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ORIGINAL ARTICLE

Nikitas Sykaras · Anthony M. Iacopino · Robert G. Triplett · Victoria A. Marker

Effect of recombinant human bone morphogenetic protein-2 on the osseointegration of dental implants: a biomechanics study

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Abstract *Background* Bone augmentation procedures in combination with dental implants enhance osseointegration in areas that demonstrate localized bone deficit. Clinical confirmation of a biomechanically stable interface is essential for functional implant loading. *Purpose:* The aim of this study was to evaluate biomechanically the effect of recombinant human bone morphogenetic protein (rhBMP)-2 on implant osseointegration and correlate it with periotest and radiographic measurements. *Materials and methods:* Hollow cylinder implants were filled with absorbable collagen sponge soaked with rhBMP-2 or left empty and implanted in dog mandibles. The animals were followed for 4, 8, and 12 weeks, periotest assessment was performed at the end of each time interval, and specimens were collected for pullout biomechanical testing and radiographic evaluation of bone-implant contact levels. *Results:* Periotest assessment did not provide evidence of statistically significant differences between the two groups and correlated well with the radiographic bone-implant contact levels. The pullout test revealed a higher correlation between force/displacement and displacement/energy for the experimental group, suggesting that the addition of rhBMP-2 did influence the rate of osseointegration. *Conclusion:* The results from the pullout test support the potential role of rhBMP-2 in clinical applications by promoting a biomechanically mature interface at 12 weeks. However, radiographic and periotest assessment of the bone-implant interface did not provide evidence of the differences observed with biomechanical testing.

Keywords Implant · Osseointegration · Pullout test · Radiographs · Recombinant human bone morphogenetic protein-2

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N. Sykaras
Department of Fixed Prosthodontics, Dental School, Athens University, Athens, Greece

A. M. Iacopino
School of Dentistry, Marquette University, Milwaukee, Wis., USA

R. G. Triplett
Department of Oral and Maxillofacial Surgery and Pharmacology, Baylor College of Dentistry, Texas A and M University System, Health Science Center, Dallas, Tex., USA

V. A. Marker
Consultant, Denver, Colo., USA

N. Sykaras (✉)
Nikis 25 Str., Marousi 15125, Athens, Greece
e-mail: nsykaras@otenet.gr
Tel.: +30-2106800636
Fax: +30-2106800636

Introduction

Endosseous implants are a well-accepted treatment modality in oral and maxillofacial reconstruction, serving as transmucosal fixtures to support single or multiple teeth, complete arch reconstructions, and reconstruct maxillofacial defects [1, 20]. Endosseous dental implants are introduced as artificial structures into sites that are surgically created within mature tissues, and the host tissue response represents a combination of wound healing and bone fracture repair [28].

During the repair process, a sequence of cellular and molecular events is initiated as a response to trauma. Bone modeling and remodeling by existing osteoblasts and osteoclasts will lead to "reorganization" of bone structure to accept the newly inserted implant [29]. At the same time, undifferentiated mesenchymal cells and osteoprogenitor cells begin to proliferate and migrate into the wound site from adjacent marrow, endosteum, and periosteum. These cells will differentiate into osteoblasts under the influence of locally acting growth factors, leading to osteoid production and subsequent mature, mineralized bone [36].

Regulation of bone induction is believed to be controlled by a group of so-called bone morphogenetic proteins (BMPs) [33]. These proteins may be able to induce cytodifferentiation along the osteoblastic lineage, upregulate the osteoblastic features of collagen I production and rate of mineralization, and potentiate the activities of other cytokines [7]. Thus far, at least 18 members have been identified in the BMP family, with BMPs 2 and 3 considered the most active ones. Recombinant DNA technology has allowed production of recombinant human BMP-2 (rhBMP-2) in large quantities, with potential clinical uses in the augmentation or substitution of bone grafts [31]. Results from animal studies [12, 13, 27, 37] and clinical trials in humans [4, 14, 25] have demonstrated the regenerative potential of rhBMP-2 for augmentation of the maxillary sinus floor, alveolar ridge preservation, localized bone regeneration, and periodontal repair.

Bone augmentation procedures are frequently employed to increase bone height and width in areas where implants need to be placed or to fill bone defects often associated with implant insertion. The combination of rhBMP-2 with dental implants in areas that demonstrate localized bone deficits could enhance the clinical applications of osseointegration by promoting a biomechanically stable interface.

Materials and methods

Animal Model

Six male adult dogs (American Foxhound) weighing 25–30 kg were used in the study according to the principles of laboratory animal care (National Institutes of Health publication no. 86-23, revised 1985) and following a protocol approved by the Institutional Animal Care and Use Committee at Baylor College of Dentistry. The study was performed in two phases. In the first, extraction of mandibular premolars bilaterally was performed in all six dogs. In the second phase, placement of dental implants followed. After arrival at the Animal Resource Unit of Baylor College, the animals were quarantined for an acclimation period of 10 days. At the beginning of the first phase, each dog was weighed and given a numbered collar for identification purposes during the study.

Surgical procedures

Initial anesthesia was induced with 20 mg/kg of ketamine HCL i.m. (Fort Dodge Animal Health, Fort Dodge, Ind., USA) and xylazine 2 mg/Kg i.m. (Ben Venue, Bedford, Ohio, USA), and after intubation, general anesthesia was maintained with a mixture of 2% halothane and O_2 at a rate of 1 l/min. The general anesthesia was delivered and monitored under the supervision of an experienced animal technician. Local anesthesia with 2-4 ml of 2% lidocaine HCl with 1:100,000 epinephrine was administered at the surgical site, and full-thickness mucoperiosteal flaps were reflected to expose the anatomic crowns of the teeth.

