Tissue Engineering with Recombinant Human Bone Morphogenetic Protein-2 for Alveolar Augmentation and Oral Implant Osseointegration: Experimental Observations and Clinical Perspectives*

Ulf M. E. Wikesjö, DDS, PhD; Giuseppe Polimeni, DDS, MS; Mohammed Qahash, DDS, MS

ABSTRACT

Surgical placement of oral implants is governed by the prosthetic design and by the morphology and quality of the alveolar bone. Nevertheless implant placement often appears difficult, if at all possible, due to aberrations of the alveolar ridge. Hence prosthetically dictated implant positioning often entails augmentation of the alveolar ridge and adjoining structures. In this review we discuss recent observations of the biologic potential, clinical relevance, and perspectives of application of recombinant human bone morphogenetic protein-2 (rhBMP-2) technologies for alveolar bone augmentation and oral implant osseointegration. Using discriminating critical-size supraalveolar defects and clinical modeling in dogs, we show that rhBMP-2 has a substantial potential for augmenting alveolar bone and supporting osseointegration of titanium oral implants. Moreover, using clinical modeling, we demonstrate re-osseointegration in advanced periimplantitis defects and long-term functional loading of titanium oral implants placed into rhBMP-2-induced bone. Our studies suggest that inclusion of rhBMP-2 for alveolar bone augmentation and oral implant fixation will not only enhance the predictability of existing clinical protocol but also allow new approaches to these procedures.

KEY WORDS: alveolar augmentation, animal models, BMP, bone morphogenetic protein, dental implants, osseointegration, tissue engineering

Over the last several decades, titanium oral implants have been successfully introduced into the clinical protocol and implemented for a number of indications including partial and complete edentulism and for maxillofacial reconstruction. One major factor influencing the outcome of this therapy is osseointegration (ie, the establishment of immediate bone-implant contact to provide bone anchorage for functional loading of the titanium implant). In perspective the classic concept of bone-driven implant placement has today been revised and in part replaced by a concept of prosthetically driven implant placement. This concept can be of fundamental importance when aesthetic areas are treated. However, insufficient quantity of bone due to periodontal bone loss, traumatic tooth extractions, and/or long-term use of removable dentures may impair a prosthetically ideal implant position. To overcome this predicament a variety of surgical techniques aiming at local augmentation of the alveolar ridge and adjoining structures have been proposed and brought into practice. The objective of this review is to

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discuss the biologic potential, clinical relevance, and perspectives of recombinant human bone morphogenetic protein-2 (rhBMP-2) technologies for alveolar bone augmentation.

REQUIREMENTS FOR ALVEOLAR BONE AUGMENTATION

Numerous surgical techniques and technologies have been suggested, evaluated, and brought into clinical practice in the recent past. Too often clinicians have been faced with the dilemma of selecting one therapy over another from a large assortment of candidate therapies. The decision-making process becomes even more delicate if one considers that scientific support is often limited and that evidence-based comparisons of therapies are rare. To avoid uncertainty surgical therapy/technology for alveolar bone augmentation should be

- based on convincing scientific evidence;
- effective for clinically relevant bone augmentation;
- consistent, for reproducible performance;
- easy to learn and use (ie, foolproof); and
- safe, having only minimal or acceptable adverse effects, if any.

PRECLINICAL MODELS FOR ALVEOLAR BONE AUGMENTATION

The search for effective and safe therapies for bone reconstruction requires preclinical evaluation to estimate their biologic potential, efficacy, and safety prior to their introduction and clinical application. Candidate therapies should first be evaluated for biologic potential and safety in well-characterized rodent *Screening Models*.[1,2] Therapies that show biologic potential and appear to be safe should be evaluated for clinical potential and efficacy using discriminating preclinical models (designated as *Critical-Size Defect Models*) in large animals, including canines or nonhuman primates. Critical-size defects are defects that must not spontaneously regenerate following reconstructive surgery without adjunctive measures.[3] Critical-size defects must also allow clinically relevant bone regeneration induced or supported by implanted biologics, biomaterials, or devices over bone regeneration in a surgical control.[4] Our laboratories have developed and characterized the *Critical-Size Supraalveolar Periodontal Defect Model* (Figure 1).[5] This model has proven to represent a "litmus test" for candidate therapies for periodontal regeneration.[4] Subsequently we modified the supraalveolar periodontal defect model to study regeneration of alveolar bone and oral implant osseointegration and thus introduced the *Critical-Size Supraalveolar Peri-Implant Defect Model* (see Figure 1).[4]

