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Periodontal wound healing/regeneration following implantation of recombinant human growth/differentiation factor-5 in a β-tricalcium phosphate carrier into one-wall intrabony defects in dogs

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Abstract

Objective: Recombinant human growth/differentiation factor-5 (rhGDF-5) is being evaluated as a candidate therapy in support of periodontal regeneration. The objective of this study was to evaluate periodontal wound healing/regeneration following the application of rhGDF-5 on a particulate β-tricalcium phosphate (β-TCP) carrier using an established defect model.

Materials and Methods: Bilateral 4 × 5 mm (width × depth), one-wall, critical-size, intrabony periodontal defects were surgically created at the mandibular second and fourth pre-molar teeth in 15 Beagle dogs. Unilateral defects in five animals received rhGDF-5/β-TCP (Scil Technology GmbH); five animals received β-TCP solo; and five animals served as sham-surgery controls. Contralateral sites received treatments reported elsewhere. The animals were sacrificed following an 8-week healing interval for histological examination.

Results: Clinical healing was generally uneventful. Sites implanted with rhGDF-5/β-TCP exhibited greater enhanced cementum and bone formation compared with β-TCP and sham-surgery controls; cementum regeneration averaged (± SD) 3.83 ± 0.73 *versus* 1.65 ± 0.82 and 2.48 ± 1.28 mm for the controls ($p < 0.05$). Corresponding values for bone regeneration height averaged 3.26 ± 0.30 *versus* 1.70 ± 0.66 and 1.68 ± 0.49 mm ($p < 0.05$), and bone area 10.45 ± 2.26 *versus* 6.31 ± 2.41 and 3.00 ± 1.97 mm^2 ($p < 0.05$). Cementum regeneration included cellular/acellular cementum with or without a functionally oriented periodontal ligament. A non-specific connective tissue attachment was evident in the sham-surgery control. Controls exhibited mostly woven bone with primary osteons, whereas rhGDF-5/β-TCP sites showed a noticeable extent of lamellar bone. Sites receiving rhGDF-5/β-TCP or β-TCP showed some residual β-TCP granules apparently undergoing biodegradation without obvious differences between the sites. Sites receiving β-TCP alone commonly showed residual β-TCP granules sequestered in the connective tissue or fibrovascular marrow.

Conclusion: rhGDF-5/β-TCP has a greater potential to support the regeneration of the periodontal attachment. Long-term studies are necessary to confirm the uneventful maturation of the regenerated tissues.

Key words: dog; periodontal regeneration; rhGDF-5; tissue engineering; β-TCP

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Conflict of interest and source of funding statement

The authors have no conflict of interest. Dr. Susanne Pippig is an employee of Scil Technology GmbH. Dr Michael Siedler was an employee of Scil Technology GmbH at the time of study. Dr. Ulf ME Wikesjö serves as consultant to Scil Technology GmbH. This study was supported by a grant from Scil Technology GmbH, Martinsried, Germany.

Current treatment concepts for periodontal regeneration are based on the native potential of tissue resources sequestered within the periodontal ligament (PDL) to produce a regenerate into a surgically created space adjoining a periodontally denuded root surface (Melcher 1976, Nyman et al. 1982, Wikesjö et al. 2003a). Provided conditions for primary intention healing, within several weeks, the regenerate matures into a functionally oriented PDL (Polimeni et al. 2006). It is highly likely that developments in molecular and cell biology, developmental biology, and tissue engineering may significantly advance this treatment concept (Bartold et al. 2000, 2006). Regenerative protocols portraying developmental mechanisms in which biological factors orchestrate cellular events including proliferation, migration, and differentiation of critical tissue resources have been suggested (Bartold et al. 2000). Indeed, a number of studies have evaluated the potential of matrix, growth, and differentiation factors to stimulate the regeneration of the periodontal attachment, some treatment concepts based on rationales originating in development (Hammarström 1997, Wikesjö et al. 1999, 2003b, 2004, Lynch et al. 2006, Ripamonti & Renton 2006).