All mandibular premolars (Fig. 1A) were extracted bilaterally using high-speed carbide burs under constant saline irrigation to separate the crowns to the root furcation level. Silk sutures were used to reposition the flaps and ensure complete coverage of the alveolar bone, followed by periapical radiographs at settings of 15 mA, 75 kVp, and 1/6 s to verify complete tooth removal.

Postoperatively, the animals received a mixture of penicillin G procaine and penicillin G benzathine (300,000 U/ml) at a dose of 1 ml/5 kg body weight i.m. The same dose was repeated after 48 h. Ten milligrams of ibuprofen per kg (Advil) (Whitehall-Robins, Madison, N.J., USA) was also administered p.o. twice a day for 2–3 days. The dogs were placed on a soft-food diet until completion of the study. After a healing period of 8 weeks, lateral radiographs were taken to evaluate the bone quality and quantity, and the animals entered the next study phase.

Implant placement

In the second phase, the animals were premedicated and anesthetized using the same protocol as above, and implant surgery was performed in each of the previously prepared alveolar ridges (Fig. 1b). Each dog was scheduled to receive six implants (three control in one side of the mandible and three experimental in the contralateral side) and followed for 4, 8, and 12 weeks (Table 1). Sides (left, right) and sites (anterior, middle, posterior) were alternatively assigned for each dog.

At baseline, all six dogs were anesthetized. Alveolar crest incisions were made, and full-thickness mucoperiosteal flaps were elevated to expose the sites for implant placement. The osteotomy sites were prepared with a trephine drill under constant saline irrigation following the protocol suggested by the manufacturer (Fig. 1c). Using surgical forceps, the bone core of the trephined osteotomy sites were broken and extracted from the surgical sites for subsequent histologic analysis (Fig. 1d). Following this procedure, titanium, plasma-sprayed, hollow cylinder implants 3.5 mm in diameter and 8 mm in insertion depth (ITI 042.071S) (Straumann, Waltham, Mass., USA) were implanted (control implants), whereas in the contralateral sites the hollow chambers of the implants were filled with a solution of rhBMP-2 (Genetics Institute, Andover, Mass., USA) soaked on absorbable collagen sponges (Helistat) (Colla-Tec, Plainsboro, N.J., USA) (experimental implants) (Fig. 1e). The rhBMP-2 concentration was 0.4 mg/ml, and a total of 20 μg of protein was delivered with each implant (Fig. 1f).

The implants were covered with large closure screws and the flaps were closed with silk sutures, allowing transmucosal penetration of the implant necks. Twelve implants scheduled for the 12-week healing period were inserted in all six dogs at baseline. The sutures were removed 7 days later. Four and 8 weeks after initial implant surgery, the same surgical procedure was followed for the implantation of additional implants in all dogs, 12 each for the 4- and 8-week healing periods (Fig. 2). Thus, at the time of killing, all animals had implants corresponding to the three observation times. The dogs were always on a soft diet and had their teeth and implants rinsed daily with 20–30 ml of 2% chlorhexidine solution (Xttrium, Chicago, Ill., USA). Periapical radiographs of the implant sites were taken immediately after implant placement.

Periotest assessment

Periotest values (PTV) were recorded with the periotest device (Siemens, Bensheim, Germany) for each implant at the time of euthanasia and before specimen collection. The dogs' heads were stabilized in such a way that the occlusal plane was parallel to the surface of the surgical table. The periotest handpiece was held perpendicular to the long axis of the implant body, with the tapping rod against the midfacial area of the implant shoulder at a distance of 0.5 mm to 2.5 mm (Fig. 3). Calibration of the handpiece was performed with the provided calibration sleeve before the first measurement of each implant. Three recordings were collected for each implant, and the average value was designated as the PTV for that implant.