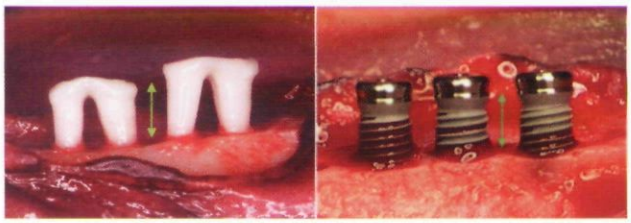

Figure 1 *Left*, Critical-Size Supraalveolar Periodontal Defect Model. The crowns of the third and fourth mandibular premolar teeth in the dog have been reduced in height to just above the crown margin. The alveolar bone has been reduced 6 mm in height around the premolar teeth, creating defect dimensions of clinical relevance (the first and second premolar teeth have been extracted, and the first molar has been reduced to the level of the alveolar bone). *Right*, Critical-Size Supraalveolar Peri-implant Defect Model. The third and fourth mandibular premolar teeth have been extracted and replaced with three 10 mm titanium oral implants inserted 5 mm into the reduced alveolar crest, creating 5 mm discriminating supraalveolar peri-implant defects. For both models experimental treatments (bone derivatives/substitutes, devices, biologics, or combinations thereof) are placed/molded around the teeth/implants. The mucoperiosteal flaps are then advanced and sutured to cover the teeth or implants for optimized healing conditions.

Once a candidate therapy has an established record of biologic potential and safety and a clinically relevant effect in a discriminating large-animal model, it may become subject to clinical modeling. Clinical-type defects that may not necessarily be discriminating critical-size defects but are recognized as difficult to manage successfully are produced in large animals to evaluate the efficacy and application of a candidate therapy. Examples of clinical modeling used to evaluate rhBMP-2 in the craniofacial skeleton include mandibular segmental defect reconstruction,[6–9] cleft palate reconstruction,[10–12] zygoma bone gap reconstruction,[13] subantral augmentation,[14,15] alveolar ridge augmentation,[16–23] peri-implantitis defect reconstruction,[18] and oral implant functional loading.[19] In the following we present studies evaluating the effect of rhBMP-2 in discriminating critical-size defect models and using clinical modeling.

ALVEOLAR AUGMENTATION AND ORAL IMPLANT OSSEOINTEGRATION

Sigurdsson and colleagues[24] first demonstrated that an rhBMP-2 construct used as an onlay induced significant alveolar bone augmentation (Figure 2). Titanium

10 mm oral implants were inserted 5 mm into the surgically reduced edentulous mandibular ridge in five beagle dogs, creating 5 mm critical-size supraalveolar periimplant defects; rhBMP-2 (at 0.4 mg/mL; Wyeth Research, Cambridge, MA, USA) in an absorbable collagen sponge carrier (ACS; Helistat™, Integra Life Sciences, Plainsboro, NJ, USA) or buffer/ACS (control) was implanted into the periimplant defects in contralateral jaw quadrants. The animals were euthanized for histometric evaluation of the implant sites after a 16-week healing interval. Defects that received rhBMP-2 exhibited significant vertical alveolar ridge augmentation along the exposed implant when compared to defects that received the control (4.2 $\pm$ 1.0 mm vs 0.5 $\pm$ 0.3 mm, $p < .002$). However, the rhBMP-2–induced bone often constituted only a thin layer on the titanium implant surface. Apparently the ACS carrier was ineffective in predictably producing a space for adequate rhBMP-2–induced bone formation. Indeed the newly formed bone exhibited osseointegration to the titanium implant; however, bone-implant contact was (as may be expected) lower than that in resident alveolar bone after the relatively short healing interval.