Urist (1965) realized the capacity of demineralized bone matrix to induce cartilage, bone, and marrow using ectopic rodent models. As the bone-inductive capacity was identified from bovine bone extracts (Wang et al. 1988) and responsible proteins cloned and expressed (Wozney et al. 1988, Celeste et al. 1990, Özkaynak et al. 1990), it became obvious that bone induction was owing to a family of specific bone-inducing proteins collectively named bone morphogenetic proteins (BMPs) (Wang et al. 1990, Sampath et al. 1992, Hötten et al. 1996). Recombinant human BMP-2 (rhBMP-2) and recombinant human osteogenic protein-1 (rhOP-1) have been shown to induce relevant bone formation in several settings in the axial and appendicular skeleton (Friedlaender 2001, Valentin-Opran et al. 2002), and have received FDA approval for clinical use including orthopaedic and maxillofacial indications.

Pre-clinical studies may be interpreted to suggest that BMPs support periodontal regeneration including alveolar bone, cementum or a cementoid tissue, and a functionally oriented PDL (Ripamonti & Reddi 1994, Sigurdsson et al. 1994, Wikesjö et al. 1999, 2003b, Selvig et al. 2002, Ripamonti & Renton 2006). Sometimes, however, initially regenerated fibrovascular tissues will morph into bone, fatty marrow and the associated root resorption/ankylosis rather than functionally oriented PDL (Sigurdsson et al. 1994, Wikesjö et al. 1999, 2003b, 2004, Selvig et al. 2002). As such, the application of BMP-2 into class II furcation defects in nonhuman primates resulted in an incomplete periodontal regeneration, while the application of OP-1 apparently supported complete regeneration (Ripamonti et al. 1994). Similar observations have been made comparing application of rhBMP-2 with rhBMP-12 using a canine supraalveolar periodontal defect model (Wikesjö et al. 2004). Whereas application of rhBMP-12, also known as recombinant human growth/differentiation factor-7 (rhGDF-7), was associated with formation of a functionally oriented PDL, application of rhBMP-2 produced a fibrovascular tissue virtually void of PDL fibres.

GDFs are members of the transforming growth factor-β (TGF-β) superfamily that include BMPs, activins, and TGF-β. These BMP-related factors promote chondroprogenitor cell aggregation (Chang et al. 1994, Storm et al. 1994, Hatakeyama et al. 2004). GDF-5 plays critical roles in mesenchymal cell recruitment and tendon/ligament cell differentiation in morphogenesis. Mutation of the GDF-5 gene produces brachypodism in mice (Storm et al. 1994). Local application of GDF-5 promotes bone formation in rat calvaria defects (Kuniyasu et al. 2003, Pöhling et al. 2006, Yoshimoto et al. 2006), enhances long bone healing (Spiro et al. 2000), and supports spinal fusion (Spiro et al. 2000, Jahng et al. 2004). Potentially, GDF-5 may also play roles in periodontal wound healing/regeneration. GDF-5 is expressed at the root forming stage in dental follicle (Morotome et al. 1998). GDF-5 induces ectopic tendon and ligament formation in vivo (Wolfman et al. 1997) and promotes PDL proliferation by affecting extracellular matrix metabolism (Nakamura et al. 2003). Recently, Moore et al. (2009) reported that GDF-5 appears to be a promising therapeutic agent for periodontal wound healing/regeneration as it supports and accelerates periodontal tissue formation. The objective of this study was to evaluate periodontal wound healing/regeneration following the local application of rhGDF-5 in a particulate β-tricalcium phosphate (β-TCP) carrier using an established defect model.

Materials and Methods

Animals

Fifteen male Beagle dogs, approximately 15 months old, weight from 10–15 kg, bred exclusively for biomedical research purposes, were used. The animals exhibited an intact dentition with a healthy periodontium. Animal selection and management, surgical protocol, and preparation followed routines approved by the Institutional Animal Care and Use Committee, Yonsei Medical Centre, Seoul, Korea. The animals had ad libitum access to water and a pelleted laboratory diet with the exception of one week immediately post-surgery when they were fed a canned soft dog food diet (Prescription Diet Canine i/d, Hill's Pet Nutrition, Inc., USA).

rhGDF-5/β-TCP

The rhGDF-5/β-TCP technology (Scil Technology GmbH, Martinsried, Germany) comprises of rhGDF-5 coated onto a synthetic inorganic carrier, β-TCP (Calciresorb, Ceraver Osteal, Roissy, France), at a concentration of 500 μg/g β-TCP (Pöhling et al. 2006). The applied dose was estimated to be 20 μg rhGDF-5/defect. All materials were supplied by Scil Technology and stored at -80°C until use.