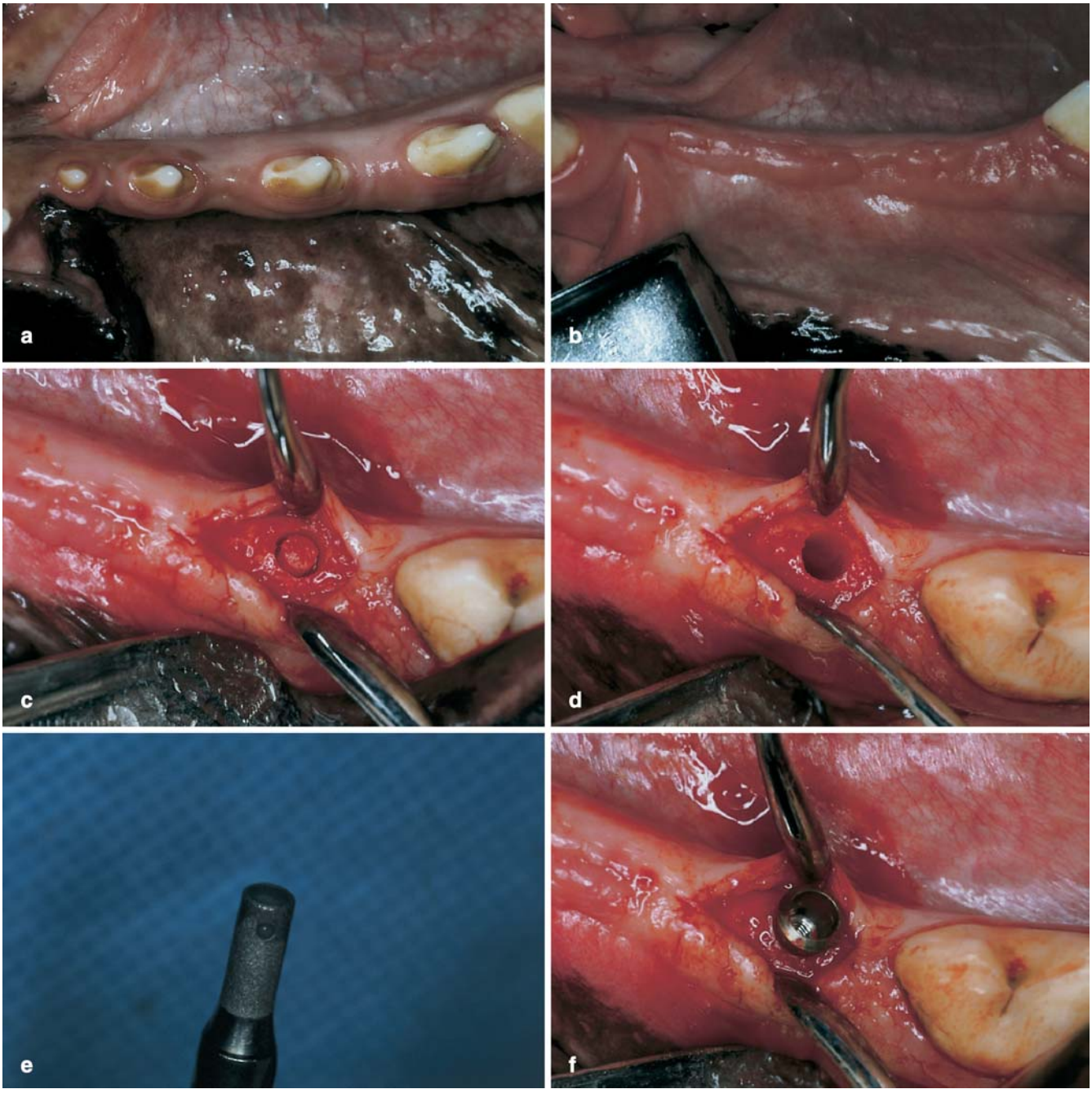

Fig. 1a–f Photographs of the animal operative sites. **a** Pre-extraction site of four mandibular premolars. **b** Alveolar ridge after 8 weeks of post-extraction healing. **c** Initial osteotomy prepared with a trephine drill. **d** Final osteotomy after bone core removal. **e** Hollow cylinder implant loaded with rhBMP-2 absorbed on collagen sponge. **f** Implant installed in osteotomy site

Table 1 Timetable of scheduled implant surgeries. *X* implant surgery, *E* euthanasia

N animals	Implants per observation interval and animal	Total *n* implants per animal	Timing of implant placement			
			Week 0	Week 4	Week 8	Week 12
6	1 control 1 experimental	6	X X	X X	X X	E E

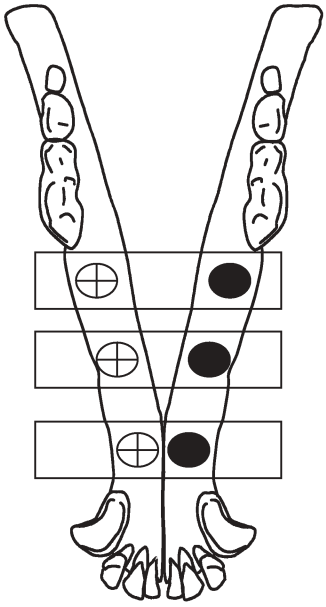

Fig. 2 Schematic representation of implant arrangement for the 4-, 8-, and 12-week intervals in each animal. *Solid circles* rhBMP-2 implants, *crossed circles* controls. Implant sites were alternately assigned for every observation period in each dog

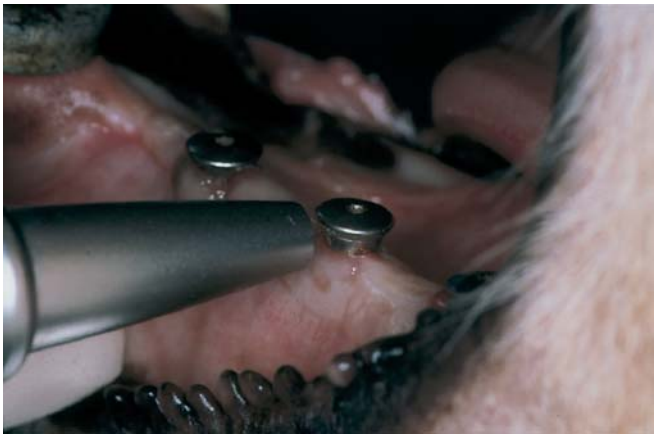

Fig. 3 Periotest handpiece held against implant shoulder

Sacrifice

At the time of killing, the animals were initially anesthetized with 20 mg/kg of ketamine HCl and 2 mg/kg of xylazine i.m., followed by a mixture of 390 mg/ml of phenobarbital sodium and 50 mg/ml of phenytoin sodium (Beuthanasia-D) (Schering-Plough, Kenilworth, N.J., USA) at a dose of 1 ml/5 kg. Then the heads were perfused with 10% buffered formalin at less than systolic pressure through the carotid arteries. The mandibles were removed en bloc using a bone saw (Stryker, Kalamazoo, Mich., USA), and each implant block was separated with a high speed cutting disc under continuous saline irrigation and placed in a numbered container with 10% buffered formalin. The specimen dimensions were 15 mm in length mesiodistally and 6–8 mm in width buccolingually, and they all included the inferior mandibular border.

