Surface-Etching Enhances Titanium Implant Osseointegration in Newly Formed (rhBMP-2–Induced) and Native Bone

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Purpose: *The influence of surface modifications on osseointegration in newly formed bone is not well established. The purpose of this study was to compare osseointegration at acid-etched versus turned implants in newly formed and native bone.* ***Methods:*** *Supra-alveolar peri-implant defects were created in 8 hound/Labrador mongrel dogs. Titanium implants 10 mm long (2 turned and 1 dual acid-etched) were placed 5 mm into the surgically reduced alveolar crest, creating 5-mm supra-alveolar peri-implant defects. Recombinant human bone morphogenetic protein-2 (rhBMP-2; 0.4 mg) in a collagen carrier was used to induce new bone formation. A macroporous, expanded polytetrafluoroethylene device was used to delineate new bone formation. The animals were euthanized at 8 weeks for histometric analysis of the experimental sites.* ***Results:*** *There were no significant differences in rhBMP-2–induced bone density (mean ± SD) at acid-etched versus turned implants (20.6% ± 5.3% vs 23.8% ± 4.7%;* P *= .232). However, there was a significant difference in bone-implant contact in favor of the acid-etched implants (12.3% ± 6.8% vs 7.9% ± 3.1%;* P *= .05). Native bone density averaged 63.9% ± 7.5% and 64.5% ± 9.0% for acid-etched and turned implants, respectively (*P *= .641). Nevertheless, bone-implant contact was significantly enhanced at acid-etched versus turned implants (59.7% ± 11.3% vs 40.7% ± 21.2%;* P *= .005).* ***Conclusions:*** *Surface dual acid-etching of titanium implants has a positive effect on osseointegration in newly formed and native bone. Significant differences in bone density do not appear to influence this effect.* INT J ORAL MAXILLOFAC IMPLANTS 2007;22:472–477

Key words: *bone, e-PTFE, osseointegration, rhBMP-2, tissue engineering, titanium implants*

Brånemark[1] defined *osseointegration* as a direct structural and functional connection between ordered living bone and the surface of a titanium implant. The most common application of osseointegration has become rehabilitation of partially and completely edentulous patients. The long-term predictability and success of these prosthetic reconstructions is primarily based on an active bond between living tissue and the implant surface at a molecular level. The active bond relies on 2 major factors, the host response and the implant biomaterial and surface texture.

Few reports have concerned osseointegration of titanium implants in tissues with compromised host response, such as irradiated bone or tissue in medically compromised subjects. It appears that osseointegration is possible in irradiated bone[2] and that patients exhibiting osteoporosis, cardiovascular diseases, controlled diabetes mellitus, hyperparathyroidism, or immune-suppressed transplant patients are at no greater risk of implant failure than systemically healthy subjects.[3–5] There is also a wide body of evidence evaluating the influence of implant biomaterials and surface texture on osseointegration in normal bone and healthy subjects.[6–9] Endosseous implants have been manufactured from a variety of metals, alloys, bone-like ceramics, and polymers and exhibit significant variations in design and surface topography.[10] Osseointegration is ultimately depen-

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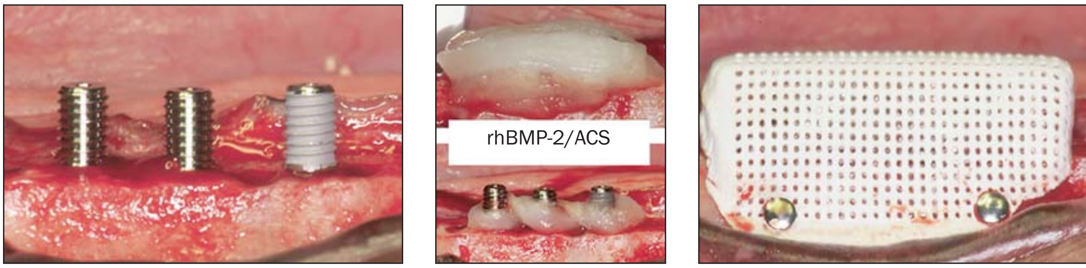