Surgical Protocol

Food was withheld the night preceding surgery. The surgical procedure was performed under general anaesthesia induced by an intravenous (i.v.) injection of atropin (0.04 mg/kg; Kwangmyung Pharmaceutical Ind. Co. Ltd., Seoul, Korea) and an intramuscular injection of a combination of xylazine (Rompun, Bayer Korea Co., Seoul, Korea) and ketamin (Ketara, Yuhan Co., Seoul, Korea) followed by inhalation anaesthesia (Gerolan, Choongwae Pharmaceutical Co., Seoul, Korea). Routine

dental infiltration anaesthesia was used at the surgical sites.

The mandibular first and third premolars were extracted before the experimental surgery and the extraction sites were allowed to heal for 8 weeks. The remaining dentition received oral prophylaxis in conjunction with the extractions.

Experimental surgeries were performed under general anaesthesia (see above). Buccal and lingual mucoperiosteal flaps were elevated to create critical-size, ''box-type,'' 4 × 5 mm (width × height), one-wall intrabony defects at the distal aspect of the second and the mesial aspect of the fourth mandibular pre-molar teeth in the right and left jaw quadrants (Fig. 1) (Kim et al. 2004). Following root planing to remove the root cementum, a reference notch was made into the root surface at the base of the defects. Unilateral defects in five animals received rhGDF-5/β-TCP; five animals received β-TCP solo; and five animals served as sham-surgery controls(Herberg et al. 2008). The defect sites were filled to the level of the alveolar crest. Contralateral sites received treatments reported elsewhere. The mucogingival flaps were advanced, adapted, and sutured using a resorbable suture material (Vicryl 5.0 Polyglactin 910, Ethicon, Johnson & Johnson, Somerville, NJ, USA).

Post-operative Management

The animals received an intramuscular administration of a broad-spectrum antibiotic (Cefazoline Sodium 20 mg/kg, Yuhan Co., Seoul, Korea) and daily topical application of a 0.2% chlorhexidine solution (Hexamedin®, Bukwang Pharmaceutical Co., Seoul, Korea) for infection control. Observations of experimental sites with regard to gingival health, maintenance of suture line closure, oedema, and evidence of tissue necrosis or infection were made daily until suture removal, and at least twice weekly thereafter. The animals were euthanized at 8 weeks post-surgery using an overdose of pentobarbital sodium (90–120 mg/kg; i.v.). Block sections including defect sites and surrounding alveolar bone and mucosal tissues were then collected. Photographic and radiographic recordings were completed intrasurgery, immediately post-surgery, and at 8 weeks post-surgery.

Histological Processing

The block specimens were rinsed in sterile saline and immersed in 10% neutral buffered formalin at a volume 10 times that of the block section for 10 days. After rinsing in sterile water, the sections were decalcified in 5% formic acid for 14 days, trimmed, dehydrated in a graded ethanol series, and embedded in paraffin. Step-serial sections, 5-μm thick, were cut in a mesial–distal vertical plane, at approximately 80-μm intervals. The sections were stained using haematoxylin/eosin and Masson's trichrome stains. The three most central sections of each defect site selected based on the width of the root canal were used for the histological and histometric analysis.

Histological Analysis

One experienced masked examiner performed the histopathologic evaluation of the tissue specimens using incandescent and polarized light microscopy (Olympus Multi-view microscope BH2, Tokyo, Japan). Three central sections stained with haematoxylin/eosin and one section stained with Masson's trichrome were evaluated including observations of bone regeneration (lamellar and woven bone), residual biomaterial and associated tissue reaction(s), cementum regeneration (cellular/acellular cementum; cementoid/cementum-like layer; intrinsic/extrinsic/mixed fibre cementum), PDL orientation/density [0: no PDL fibres; (1) low-density PDL fibres; (2) moderate-density PDL fibres; (3) high-density PDL fibres or same as the native adjoining PDL], ankylosis, and undermining root resorption.