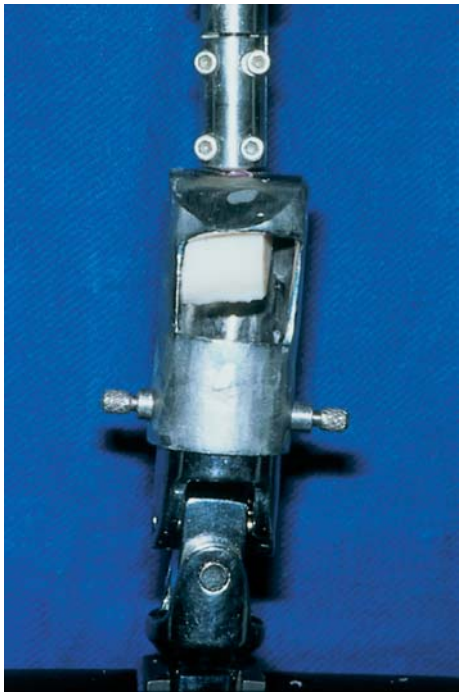

Fig. 4 Assembled custom jig

Radiographs

The specimens were stabilized with a jig so that the plane of the cut surface was perpendicular to the radiographic film and the implant long axis was parallel to the film plane. The radiographic cone was adapted to the other side of the jig with a focus-film distance of 25 cm, directing the X-ray beam perpendicular to the long axis of the implant. The settings of the X-ray machine (GX 700) (Gendex, Milwaukee, Wis., USA) were 15 mA, 75 kVp, and 1/6 s, and a size-2 film of speed D was used (Eastman Kodak, Rochester, N.Y., USA). Radiographic films were developed in the same automatic machine (A/T2000XR) (Air Techniques, Hicksville, N.Y., USA) using fresh chemical solutions. The radiographs were used to calculate bone-to-implant contact in the mesiodistal dimension (sagittal plane).

Biomechanical test

The closure screws were removed from the implants, and the 7-mm long, solid abutments were hand-tightened, having been inserted to prevent possible collapse of the implant necks during the pullout test. All the soft tissue surrounding the necks of the implants was carefully removed with a periosteal elevator. Biomechanical testing was performed with a universal testing machine (model 1011) (Instron, Canton, Mass., USA) within 2 h of the animals' euthanasia. During that time, the specimens were kept at 5°C and immersed in 10% buffered formalin.

A specially designed and custom-built jig was utilized for the pullout test (Fig. 4). It consisted of two members. The lower member was cast in a cobalt-chromium alloy, with a coronal hole oversized by 1 mm allowing the implant neck to pass through. Heavy body impression material was injected onto the bone surface surrounding the implant neck to provide better adaptation of the jig to the specimen and allow more uniform stress distribution. The upper member of the jig was a stainless steel rod with a machined, no. 8 Morse taper, which was formed when its two-part apical end was assembled around the coronal flaring of the implant (Fig. 5) and tightened with four screws. The upper and lower members of the jig were connected to the upper and lower jaws of the Instron

Fig. 5 Photomicrograph of implant's coronal portion with closure screw, demonstrating internal Morse taper and external flaring of the neck (×25)

machine with universal joints to ensure that the long axis of the implant was aligned with the direction of the pull. Calibration of the load cell was performed before each test, and continuous tensile loading was applied at a crosshead speed of 1 mm/min. The testing of each specimen was manually terminated when the load-vs-time curve started to decline.

Variables and statistical analysis

Load-time curves were plotted automatically for each test specimen. These charts were then transferred to a computer with a scanner, and the following parameters were calculated to characterize the bone-implant interface (Fig. 6):

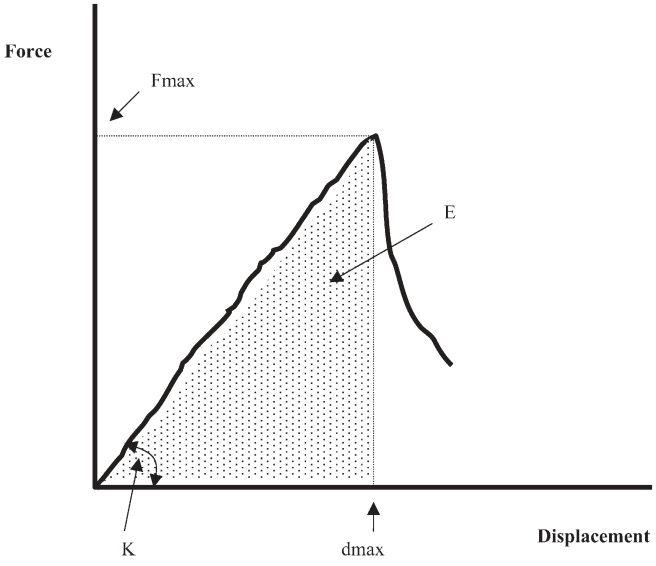

Fig. 6 Force-displacement graph showing the calculated variables

1. Peak force (F_{max} in N) defined as the highest value on the Y axis corresponding to the point where the force-displacement curve started to decline
2. An approximation of the maximum displacement (d_{max} in mm) calculated from the total time to failure and the crosshead speed
3. Interface toughness (E in N/cm) calculated as the area under the force-displacement curve
4. Interface stiffness (K in N/mm) defined as the slope of the linear region of the curve