Fig 1 Turned and dual acid-etched titanium implants were placed into the edentulous, surgically reduced posterior mandible in the dog in such a manner that 5-mm supra-alveolar peri-implant defects were created. The implant sites received rhBMP-2 (0.4 mg)/ACS. A space-providing porous e-PTFE device was placed to cover the implants and rhBMP-2 construct. Mucoperiosteal flaps were advanced, adapted, and sutured to submerge the surgical site for primary intention healing.

dent on the biocompatibility of these components. Currently the most widely used biomaterials for implant manufacture are commercially pure titanium and titanium alloy.

Surface modifications and their influence on osseointegration have been the subject of many investigations. Several reports demonstrate that surface modifications may influence osseointegration in native bone.[6,8,11–15] It is believed that surface modifications (ie, rough surfaces) not only provide a larger surface area but may also induce a favorable host response, leading to enhanced, possibly accelerated, osseointegration. The use of various experimental models to study the osseointegration of implant surfaces has usually been limited to native bone. The purpose of this study was to compare osseointegration of surface-etched and turned titanium implants in newly formed and native bone.

MATERIALS AND METHODS

Animals

Eight young-adult male hound/Labrador mongrel dogs were obtained from a dealer approved by the US Department of Agriculture. Animal selection, management, surgery protocol, and alveolar defect preparation followed routines approved by the Animal Care and Use Committee, W. L. Gore & Associates, Flagstaff, Arizona.

Space-Providing Porous Barrier Device

A space-providing expanded polytetrafluoroethylene (e-PTFE) device (Reinforced GORE-TEX e-PTFE, W.L. Gore & Associates) was used. The device, which was custom-made for the critical-size, supra-alveolar peri-implant defect model used, featured a laminated polypropylene mesh reinforcement for structural and dimensional integrity and laser-etched 300-μm pores at 0.8-mm intervals (center-to-center), allowing penetration by vascular and connective tissue elements from the gingival tissue (Fig 1).

Recombinant Human Bone Morphogenetic Protein-2

Lyophilized recombinant human bone morphogenetic protein-2 (rhBMP-2; Wyeth Research, Cambridge, MA), reconstituted with sterile water, diluted with buffer, and soak-loaded onto a sterile absorbable collagen sponge (ACS; Integra Life Sciences, Plainsboro, NJ), was used to induce new bone formation at the defect sites. Each defect site received 0.4 mg rhBMP-2. Four animals received rhBMP-2 at 0.2 mg/mL soak-loaded onto a 0.2-mL volume of ACS,[16] and 4 animals received rhBMP-2 at 1.43 mg/mL soak-loaded onto a 0.28-mL volume of ACS.[17] There were no statistically significant differences in bone density or bone-implant contact (BIC) between these groups.

Titanium Implants

Custom-made (Biomet/Implant Innovations, Palm Beach Gardens, FL), turned and dual acid-etched (Osseotite) commercially pure titanium implants, 10 mm in length, were used; both surface technologies were representative of the manufacturer's clinical products. The implants were manufactured with a reference thread 5 mm from the top surface. The reference thread was designed to facilitate surgical placement of the implants and to serve as a reference point for the histologic and histometric analysis.

Experimental Procedure

Bilateral supra-alveolar peri-implant defects were surgically created in the mandibular premolar region (Fig 1). One acid-etched and 2 turned implants were inserted to a depth of 5 mm within the surgically reduced alveolar ridge to the level of the reference thread in the third and fourth premolar regions, creating 5-mm, supra-alveolar peri-implant defects. One peri-implant defect in each animal was implanted with rhBMP-2/ACS combined with the space-providing, macro-porous e-PTFE device placed to cover the titanium implants and the rhBMP-2 construct. The e-PTFE device was fixed to the alveolar bone with med-