Histometric Analysis

One calibrated masked examiner performed the histometric analysis using a PC-based image analysis system (Image-Pro Plus™, Media Cybernetic, Silver Spring, MD, USA) and incandescent and polarized light microscopy (Olympus Multi-view microscope BH2). The following parameters were analysed for the three central sections (Fig. 2):

- Defect height: distance from the apical extension of the root surface notch to the cemento–enamel junction (CEJ);
- Epithelial attachment: distance from the CEJ to the apical extension of an epithelial attachment on the root surface. This parameter included any gingival recession;
- Connective tissue attachment: the extent of a non-specific connective tissue attachment was calculated as the defect height minus the sum of cementum regeneration and the epithelial attachment;
- Cementum regeneration: distance from the apical extension of the root surface notch to the coronal extension of the newly formed cementum or a cementum-like substance on the root surface;
- Bone regeneration (height): distance from the apical extension of the root surface notch to the coronal extension of the newly formed bone along the root surface;
- Bone regeneration (area): new alveolar bone (including embedded residual β-TCP particles) within a template that served as a standardized proxy for the defect site. The template was aligned parallel to the root surface interfacing the apical extension of defect at the root surface notch. A template was used as the

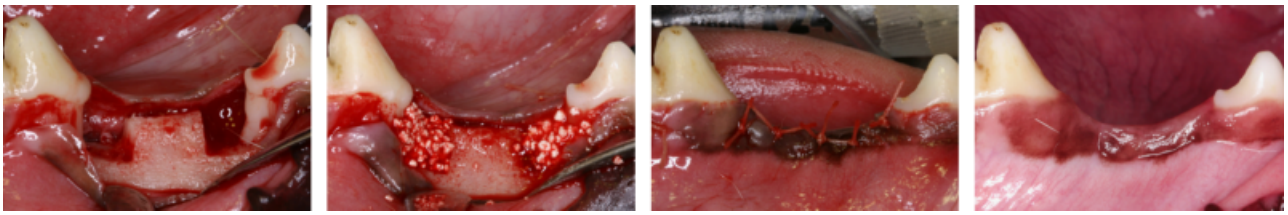

Fig. 1. Surgically created, critical-size, one-wall, intra-bony periodontal defects at the distal of the second and mesial of the mandibular fourth pre-molar teeth (left). Application of recombinant human growth/differentiation factor-5/β-tricalcium phosphate (β-TCP) (left center). Mucoperiosteal flaps adapted and sutured for primary intention healing (right center). Healing at week 8 post-surgery (right). β-TCP and sham-surgery (no biomaterial) controls received the identical surgical protocol.

lateral border of the defects was not clearly defined in the histology.

Statistical Analysis

Summary statistics (mean ± SD) based on animal means for the experimental treatments were calculated using the three central sections from each defect; defects being averaged for each site. Animal means were used to test for differences between experimental conditions using one-way analysis of variance and post hoc test. The level of significance was set at 5%.

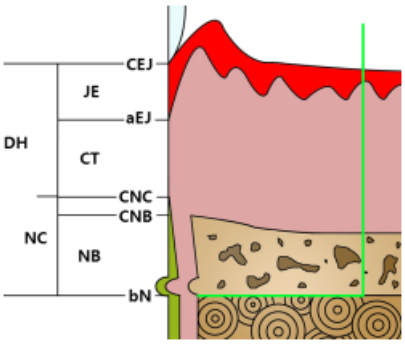

Fig. 2. Landmarks/parameters used in the histometric analysis. The green template serves as a proxy for the defect site for estimation of bone regeneration area. CEJ, cementoenamel junction; aEJ, apical epithelium junction; CNC, coronal new cementum; CNB, coronal new bone; bN, base notch; JE, junctional epeithelium; CT, connective tissue attachment; NB, new bone; NC, new cementum; DH, defect height.

Results

Clinical and Radiographic Observations

All but one defect site healed uneventfully with minimal signs of inflammation and some gingival recession (Fig. 1). One animal experienced a wound dehiscence in a site implanted with rhGDF-5/β-TCP within 7 days post-surgery due to failing suturing. This animal was excluded from the study and replaced.

The radiographic evaluation showed variable new bone formation; however, the rhGDF-5/β-TCP and β-TCP groups showed more bone formation compared with that observed for the sham-surgery control. The β-TCP particulate biomaterial appeared incompletely resorbed.

Histologic Observations

All sites showed new bone and cementum formation along the planed root surface (Figs 3–6). A few sites (rhGDF-5/β-TCP 4, β-TCP 3, and sham-surgery 3) showing old cementum or unresorbed suture material with associated minor inflammatory lesions were excluded from the analysis. One site implanted with rhGDF-5/β-TCP exhibited ankylosis and root resorption with several osteoclasts alongside of resorbed root surface. This site was also excluded from the histometric analysis.