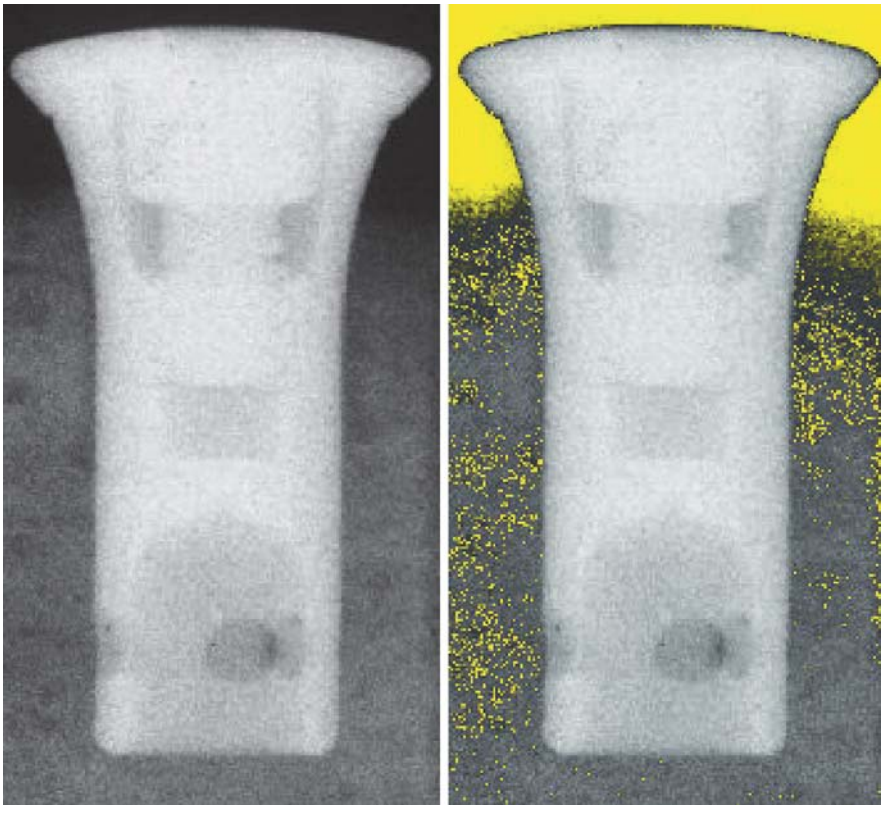

Fig. 7 Example of radiographic histomorphometry. Areas of no contact were detected with a luminance threshold and are colored yellow

All radiographic films were mounted on slide frames and scanned in a 35-mm LS-1000 scanner (Nikon, Japan). The scanning resolution was 9.4-μ^2 per pixel, with a pixel density of 106/mm and 8-bit gray output format. The digitized images were saved as TIFF files and analyzed with Optimas software (Bioscan, Edmonds, Wash., USA). Rectangular ranges of interest (ROI) were selected including the insertion depth of the implant body with surrounding bone. The images were viewed under 200× magnification, and manual sampling outside the specimen boundaries registered ten points of the film area corresponding to the absence of tissue. Their luminance was automatically calculated on a numerical scale of 0–255, and the full range of values was set as the upper and lower threshold limits for detection of void spaces within ROI. Void spaces were colorized, and bone-to-implant contacts were traced and calculated as percentages of total implant insertion length (Fig. 7).

The data were compared using *t*-tests with the level of significance set at $P<0.05$, and Spearman's coefficient analysis was used to determine levels of correlation between the variables.

Results

All dogs healed without any major complications, and a few rhBMP-2 implant sites exhibited some minor inflammatory reaction that was localized in the gingival tissue surrounding the implant necks, lasting for 7–10 days after implantation. At the time of death, ten implants were lost (rejected), and of the remainder, four were associated with large bone defects (fenestrations, dehiscences) and excluded from the biomechanical testing.

Table 2 summarizes the mean values of all variables for the controls and rhBMP-2 implants at 4, 8, and 12 weeks. The mean pullout forces at 4 and 8 weeks had a tendency to be higher for controls than for rhBMP-2 implants, whereas at 12 weeks the latter exhibited a mean peak force of 795 N, vs 618 N for controls. The increase in peak force as a function of time was significant ($P=0.02$) for implants combined with rhBMP-2 but not for controls, and the slope of linear regression for the rhBMP-2 implants at 78.8 N/week was more than three times greater than the slope of 25.1 N/week for the controls (Fig. 8).

When force values were compared with the corresponding displacements, a higher correlation was observed for the rhBMP-2 implants ($r^2=0.92$) than for controls ($r^2=0.40$) (Fig. 9). A similar trend was observed when toughness values were analyzed in relation to displacement, with the rhBMP-2 implants demonstrating a higher correlation ($r^2=0.85$) than controls ($r^2=0.52$) (Fig. 10).