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ical grade stainless steel tacks (FRIOS Augmentation system, Friadent, Mannheim, Germany). The periostea were fenestrated at the base of the mucogingival flaps to allow tension-free flap apposition. The mucoperiosteal flaps were advanced, adapted 3 to 4 mm coronal to the e-PTFE device, and sutured (GORE-TEX Suture CV5, W. L. Gore & Associates). Only jaw quadrants subject to this treatment (1/animal) were included in this study. The evaluation of contralateral jaw quadrants has been reported elsewhere.[16,17]

Postsurgery Procedure

The animals were fed a soft dog-food diet. They received buprenorphine (0.04 mg/kg intravenously, intramuscularly, or subcutaneously) every 5 hours for analgesia the first few days postsurgery. A broad-spectrum antibiotic (enrofloxacin; 2.5 mg/kg, intramuscularly twice daily) was used for infection control for 14 days. Plaque control was maintained by twice-daily topical application of chlorhexidine (chlorhexidine gluconate; Xttrium Laboratories, Chicago, IL; 40 mL of a 2% solution).

The animals were anesthetized and euthanized at 8 weeks postsurgery by an intravenous injection of concentrated sodium pentobarbital. Titanium implants with surrounding soft and hard tissues were removed en bloc and immersed in 10% buffered formalin. The e-PTFE devices were not removed during the healing period.

Histologic Processing

The tissue blocks were dehydrated in alcohol and embedded in methylmethacrylate resin (Technovit 7200 VLC; Heraeus Kulzer, Hanau, Germany). The implants were cut mid-axially in a buccolingual plane using the cutting-grinding technique (EXAKT Apparatebau, Norderstedt, Germany) and were ground and polished to a final thickness of 40 µm.[18,19] The sections were stained with Stevenel's blue and van Gieson's picro fuchsin.

Analysis

A single experienced calibrated investigator blinded to the experimental conditions performed the histologic analysis using incandescent and polarized light microscopy (BX 60; Olympus America, Melville, NY), a microscope digital camera system (DP10; Olympus America), and a PC-based image analysis system (Image-Pro Plus; Media Cybernetics, Silver Spring, MD). The following parameters were recorded for the buccal and lingual surfaces of the most central section for each implant:

- Bone density (new bone): Ratio of new bone to marrow spaces.
- Bone density (native bone): Ratio of bone to marrow spaces adjacent to the implant.
- Osseointegration (new bone): Percent BIC as measured between the reference thread and the point of the coronal extension of newly formed bone along the implant
- Osseointegration (native bone): Percent BIC within the alveolar base as measured from the apical aspect of the reference thread to the apex of the implant.

Summary statistics (means ± SD) based on means per animal for the experimental conditions were calculated using selected sections. Paired *t* tests were performed to evaluate differences between treatment conditions (n = 8). Significance was accepted at a probability level of $P \leq .05$.

RESULTS

All jaw quadrants exhibited rhBMP-2–induced fine trabecular woven bone approximating the titanium implants with limited BIC (Fig 2). The larger area underneath the e-PTFE device was filled with fibrovascular tissue featuring osteogenic activity. The geometry of the ridge was well maintained, with the newly formed bone conforming to the e-PTFE device without any suggestion of tissue compression. There was only a limited inflammatory reaction associated with the e-PTFE device. There was no evidence of residual ACS.

There were no significant differences in bone density in rhBMP-2–induced bone at acid-etched and turned titanium implants (20.6% ± 5.3% vs 23.8% ± 4.7%; $P = .232$). However, there was a significant difference in BIC in favor of the acid-etched implants (12.3% ± 6.8% vs 7.9% ± 3.1%; $P = .05$; Fig 3). Bone density in native bone amounted to 63.9% ± 7.5% and 64.5% ± 9.0% for acid-etched and turned implants, respectively ($P = .641$). BIC in native bone was significantly increased at acid-etched compared to turned implants (59.7 ± 11.3% vs 40.7 ± 21.2%; $P = .005$; Fig 3).