Cementum regeneration, generally a blend of cellular, intrinsic or mixed fibre cementum with or without functionally oriented PDL, was observed in all specimens; PDL fibre density appeared somewhat greater in sites receiving rhGDF-5/β-TCP and β-TCP compared with the low PDL fibre density sham-surgery control (Figs 4 and 5). The amount of cementum regeneration varied in each group. An unspecific loose connective tissue attachment was also evident in the sham-surgery control (Figs 3 and 4).

Newly formed bone exhibited a mixed appearance of woven and lamellar bone. β-TCP and sham-surgery control sites included mostly woven bone with primary osteons, whereas sites receiving rhGDF-5/β-TCP showed more lamellar bone (Figs 3 and 6).

Sites receiving rhGDF-5/β-TCP and β-TCP showed residual β-TCP granules apparently undergoing biodegradation as multinuclear osteoclast-like cells were observed without obvious differences between the sites. Sites receiving β-TCP alone commonly showed residual β-TCP granules sequestered in the

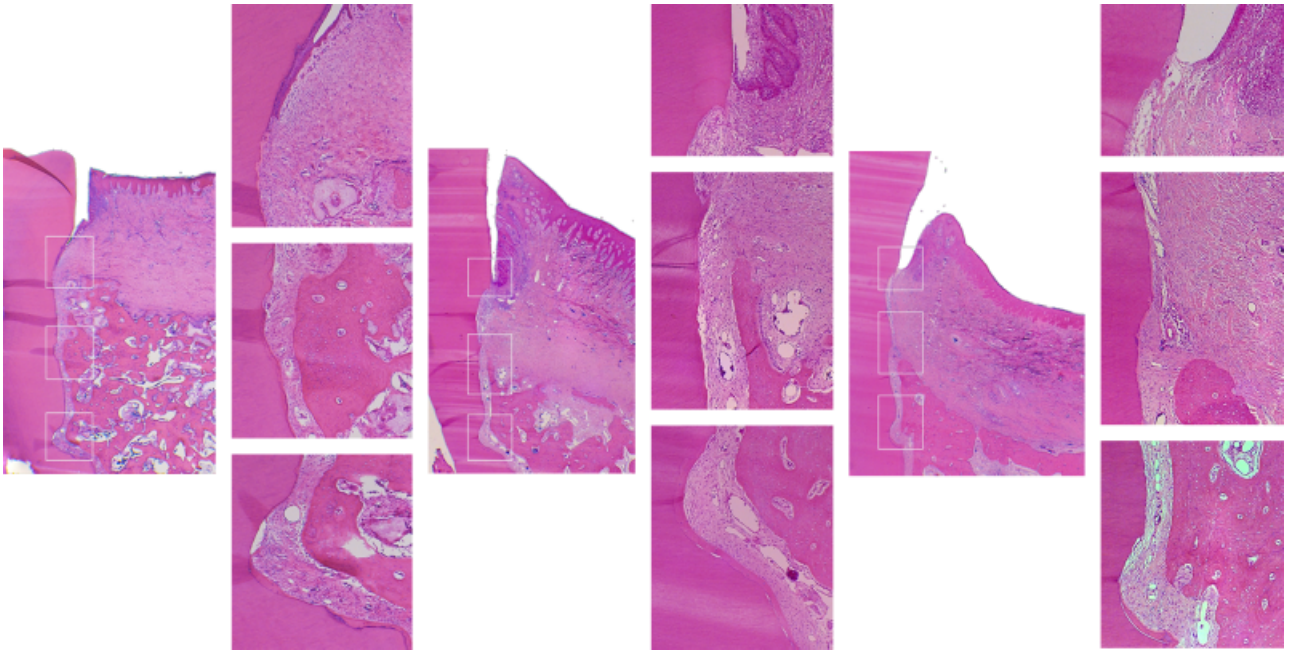

Fig. 3. Photomicrographs from sites implanted with recombinant human growth/differentiation factor-5/β-tricalcium phosphate (β-TCP) (left), β-TCP (centre), or receiving sham-surgery (right) displaying the sites from the apical extension of the root planing (apical insert) along the root surface to the coronal extension of the newly formed alveolar bone and cementum (mid-root insert) and the apical extension of an epithelial attachment (haematoxylin/eosin, original magnification × 10 & × 40).