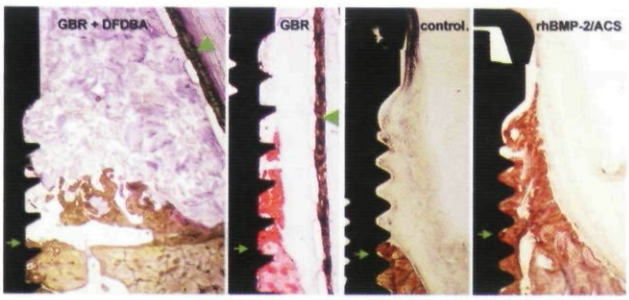

Figure 2 Photomicrographs from 16 weeks postsurgery show critical-size supraalveolar periimplant defects receiving guided bone regeneration (GBR) with a purpose-designed GBR expanded polytetrafluoroethylene membrane (*green arrowheads*) combined with decalcified freeze-dried bone allograft (DFDBA) matrix versus GBR alone, or implanted with recombinant human bone morphogenetic protein-2 in an absorbable collagen sponge carrier (rhBMP-2/ACS) versus ACS alone (control). Compare and contrast the regenerative potential of alveolar bone following the various protocols. Notably, the physiologic concentration of bone growth factors including bone morphogenetic proteins sequestered in DFDBA has no obvious effect on alveolar regeneration, the DFDBA particles being invested in fibrous connective tissue without apparent evidence of bone metabolic activity. Only pharmacologically relevant concentrations of rhBMP-2 support meaningful alveolar augmentation. The healing interval was 16 weeks. *Green arrows* delineate the apical extension of the supraalveolar periimplant defect. (Reproduced with permission from Sigurdsson TJ et al[24]; Caplanis N et al.[25])

The observations by Sigurdsson and colleagues[24] appear even more significant when compared with those of Caplanis and colleagues,[25] who evaluated the surgical implantation of decalcified freeze-dried bone allograft (DFDBA) in conjunction with guided bone regeneration (GBR) or GBR alone in the same discriminating animal model; both treatment concepts are common in today's clinical practice. In each of five beagle dogs, contralateral 5-mm critical-size supraalveolar periimplant defects including two titanium oral implants were implanted with (1) a purpose-designed GBR expanded polytetrafluoroethylene (ePTFE) membrane (W.L. Gore & Associates Inc., Flagstaff, AZ, USA) and DFDBA re-hydrated in autologous blood or (2) the GBR membrane alone. Tissue blocks including the implant sites were harvested and prepared for histometric analysis following a 16-week healing interval (see Figure 2). The DFDBA biomaterial was discernible in all defect sites that received this treatment. DFDBA particles appeared solidified within a dense connective tissue matrix and in close contact to the titanium implant surface, without evidence of osseointegration. Vertical alveolar ridge augmentation along the implant surface was limited to 1.5 $\pm$ 0.9 mm and 1.1 $\pm$ 0.4 mm for the GBR/DFDBA combination and for GBR alone, respectively. There were no significant differences between experimental conditions for any parameter examined. Notably, physiologic concentrations of bone growth factors and bone morphogenetic proteins (BMPs) sequestered in the DFDBA matrix had no relevant effect on alveolar bone augmentation, given that the DFDBA particles were invested in fibrous connective tissue without apparent evidence of bone metabolic activity. The results suggest that DFDBA has no relevant osteoinductive, osteoconductive, or other adjunctive effect to GBR, and that GBR membranes have a limited potential for augmenting alveolar bone, at least when used for onlay indications. Only pharmacologic concentrations of rhBMP-2 have been shown to support meaningful alveolar bone augmentation in this discriminating defect model.

Other studies using the supraalveolar periodontal defect model have shown that gingival connective tissue occlusion is not an absolute requirement for periodontal regeneration including alveolar bone.[26–28] Similar amounts of alveolar bone regeneration have been observed in periodontal defects implanted with occlusive and open-structure porous ePTFE devices.[26] Thus for the next set of studies, we designed a