DISCUSSION

This study shows that surface dual acid-etching of endosseous titanium implants has a positive effect on osseointegration in both newly formed rhBMP-2–induced and native bone using a discriminating large-animal model. Significant differences in bone density between newly formed and native bone did not appear to influence this effect. These observations corroborate several previous reports demon-

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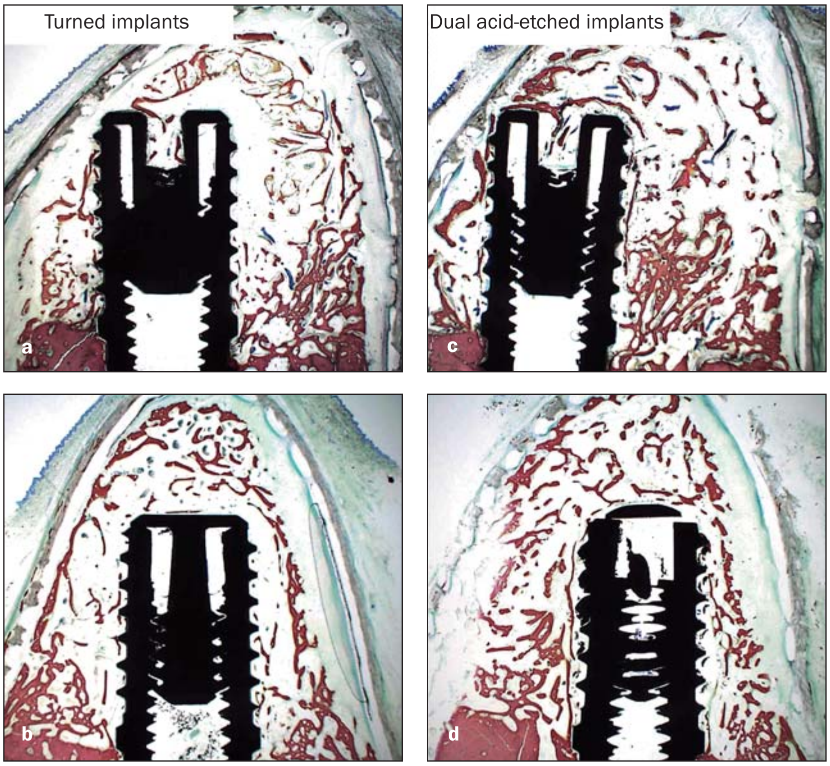

Fig 2 Photomicrographs showing *(a and b)* turned and *(c and d)* dual acid-etched titanium implants in rhBMP-2/ACS–induced bone at 8 weeks postimplantation.

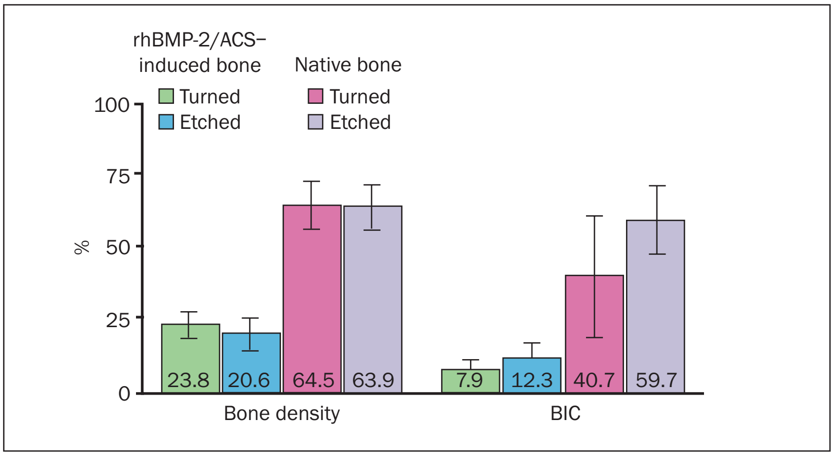

Fig 3 Mean ± SD bone density and BIC at turned and dual acid-etched titanium implants in newly formed (rhBMP-2/ACS–induced) and native bone. There was a significant difference in BIC in favor of the acid-etched implants (P = .05) in newlt formed bone. There was also a significant difference in BIC in favor of the acid-etched implants in native bone (P = .005).