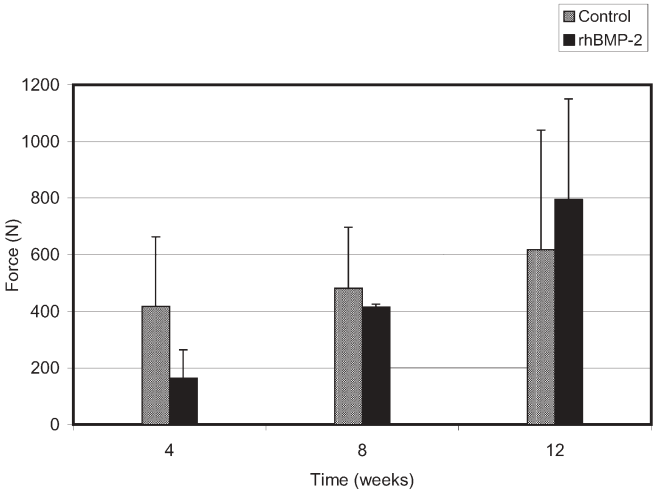

Fig. 8 Mean pullout values and standard deviations at 4, 8, and 12 weeks

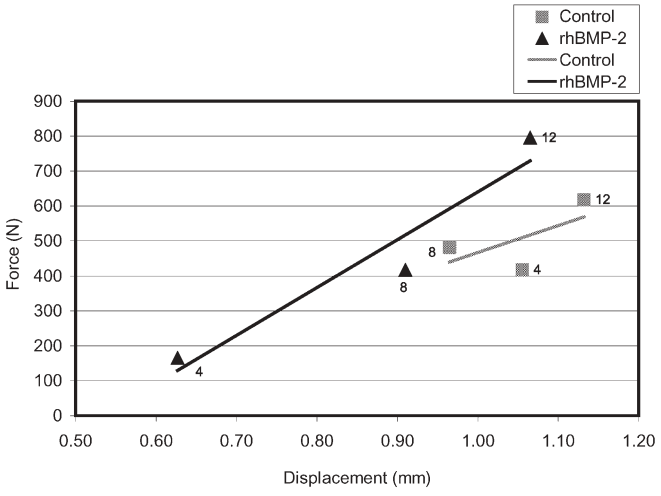

Fig. 9 Force-displacement correlation (control $r^{2=}0.40$, rhBMP2 $r^{2=}0.92$)

Table 2 Mean values and standard deviations of all variables for both groups at 4, 8, and 12 weeks. *PTV* periotest values

		Pullout force (N)		Displacement (mm)	Stiffness (N/mm)	Toughness (N/cm)	Bone contact (%)	PTV
4 weeks	Control	417.50±246.81	min 56 max 610	1.06±0.09	406.82±247.89	24.78±13.64	65.25±43.99	−5.25±1.5
	rhBMP-2	164.83±99.08	min 78 max 273	0.63±0.25	249.39±63.34	6.20±4.20	80.00±11.53	−6.30±1.5
8 weeks	Control	482.00±214.99	min 339 max 799	0.97±0.15	493.73±174.88	30.80±15.00	81.75±8.54	−4.00±1.2
	rhBMP-2	416.00±9.90	min 409 max 423	0.91±0.06	457.69±17.57	25.05±5.30	80.50±27.58	−6.00±1.4
12 weeks	Control	618.00±422.77	min 120 max 1237	1.13±0.18	543.82±340.66	53.56±40.89	71.00±39.85	−5.20±1.5
	rhBMP-2	795.50±354.89	min 326 max 1186	1.07±0.51	751.04±197.55	70.10±60.19	84.50±7.19	−4.50±1.0

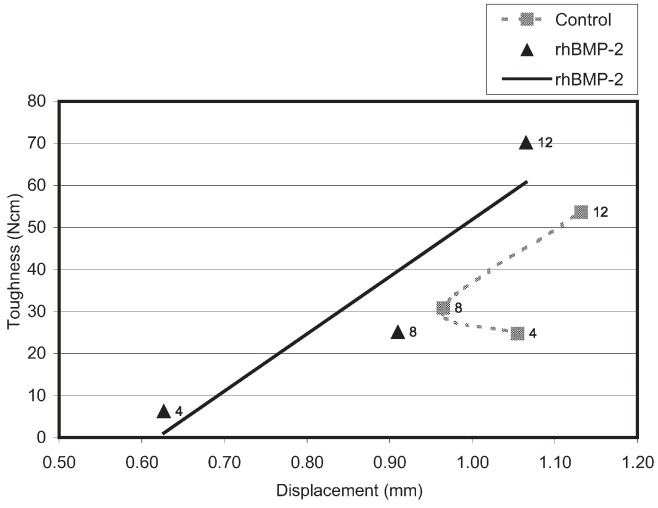

Fig. 10 Toughness-displacement correlation (control r^2=0.52, rhBMP2 r^2=0.85)