macro-porous (ePTFE) GBR device to support bone formation induced by rhBMP-2 in an ACS carrier. The concept behind the design was to provide an unobstructed space to obviate compression of the rhBMP-2/ACS construct and also to allow vascularity from the gingival connective tissue to support rhBMP-2 bone induction (Figure 3). Bilateral critical size supraalveolar periimplant defects were created in eight hound-Labrador mongrel dogs.[29,30] Each defect/jaw quadrant included two turned and one acid-etched titanium implant. Four animals received the space-providing dome-shaped porous GBR device or rhBMP-2/ACS (0.4 mg of rhBMP-2; total implant volume, 2.0 mL) combined with the porous GBR device in contralateral jaw quadrants, and four animals received rhBMP-2/ACS (0.4 mg of rhBMP-2; total implant volume, 2.0 mL) alone or rhBMP-2/ACS (0.4 mg of rhBMP-2; total implant volume, 0.3 mL) combined with the porous device in contralateral jaw quadrants. The animals were euthanized at 8 weeks postsurgery for histometric analysis of the implant sites. This study showed that GBR used alone enhanced bone formation to a limited degree, similar to what was observed by Caplanis and colleagues.[26] Vertical bone gain at turned and acid-etched oral implants averaged 1.8 ± 2.0 mm and 1.3 ± 1.3 mm, respectively, and new bone area measured 1.8 ± 1.3 mm^2 and 1.2 ± 0.6 mm^2, respectively.[29] Moreover, as observed by Sigurdsson and colleagues,[25] jaw quadrants receiving rhBMP-2/ACS alone showed significant augmentation of the alveolar ridge; however, the geometry of the induced alveolar bone was irregular. Vertical bone gain averaged 3.5 ± 0.9 mm and rhBMP-2- induced bone area 7.5 ± 6.2 mm^2 at the turned oral implants.[30] In contrast the combination of the dome-shaped space-providing porous GBR device and rhBMP-2/ACS predictably resulted in the formation of alveolar bone filling the large space provided by the GBR device, irrespective of whether the rhBMP-2 implant originally filled the wound space provided device or occupied only a fraction of the space.[29,30] Vertical bone gain at turned implants averaged 4.7 ± 0.2 mm at sites receiving rhBMP-2/ACS and the GBR device, and the rhBMP-2/ACS-induced bone area averaged 9.6 ± 0.7 mm^2. There was a highly significant correlation between induced bone area and the space provided by the GBR device ($p < .001$).[30] The newly formed bone provided osseointegration without remarkable differences between turned and acid-etched titanium implants. This study provides an important insight in tissue-engineering principles using BMPs, namely, that adequate space provision appears to be critical to drawing clinically significant benefits from the BMP implant.

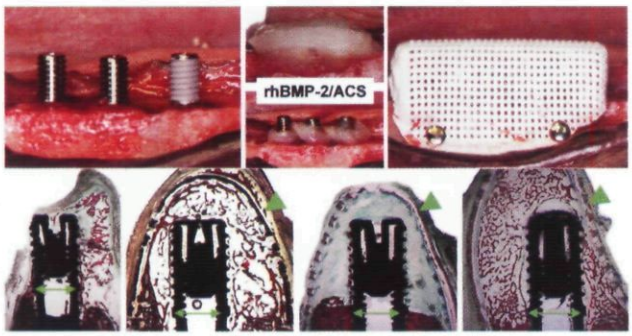

Figure 3 Clinical illustrations showing supraalveolar periimplant defects including two turned oral implants and one acid-etched titanium oral implant. Contralateral defect sites in four animals received recombinant human bone morphogenetic protein-2 (rhBMP-2) (1.4 mg/mL implant volume) in an absorbable collagen sponge (ACS) carrier in combination with a porous space-providing guided bone regeneration (expanded polytetrafluoroethylene) device (*green arrowheads*) versus rhBMP-2 (0.2 mg/mL implant volume) in ACS alone (total dose/defect, 0.4 mg rhBMP-2). Contralateral defect sites in four additional animals received rhBMP-2 (0.2 mg/mL implant volume) in ACS (rhBMP/ACS) in combination with the space-providing GBR device (total dose/defect, 0.4 mg rhBMP-2) versus the GBR device plus ACS alone. Note the irregular bone formation in sites receiving rhBMP-2/ACS alone (*far left*) versus bone formation conforming to the space provided by the GBR device in sites receiving the rhBMP-2/ACS plus GBR combination (*left center*). The right center photomicrograph shows limited (if any) bone regeneration following implantation of the GBR device without rhBMP-2 versus bone formation filling the space provided by the GBR device in sites receiving the rhBMP-2/ACS plus GBR combination (*far right*). The healing interval was 8 weeks. *Green arrows* delineate the apical extension of the supraalveolar periimplant defect. (Reproduced with permission from Wikesjö UME et al[29]; Wikesjö UME et al.[30])