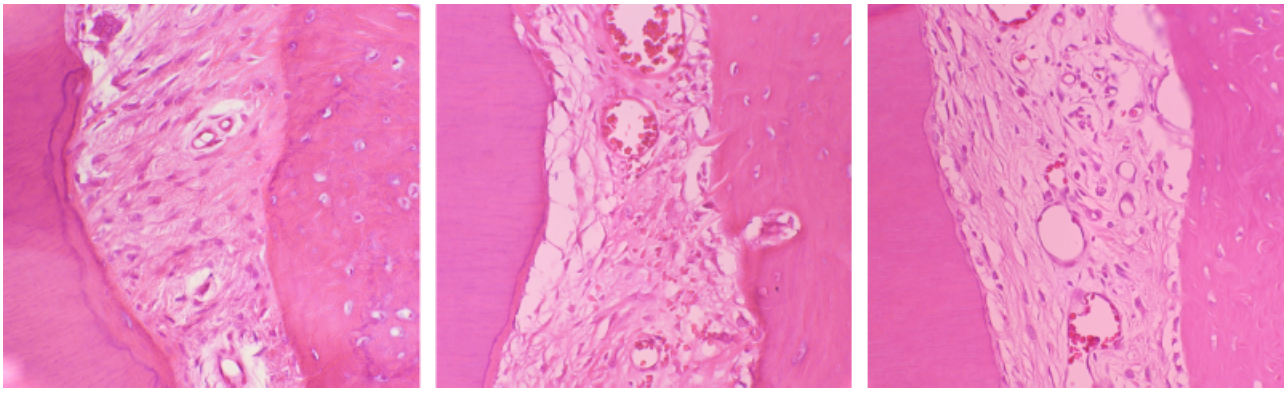

Fig. 4. Photomicrographs from sites implanted with recombinant human growth/differentiation factor-5 (rhGDF-5)/β-tricalcium phosphate (β-TCP) (left), β-TCP (centre), and sham-surgery (right). The newly formed periodontal ligament (PDL) appears denser at sites receiving rhGDF-5/β-TCP compared with that at β-TCP and sham-surgery controls; the PDL fibers embedded perpendicularly and obliquely into newly formed cementum and alveolar bone (left). Sites implanted with β-TCP solo show fewer PDL fibers, some apparently arranged parallel to the root surface, some infused into newly formed cementum and alveolar bone (centre). The sham-surgery control shows connective tissue fibres commonly arranged parallel to the root surface (haematoxylin/eosin, original magnification × 200).

connective tissue or the fibrovascular marrow (Figs 3 and 6).

Histometric Observations

The results of the histometric evaluation are shown in Table 1 and Fig. 7. The epithelial attachment averaged 0.65 ± 0.33, 2.64 ± 0.83, and 0.74 ± 0.50 mm for the rhGDF-5/*β*-TCP group, and the *β*-TCP and sham-surgery controls, respectively; the *β*-TCP control exhibiting a significantly extended epithelial attachment compared with the rhGDF-5/*β*-TCP group and sham-surgery control ($p < 0.05$). A non-specific connective tissue attachment of variable extension was observed in all sites irrespective of the treatment and with no clear distinction between treatments.

Cementum regeneration averaged 3.83 ± 0.73, 1.65 ± 0.82, and 2.48 ± 1.28 mm for the rhGDF-5/*β*-TCP group, the *β*-TCP, and sham-surgery controls, respectively. The rhGDF-5/*β*-TCP group showed significantly greater cementum formation compared with the *β*-TCP group ($p < 0.05$).

Bone regeneration (height) averaged 3.26 ± 0.30, 1.70 ± 0.66, and 1.68 ± 0.49 mm for rhGDF-5/*β*-TCP group, and *β*-TCP and sham-surgery controls, respectively. The rhGDF-5/*β*-TCP group exhibited significantly greater bone formation compared with *β*-TCP and sham-surgery control ($p < 0.05$). Moreover, bone regeneration area was significantly enhanced for the rhGDF-5/*β*-TCP group compared with the *β*-TCP and sham-surgery con-