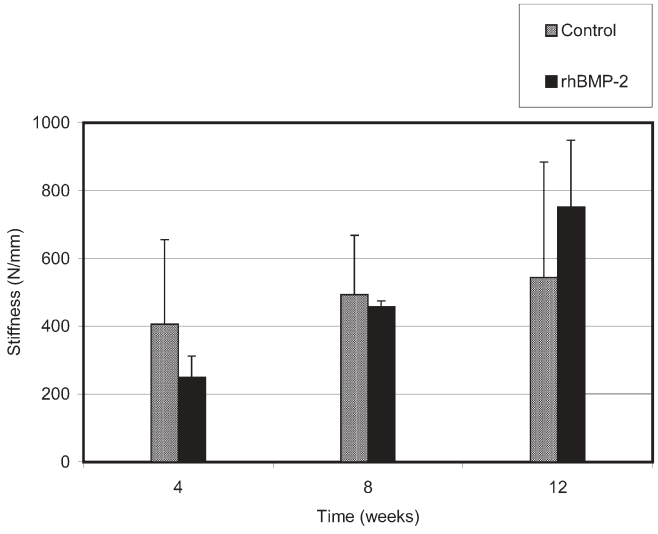

Fig. 11 Mean stiffness values at 4, 8, and 12 weeks

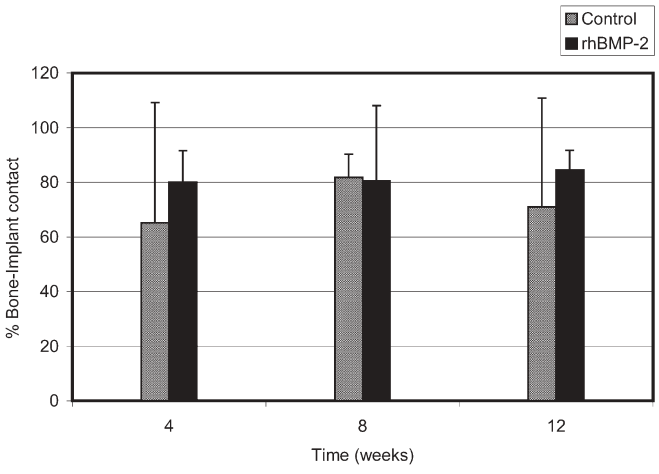

Fig. 12 Mean radiographic bone-implant contact values in the mesiodistal dimension at 4, 8, and 12 weeks

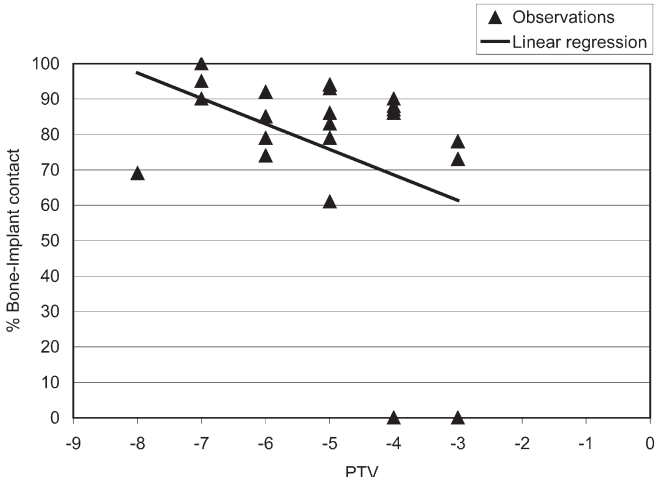

Fig. 13 Regression analysis between periotest values (*PTV*) and radiographic bone-implant contact (r=0.38)

Stiffness values increased over time at weekly rates of 62.7 N/mm for the rhBMP-2 implants and 17.1 N/mm for the controls, providing evidence of a statistical difference (P=0.02) in stiffness values for the rhBMP-2 implants between all time periods but not for the controls (Fig. 11).

When the bone-implant contact was radiographically calculated as a percentage of the total implant length, no statistical difference was found between or within the two groups at any time ((P=0.36) Fig. 12). In addition, correlation analysis of the radiographic bone-implant contact values with the other four variables did not show any pattern of association and was not statistically different between the two groups (P>0.05).

Periotest values ranged from −8.00 to −3.00, and the mean values are listed in Table 2. The PTV comparisons with *t*-test between and within the two groups at all time periods provided no evidence of statistically significant differences (P>0.05). Pearson's correlation coefficient analysis of PTV with radiographic bone-implant contact levels demonstrated a value of r=−0.38 with a subsequent negative regression trend (Fig. 13).

Discussion

In the present study, rhBMP-2 delivered with a bovine collagen carrier was used to induce bone formation in combination with dental implants. The specific implant type was chosen because of its apical chamber that provided space for the collagen/rhBMP-2 combination and because of its apical perforations that allowed diffusion of the differentiation factor to the surrounding osteotomy walls. The decision to leave the apical chambers of the control implants empty was based on evidence of the collagenous matrix itself to have no effect on bone formation [9, 21, 24]. For this reason, our aim was to compare two clinical treatments for implant placement asso-

ciated with bone defects: perform nothing or apply rhBMP-2.

Biomechanical testing is a common approach for evaluating the bone-implant interface, and usually three types of tests have been reported in the literature: pullout [3], pushout [5], and torque [6]. In the present study, the pullout test was employed because this specific implant does not have an engaging prosthetic interface that would allow application of reverse torque. Furthermore, the coronal flaring of the implant and the process of specimen collection en bloc, with the inferior border of the mandible intact, would affect the accuracy of a pushout test.

Usually, the behavior of a material under tensile loading is studied with stress-strain curves, and in our study, the force/displacement graphs provided information about not only failure load and the corresponding displacement but also stiffness and toughness associated with the interfacial zone. Standardization of the experimental procedure allowed consistent interpretation of the biomechanical data in relation to the underlying biologic conditions.