In other studies, rhBMP-2 constructs have been evaluated for inlay indications using intrabony defect models. Jovanovic and colleagues[23] showed rhBMP-2/ACS to be an effective treatment when implanted into space-providing alveolar ridge defects. Combining rhBMP-2/ACS with GBR provided no additional value. Surgically created mandibular full-thickness 15 × 10 mm saddle-type alveolar ridge defects (two defects per jaw quadrant) in seven hound dogs were randomly assigned to receive rhBMP-2/ACS, rhBMP-2/ACS combined with GBR (rhBMP-2 at 0.2 mg/mL), or control treatments. The GBR protocol used traditional occlusive (ePTFE) GBR membranes. The animals were euthanized at 12 weeks postsurgery, for histologic evaluation. Postsurgical complications included wound failure in as

many as 44% of the defects that received the occlusive GBR membranes with or without rhBMP-2. Histologic analysis revealed bone fill averaging 101% for defects that received rhBMP-2/ACS or rhBMP-2 combined with GBR (without wound failure) and 92% for defects receiving GBR alone (without wound failure). Bone fill for the surgical control averaged 60%, revealing the strong healing potential in this type of intrabony defect following flap surgery alone. Cochran and colleagues[16] made similar observations in more limited intrabony defects. Bilateral 4-mm intrabony defects were surgically created around endosseous oral implants in the edentulous mandible in six foxhounds. rhBMP-2/ACS (rhBMP-2 at 0.2 mg/mL) or buffer/ACS (control) was placed into the defects. Half of the defect sites were additionally prepared for GBR by the use of traditional occlusive (ePTFE) GBR membranes. The animals were euthanized at 4 weeks and 12 weeks postsurgery. Implantation of rhBMP-2 resulted in enhanced defect resolution compared to control (47% vs 34%) as early as 4 weeks postsurgery.

The observations above demonstrate that rhBMP-2 may be used to augment alveolar bone when used as an onlay and as an inlay. The observations also point to the importance of space provision for rhBMP-2–induced bone formation. Supraalveolar defects (onlay indications) such as the critical-size periimplant defect model may require rhBMP-2 constructs that exhibit structural integrity providing space for alveolar augmentation or may need to be combined with suitable space-providing devices to optimize bone formation. In contrast, space-providing intrabony defects (inlay indications) such as the saddle-type defect and the intrabony periimplant defect described above may be treated successfully with rhBMP-2 constructs with lesser biomechanical properties. The use of standard GBR membranes does not provide additional value to the rhBMP-2 technology. Notably, occlusive GBR devices or membranes such as those described above may decelerate BMP-induced bone formation[16,31] as well as readily become exposed, thereby compromising overall wound healing.[23]

Two recent studies have evaluated rhBMP-2 candidate carriers that exhibit structural integrity suitable for alveolar onlay indications. Sigurdsson and colleagues[32] showed that rhBMP-2 in an allogeneic freeze-dried demineralized bone matrix (DBM)/autologous blood carrier might have substantial clinical utility for augmenting demanding alveolar ridge defects and for allowing early placement and osseointegration of oral implants. Bilateral critical-size (5–6 mm) supraalveolar ridge defects in five beagle dogs received unsupported rhBMP-2/DBM/blood onlays (rhBMP-2 at 0.2 mg/mL). Non-submerged 10 mm oral implants were placed into the rhBMP-2–induced alveolar ridge at weeks 8 and 16 postsurgery. The animals were euthanized for histometric evaluation of the implant sites at week 24 postsurgery. Approximately 90% of the bone-anchoring surface of the implants was invested in rhBMP-2–induced bone. Similar levels of bone-implant contact (approximately 55%) were observed in induced and resident bone, irrespective of the osseointegration interval (8 or 16 weeks). There was no significant difference in bone density between rhBMP-2–induced bone and resident bone. However, the use of cadaver material such as allogeneic freeze-dried DBM may have difficulty finding public acceptance; thus synthetic carrier technologies for alveolar indications need to be explored. In a subsequent study, Wikesjö and colleagues[33] showed that surgical implantation of rhBMP-2 in a synthetic calcium phosphate cement carrier (α-BSM®, Etex Corporation, Cambridge, MA, USA) appears to be an effective protocol for vertical alveolar ridge augmentation procedures and immediate titanium implant osseointegration (Figure 4). Six adult hound-Labrador mongrel dogs with 5 mm critical-size supraalveolar periimplant defects were used. Three animals received

