phase of inflammation as neutrophils and monocytes accumulate onto the root surface. Within days the late phase of inflammation dominates the healing picture as macrophages migrate into the wound trailed by granulation tissue formation. Maturation of this fragile provisional tissue into a connective tissue attachment occurs within a week when

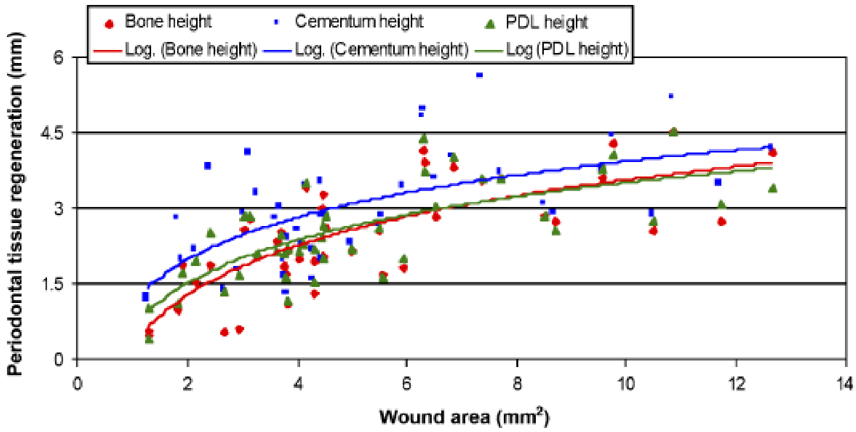

Fig. 3. Relationship between periodontal tissue regeneration and wound area. Lines represent the logarithmic trend of the data.

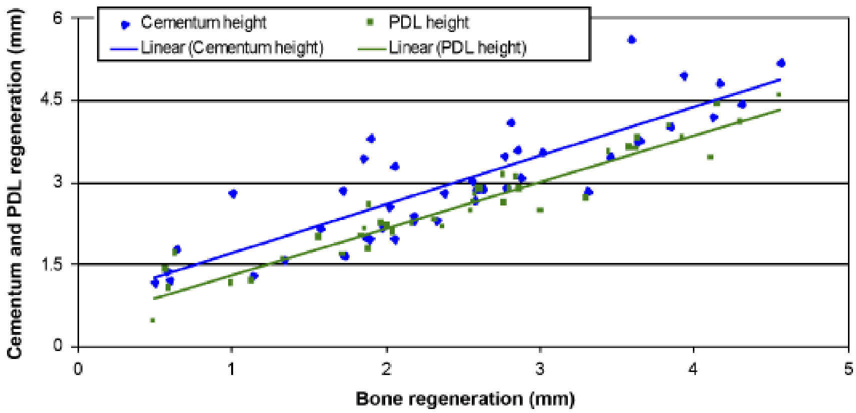

Fig. 4. Relationship between cementum and periodontal ligament (PDL) regeneration and bone regeneration. Lines represent the linear trend of the data.

a more mature connective tissue may be observed at least in part of the wound, wound maturation likely being dependent on wound volume and other local factors (Wikesjö et al. 1991). Within 2 weeks, wound maturation is characterized by extensive connective tissue formation and limited residual granulation tissue. This newly established connective tissue may or may not show a discernable collagen fibre attachment to the root surface; some fibres oriented parallel to the root surface. Small amounts of woven bone formation may be observed in the apical aspect of a defect site (Herr et al. 1995, Matsuura et al. 1995, Araujo et al. 1997). Within 4 weeks the periodontal defect is represented almost completely by mature connective tissue and very limited granulation tissue. Bone formation appears increased compared with that at 2 weeks but is still limited depending on defect volume. The spatial distribution and relationship between collagen fibres and root surface does not appear different from that at 2 weeks with the exception that some fibres, apparently embedded in a ground substance, protrude from the root surface (Haney et al. 1993, Herr et al. 1995, Matsuura et al. 1995, Araujo et al. 1997). Within 8 weeks also the coronal aspect of the periodontal defect is occupied by woven bone. The apical aspect is characterized by lamellar bone. Newly formed cementum covers almost the entire root surface. There is evidence of intrinsic collagen fibres included in a ground substance matrix within this newly formed cementum. A mature PDL is present in the apical aspect of the defect. In the central and coronal aspect, collagen fibres protruding from the newly formed cementum reach a not yet fully mineralized tissue adjacent to woven bone (Sigurdsson et al. 1994, Lindhe et al. 1995, Matsuura et al. 1995, Park et al. 1995, Araujo et al. 1997, Wikesjö et al. 2003a, b, c, d). Within 24 weeks the defect site is occupied by lamellar bone, marrow and limited residual connective tissue. Cellular intrinsic and extrinsic fibre cementum may be observed along the entire root surface. In the coronal aspect of defects where periodontal regeneration did not appear to occur in toto an unspecific connective tissue attachment may be observed that may and may not include newly formed cementum or a cementum-like tissue (Wikesjö et al. 2003b).