The rhBMP-2 implants demonstrated lower pullout forces than controls at 4 and 8 weeks, suggesting an altered host tissue response due to application of the differentiation factor. Depending on their concentration gradient, BMPs can attract various types of cells [23], acting as chemotactic, mitogenic, or differentiating agents [22]. Bone marrow stromal cells form an important source of mesenchymal pleuripotential progenitors capable of differentiating along the osteoblastic and adipocytic lineages, depending on the rhBMP-2 dose [32]. It is possible that the slow release rate of rhBMP-2 during the first days after implantation may have resulted in low local concentrations, thus promoting differentiation of adipocytes. There is also evidence that BMP-2 promotes expression of cyclo-oxygenase-2 and osteoclast differentiation factor in osteoblast-like cells, thus regulating osteoclastogenesis [18]. Based on the evidence above, the reduced failure loads at 4 weeks for the rhBMP-2 may be explained by the presence of cell types other than osteoblasts.

As the healing process continued, gradual degradation of the collagen sponge may have liberated increasing amounts of rhBMP-2, rendering it capable of eliciting an osteoblastic response. However, upregulation of the osteoblastic phenotype by BMPs is stage-specific, with increased production of type I collagen initially, followed by increased mineralization [8, 15]. The increase in peak force after the 4th week at a rate of 78.8 N/week for the rhBMP-2 implants, compared to the 25.1 N/week for controls, may be an indication of delayed yet gradually increasing strength of the developing bone-implant interface. At 8 weeks, rhBMP-2 implants exhibited a mean pullout force that was 86% of the controls' failure load, peaking up to 129% at 12 weeks.

Stiffness values represent a measure for the elastic properties of the interface, with higher values suggesting more rigid fixation. Differences in rigidity may be the result of variations in bone-implant contact levels and degree of mineralization. The observed stiffness rates along with the correlations between toughness, peak force, and the corresponding displacements indicate a progressive maturation of the interface for the rhBMP-2 implants starting after a 4-week healing period.

Previous studies utilizing threaded titanium implants in combination with BMPs have demonstrated an increased rate of osseointegration [34], higher torque values at 3 and 12 weeks [2], and bone formation within the apical hole 1 month after implantation [35]. However, Jeppsson et al. [16, 17], in a series of studies, reported an inhibitory effect of rhBMP-2 on bone formation inside the apical chamber which may be model-specific. It is important to consider carefully and understand the various parameters that play roles in the clinical outcome.

Cook et al. [10] studied the effect of recombinant human osteogenic protein 1 on the osseointegration of implants placed into fresh extraction sites and emphasized the importance of implant fit for new bone formation. Threads are used to improve initial stability [11], and threaded implants combined with BMPs may have a more favorable response. In our study, the implant success rate was 72% and may have been affected by the implant design, short implant length, ratio of cortical vs cancellous bone, and the challenging animal model. In addition, a two-stage surgical protocol may affect healing and the action of BMPs by providing a more secluded and protected environment than one-stage implants.

Finally, although the matrix may not contribute any additional factors necessary for bone induction, it is a fundamental and very important component of the growth process. One of the carrier functions is to maintain the growth factor at the implantation site and thus enhance its local concentration. It is believed that BMPs do not bind to the carrier [30] but rather become physically entrapped in its structure, which makes certain designs more favorable for bone induction than others. Considerations include biodegradability, structural integrity, absence of immunogenicity, absorption, and rate of BMP release.

Although torque was not applied to these cylindrical, threadless implants, the observed toughness values are thought to provide an approximation that can be used to compare with torque. The observed toughness of 54 N/cm and 70 N/cm for controls and rhBMP-2 implants, respectively, suggests that a healing period of 12 weeks is necessary in order to develop an interface able to withstand the clinical load of 35 N/cm in torque that is recommended for final abutment connection.

Radiographic evaluation of the bone-implant contact did not provide evidence of the differences observed in biomechanical testing. This may be due to the limited radiographic resolution level, which does not allow observation of cellular and subtle histological differences. In addition, two-dimensional radiographic evaluation in one plane (mesiodistal) does not provide enough information for the whole implant circumference and possible implant regeneration inside the apical hollow chamber of the implant.

The periotest has been used in a number of studies [7, 20] to assess implant mobility, and PTV of −8 to +9

correspond to a mobility index of 0 with no distinguishable movement [26]. In our study, PTV ranged from −8 to −3, providing clinical evidence of increased implant stability. Nevertheless, no statistically significant correlation was found between the PTV and peak force, maximum displacement, stiffness, or total energy, setting a limitation on the clinical value of the periotest measurements. However, PTV correlated with the radiographic appearance of bone levels (r=−0.38), confirming the lower recording values with increased bone levels. In their study of ITI implants' osseointegration based on periotest measurements, Mericske-Stern et al. found no correlation between bone density and periotest values [19]. These findings emphasize the significance of qualitative parameters on the bone-implant interface and demonstrate the limitation of both radiographs and the periotest in clinically evaluating osseointegration and functional loading readiness.

Conclusions

The low pullout force value of the rhBMP-2 implants compared to the control group, especially at 4 weeks, suggests an altered host tissue response due to application of the growth factor. However, the gradual increase in peak force values of the rhBMP-2 implants, resulting in statistically significant differences over 12 weeks in comparison to controls, indicates improved levels of osseointegration. Radiographic and periotest assessment of the bone-implant interface did not provide evidence of the differences observed with biomechanical testing. The results from the displacement, energy, and stiffness measurements support the potential role of rhBMP2 in clinical applications in promoting a biomechanically mature interface at 12 weeks.

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