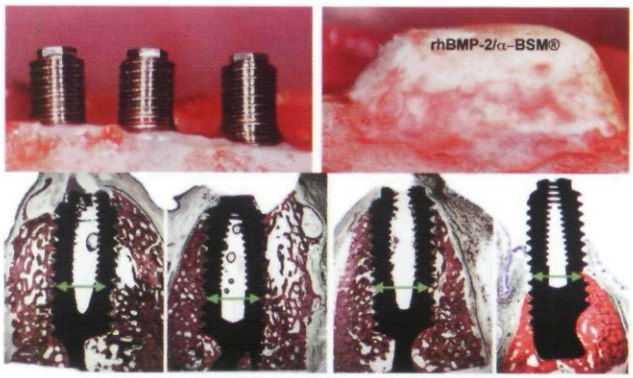

Figure 4 Clinical illustrations showing supraalveolar periimplant defects including three titanium oral implants. The defect sites received recombinant human bone morphogenetic protein-2 (rhBMP-2) at 0.4 mg/mL in a calcium phosphate putty (α-BSM®). Note the robust bone formation and osseointegration in sites receiving rhBMP-2/α-BSM® versus that observed at sites receiving α-BSM® alone (*lower right*). The healing interval was 16 weeks. *Green arrows* delineate the apical extension of the supraalveolar periimplant defect. (Reproduced with permission from Wikesjö UME et al.[33])

rhBMP-2/α-BSM® (rhBMP-2 at 0.40 or 0.75 mg/mL) in contralateral jaw quadrants (total implant volume per defect, approximately 1.5 mL). Three animals received α-BSM® without rhBMP-2 (control). The animals were euthanized at 16 weeks postsurgery, and block biopsy specimens were processed for histologic and histometric analysis. rhBMP-2/α-BSM® induced substantial augmentation of the alveolar ridge. Control sites exhibited limited new bone formation. Vertical bone augmentation averaged 4.9 ± 1.0 mm (for rhBMP-2 at 0.40 mg/mL), 5.3 ± 0.3 mm (for rhBMP-2 at 0.75 mg/mL), and 0.4 ± 0.4 mm (for control); new bone area averaged 8.5 ± 4.2 mm^2, 9.0 ± 1.9 mm^2, and 0.5 ± 0.4 mm^2, respectively; new bone density averaged 55.1 ± 6.4%, 61.1 ± 6.0%, and 67.7 ± 9.5%, respectively; and new bone-implant contact averaged 26.9 ± 17.5%, 28.5 ± 1.4%, and 24.6 ± 16.1%, respectively. Residual α-BSM® made up < 1% of the new bone. Bone density for the contiguous resident bone ranged from 65 to 71%, and bone-implant contact ranged from 49 to 64%. This novel technology shows considerable promise for a number of clinical indications since the α-BSM® putty may be easily shaped to desirable contours and sets to provide space for rhBMP-2–induced bone formation. Moreover, the α-BSM® putty is injectable for inlay indications, and its use may well prove to be a formidable technique for augmentation of the maxillary sinus in conjunction with placement of oral implants in the posterior maxilla, predictably pinpointing bone formation at the implant body.

The studies described above all have shown a considerable benefit of rhBMP-2 for alveolar augmentation and for osseointegration of titanium oral implants. It has also been shown that rhBMP-2 supports significant re-osseointegration of titanium implants exposed to long-term periimplant infection (periimplantitis). Hanisch and colleagues[18] were the first to show bone fill and renewed bone-implant contact (re-osseointegration) in bone defects resulting from periimplantitis. Ligature-induced periimplantitis lesions were created around hydroxyapatite-coated titanium oral implants in the posterior mandible and maxilla over a period of 11 months in four adult rhesus monkeys. The induced periimplantitis lesions exhibited a microbiota similar to that of advanced human periimplantitis and periodontal disease and also showed a complex vertical-horizontal defect morphology. At reconstruction the defects were surgically débrided and the implant surfaces properly cleaned prior to the surgical implantation of rhBMP-2/ACS (rhBMP-2 at 0.4 mg/mL). Control defects in contralateral mandibular and maxillary jaw quadrants received buffer/ACS. Histometric analysis performed after a 16-week healing interval revealed a threefold greater vertical bone gain in rhBMP-2–treated defects as compared to the control ($p < .01$). Of importance, the rhBMP-2–treated defects exhibited convincing evidence of re-osseointegration (Figure 5). The results from this demanding nonhuman primate model suggest that surgical implantation of rhBMP-2 may have significant clinical utility in the reconstruction of periimplantitis defects and of alveolar defects of lesser complexity.