A significant association was observed between wound area and bone regeneration as judged by the magnitude of the β coefficient. The present study corroborates previous studies showing a significant association between wound area and bone regeneration under a number of different biological and experimental conditions (Polimeni et al. 2004a, b, c, d, 2005). Notably, this association was still present after adjusting for potential effects of possible confounding factors. Moreover, bone regeneration did not occur in a linear fashion with increasing wound area. For small wound areas bone regeneration increased progressively with increasing wound area; on the other hand, only a small additional gain was observed with increasing wound area for larger defects. Defect sites, which possess a wide alveolar ridge usually feature a large wound area, and this may be one reason why such sites experience enhanced bone regeneration (Polimeni et al. 2004c). However, a previous study showed no significant correlation between wound area and bone regeneration at sites featuring a wide alveolar ridge that also received a space-providing device concluding that the regenerative potential at these sites may have been exhausted: ''. . . once the healing potential of the site is exhausted, an increase in the magnitude of a prognostic factor, which under other circumstances would have resulted in increased bone regeneration, may not further influence the result . . .'' (Polimeni et al. 2004a).

In the present study, periodontal tissues essentially regenerated in parallel. The high degree of concordance and the significant linear relationship between cementum, PDL, and bone regeneration clearly demonstrated that their formation occurred in parallel. Moreover, a strong relationship was observed between space provision and regeneration of the periodontal tissues. In other words, biological conditions in this case space provision, affecting regeneration of one component of the periodontal attachment similarly influenced regeneration of the other periodontal structures as if one and not separate entities. In spite of cementum regeneration being significantly higher than the other tissues, it is not clear which tissue is influencing the other or if this relationship among the tissues truly exists but the main point is that they regenerate to a similar level and they appear similarly influenced by prevailing biologic conditions. In perspective, it may be legitimate to consider the extent of bone regeneration a reasonable surrogate parameter to evaluate the entire regenerative process, at least in an 8-week perspective using the current discriminating defect model. It may not be unreasonable to assume that in a longer time perspective, tissue maturation may prove regeneration of the cementum/PDL complex to exceed that of the alveolar bone. It must also be realized that the innate regenerative potential of the periodontal attachment and healing dynamics observed herein followed optimal circumstances for periodontal wound healing/regeneration, i.e. wound stability, space provision and wound closure for primary intention healing. The clinical dilemma is to master these critical prerequisites immediately favouring primary intention healing and supporting the native potential for periodontal regeneration in the surgical management of a periodontal defect to at all allow meaningful wound maturation/regeneration of the defect site.

Conclusion

Observations from the present study suggest that cementum, PDL and alveolar bone virtually regenerate in parallel under optimal circumstances for periodontal wound healing/regeneration. Moreover, space provision positively influences the extent of periodontal regeneration.

Acknowledgements

The clinical phase of this study was supported by and conducted at W.L. Gore & Associates Inc. Medical Product Division, Flagstaff, AZ, USA.

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Clinical Relevance

Scientific rationale: The objective of this study was to evaluate the regenerative potential of the periodontal attachment and healing dynamics as observed from the spatial distribution of newly formed cementum, periodontal ligament (PDL) and alveolar bone under optimal circumstances for periodontal wound healing/regeneration using a discriminating animal model.

Principal findings: Cementum, PDL and alveolar bone virtually regenerate in parallel under optimal circumstances for periodontal wound healing/regeneration. Moreover, space provision positively influences regeneration of all periodontal tissues similarly.

Practical implications: Optimal circumstances for periodontal wound healing/regeneration are crucial to unleash the innate regenerative potential of the periodontium. When these circumstances are achieved cementum, PDL and alveolar bone are expected to regenerate in parallel and the diagnosis of one of them is likely to imply the presence of the others.