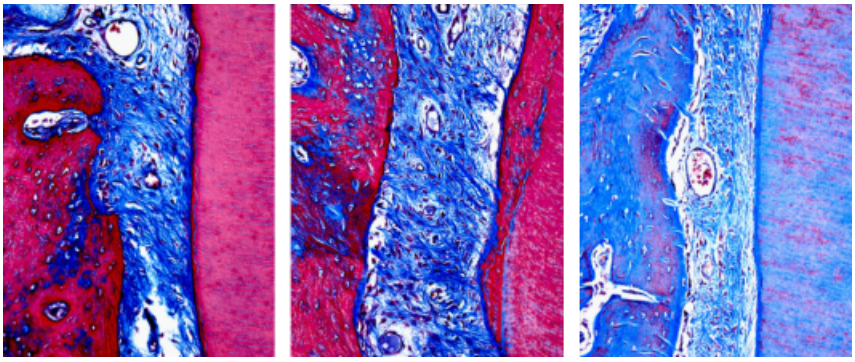

Fig. 5. Photomicrographs from sites implanted with recombinant human growth/differentiation factor-5 (rhGDF-5)/β-tricalcium phosphate (β-TCP) (left). Newly formed periodontal ligament (PDL) appears dense and the PDL fibres embedded perpendicularly and obliquely into newly formed cementum and alveolar bone. β-TCP (centre) showing moderate fibre density, some arranged oblique to the root surface. Sham surgery control (right) showing low PDL fibre density and connective tissue fibres commonly arranged parallel to the root surface. (Masson's trichrome stain, original magnification × 200).

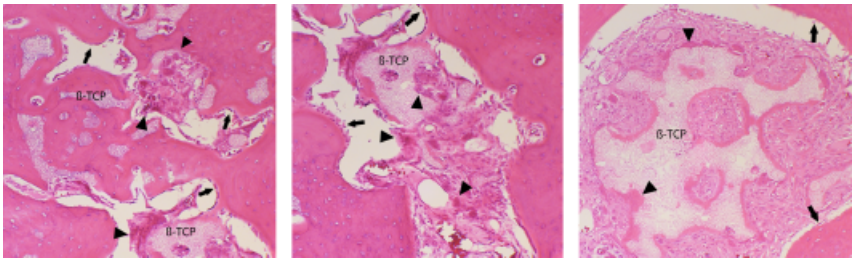

Fig. 6. Photomicrographs from sites implanted with recombinant human growth/differentiation factor-5/β-tricalcium phosphate (β-TCP) showing residual β-TCP in remodelling and incorporation phase (left and centre). Numerous osteoclasts (arrow head) and osteoblasts (arrow) are shown around residual β-TCP particles. The right photomicrograph shows a site implanted with β-TCP solo showing residual β-TCP encapsulated in fibrovascular tissue including numbers of osteoclasts and osteoblasts (hematoxylin/eosin, original magnification × 100).

Table 1. Histometric analysis (group means ± SD in mm/mm^2)

	rhGDF-5/β-TCP	β-TCP	Sham-surgery
Defect height	4.58 ± 0.54	4.86 ± 0.38	4.69 ± 0.36
Epithelial attachment	0.65 ± 0.33†	2.64 ± 0.83	0.74 ± 0.50†
Connective tissue attachment	0.10 ± 0.10	0.57 ± 0.90	1.47 ± 1.42$^{\#}$
Cementum regeneration	3.83 ± 0.73†	1.65 ± 0.82	2.48 ± 1.28
Bone regeneration (height)	3.26 ± 0.30*†	1.70 ± 0.66	1.68 ± 0.49
Bone regeneration (area)	10.45 ± 2.26*†	6.31 ± 2.41*	3.00 ± 1.97

$^{*}p<0.05$ compared with sham-surgery.
$^{\dagger}p<0.05$ compared with β-TCP.
$^{\#}p<0.05$ compared with β-TCP and rhGDF-5/β-TCP.
TCP, tricalcium phosphate; rhGDF-5, recombinant human growth/differentiation factor-5.

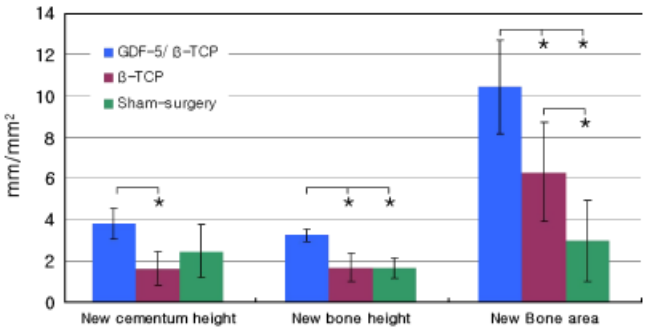

Fig. 7. Main results from the histometric analysis ($^{*}p<0.05$). GDF-5, growth/differentiation factor-5; β-TCP, β-tricalcium phosphate.

trols ($p<0.05$), the β-TCP control also exhibiting significantly enhanced bone formation compared with the sham-surgery control ($p<0.05$), the corresponding values being 10.45 ± 2.26, 6.31 ± 2.41, and 3.00 ± 1.97 mm^2.