A critical test for any technology aimed at alveolar augmentation in support of placement and osseointegration of titanium oral implants is functional loading. In a recent study Jovanovic and colleagues[19] showed that rhBMP-2 induces normal physiologic bone, allowing the installation, osseointegration, and long-term functional loading of titanium oral implants. Mandibular alveolar-ridge full-thickness 15 × 10 mm saddle-type defects, two per jaw quadrant, were surgically created in each of six young adult American foxhounds. The defects were immediately implanted with rhBMP-2/ACS (rhBMP-2 at 0.2 mg/mL). Healing was allowed to progress for 3 months, at which time turned titanium oral implants were installed into the rhBMP-2–induced

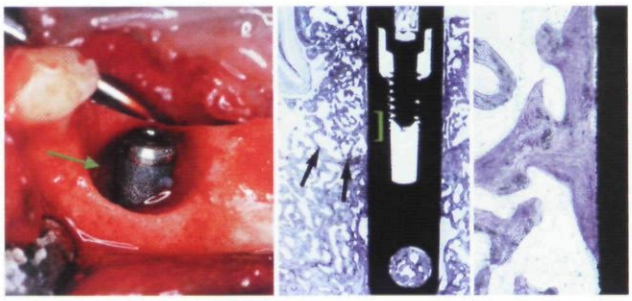

Figure 5 Clinical view (*left*) after surgical exposure and débridement of a periimplantitis defect; the *green arrow* indicates the site shown in the accompanying photomicrographs. Photomicrograph (*center*) shows the defect site following implantation of recombinant human bone morphogenetic protein-2 (0.4 mg/mL implant volume) in an absorbable collagen sponge carrier and a 16-week healing interval. Extensive new bone formation approaching the top surface of the titanium implant can be observed. *Black arrows* delineate the base of the defect. Also note re-osseointegration to the previously exposed implant surface (*right*, high magnification of bracketed area of photomicrograph at center). (Reproduced with permission from Hanisch O et al.[18])

bone and into the adjacent resident bone. After 4 months of osseointegration, the implants were exposed to receive abutments and prosthetic reconstruction. The prosthetically reconstructed implants were exposed to functional loading for 12 months; the animals were then euthanized for histometric analysis. The rhBMP-2–induced bone exhibited features of the resident bone, including a re-established cortex. Implants exposed to functional loading for 12 months exhibited some crestal resorption. The implants exhibited a mean bone contact approximating a respectable 50% in rhBMP-2–induced bone and 75% in resident bone. There were no significant differences between implants placed into rhBMP-2–induced bone and those placed into resident bone, for any parameter evaluated. While previous preclinical studies have convincingly demonstrated clinically relevant alveolar bone augmentation following surgical implantation of rhBMP-2 and implant osseointegration, this study was the first to show the functional utility of rhBMP-2–induced bone in implant dentistry.

CONCLUSIONS

Preclinical studies have shown that recombinant human bone morphogenetic protein-2 induces normal physiologic bone in clinically relevant defects in the craniofacial skeleton. The newly formed bone assumes characteristics of the adjacent resident bone and allows the placement, osseointegration/re-osseointegration, and functional loading of titanium oral implants. Clinical studies optimizing dose, delivery technologies, and conditions for stimulation of bone growth will bring about a new era in implant dentistry. The ability to predictably promote osteogenesis through the use of bone morphogenetic protein technologies is not far from becoming a clinical reality and will no doubt have a profound effect on the way in which dentistry is practiced.

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Earlier versions of this text have been published for reviews in journals and book chapters. The text is continuously subject to revisions and updating as new information becomes available in our laboratory.

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