Discussion

Evaluation of candidate technologies for periodontal regeneration ultimately commands analysing all components of the periodontal attachment. The canine one-wall intrabony defect model used herein allows an evaluation of the alveolar bone, cementum, PDL, and gingival tissues. Previous studies have used this defect model for the evaluation of a variety of biomaterials and regenerative techniques (Kim et al. 2002, 2004, 2005, Park et al. 2003, Song et al. 2005, Yeo et al. 2005). The present study shows that one-wall intrabony defects implanted with rhGDF-5/β-TCP exhibit enhanced regeneration of the periodontal attachment compared with sites receiving the β-TCP carrier or sham-surgery control. Importantly, regeneration of the periodontal tissues progressed without adverse tissue reactions with the apparently discrete exception for root resorption/ankylosis in one site receiving rhGDF-5/β-TCP.

This study showed increased bone formation in one-wall intrabony defect sites implanted with rhGDF-5/β-TCP compared with that in sites implanted with β-TCP alone or sham-surgery. The newly formed bone approached the preoperative level of the alveolar bone, approximately 1 mm apical to the CEJ. In contrast, the sham-surgery group showed minimal bone formation. Similarly, sites implanted with β-TCP alone exhibited limited linear bone formation along the root surface; however, bone regeneration area was significantly increased compared with the sham-surgery control, demonstrating an osteoconductive potential of the particulate β-TCP biomaterial. In vitro studies suggest that rhGDF-5 promotes osteogenic differentiation of stromal cells (Shen et al. 2006, Zeng et al. 2007). In addition to direct effects on cell differentiation and proliferation, rhGDF-5 induces angiogenesis in vitro and in vivo (Yamashita et al. 1997, Zeng et al. 2007). Angiogenesis and vascular invasion are important steps in the sequential cascade of bone formation (Reddi 1992). In the present study, both effects, promoting differentiation at cellular level and angiogenesis at tissue level, might have supported bone formation.

Cementum regeneration appeared mostly cellular but also included acellular cementum. Newly formed cellular cementum exhibited features of a mixed (intrinsic/extrinsic) fibre cementum with a low- to medium-density PDL, occasionally reaching the same density as the native PDL following the 8-week healing interval. Previous studies have described a uniformly thin and acellular mineralized tissue on the denuded dentin surfaces (Lindskog & Blomlöf 1992, Miyaji et al. 2006). Formation of this mineralized tissue has been suggested to be dependent on initial resorption of the dentin surface, and BMPs may promote this resorption and cementum formation by facilitating osteoclastic effects (Wikesjö et al. 1992, Miyaji et al. 2006). In this study, sites receiving rhGDF-5/β-TCP exhibited significantly greater cementum regeneration than that observed in the β-TCP control pointing to stimulating effects on migration and proliferation of cells from the PDL and, in addition potentially pointing to an effect of initial dentin surface resorption.

A newly formed PDL was observed between the cementum and new bone along the defect root surface. The PDL could be considered immature, as it was not as dense as the adjoining pristine PDL. The collagenous fibres were embedded perpendicularly or obliquely to the cementum. Sites implanted with rhGDF-5/β-TCP showed a denser PDL than that observed in the sham-surgery control, which displayed a looser connective tissue with few fibres inserting into newly formed bone and cementum. These observations suggest that rhGDF-5 might enhance regeneration of all components of the periodontal attachment including cementum, alveolar bone and PDL.

Conclusion

The results in the present study suggest that rhGDF-5 in a particulate β-TCP carrier has a greater potential to support periodontal regeneration. Long-term studies are necessary to confirm the uneventful maturation of the regenerated tissues.

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Clinical Relevance

Scientific rationale for the study: rhGDF-5 is being evaluated as a candidate therapy for periodontal wound healing/regeneration. The objective of this study was to evaluate cementum and alveolar bone formation, and aberrant healing events following surgical implantation of rhGDF-5 in a β-TCP carrier using an established canine periodontal defect model.

Principal findings: Sites implanted with rhGDF-5/β-TCP exhibited greater enhanced cementum and bone formation compared with β-TCP and sham-surgery controls in one-wall intrabony defects in dogs.

Practical implications: The rhGDF-5/β-TCP construct appears to be a promising technology in support of periodontal wound healing/regeneration motivating clinical evaluation.