strating that surface modifications influence osseointegration in native bone.[6,8,11,12,14,20–23]

Reports on the influence of implant surface modifications on osseointegration in newly formed bone are sparse. Many studies have focused instead on the complex task of alveolar augmentation/regeneration rather than comparisons between implant surface modifications in regenerated newly formed bone. Large-animal model systems considered and employed for such studies have included extraction sites and dehiscence, fenestration, saddle type, 1-wall, or supra-alveolar defects such as those used in the present investigation (Fig 4). With the exception of the supra-alveolar defect model, large-animal models have relied on the osteogenic potential of the native alveolar bone for regeneration. This potential may be enhanced by devices for guided bone regeneration or stimulated by osteoconductive biomaterials. The supra-alveolar defect model, on the other hand, has limited innate osteogenic potential[16,24,25] and thus uniquely lends itself to evaluation of genuinely osteoinductive treatment concepts.[16,17,25–27]

For perspective, Karabuda et al[7] used fresh mandibular extraction sockets in dogs to evaluate osseointegration of hydroxyapatite (HA)-coated and titanium plasma-sprayed (TPS) implants and found higher BIC for HA-coated compared to TPS implants following an 8-week healing period. Botticelli et al[28] used standardized circumferential peri-implant defects in dogs, much like extraction sockets, to evaluate bone fill

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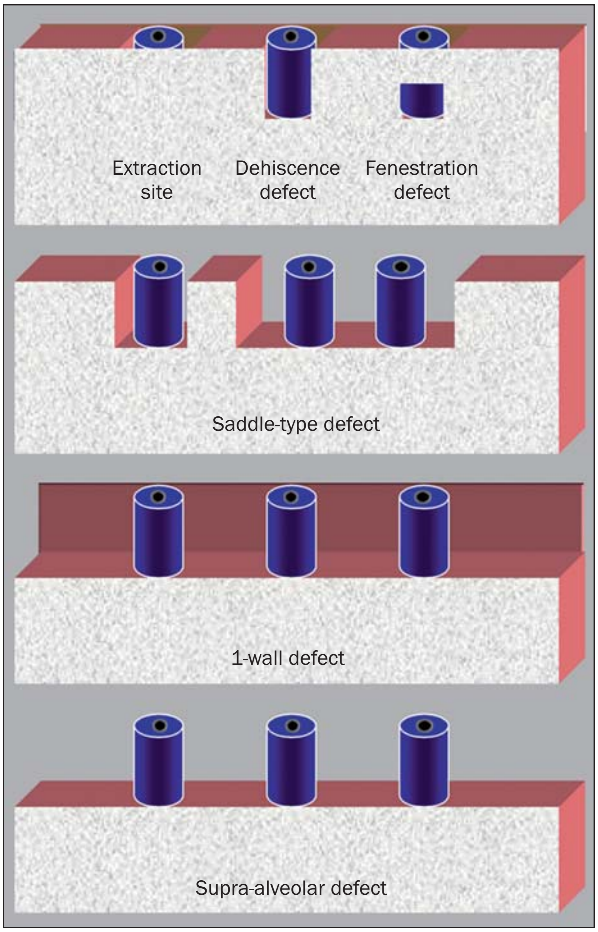

Fig 4 Defect models considered for alveolar augmentation/ bone regeneration and osseointegration.

and osseointegration at sand-blasted, large-grit, acid-etched (SLA) and turned implant surfaces. They showed significantly greater bone formation and BIC for SLA compared to turned surfaces at 16 weeks postimplantation. Rasmusson et al[22] used large mandibular buccal dehiscence defects in dogs to compare osseointegration at grit-blasted and turned implants. They found significantly greater BIC at grit-blasted compared to turned implants at 16 weeks. Persson et al[29] evaluated reosseointegration of SLA and turned implants in dogs. They found that reosseointegration was substantial for implants with SLA surfaces but only minimal for exposed smooth (turned) surfaces. Reosseointegration (BIC) at SLA surfaces averaged 84% compared to 22% at turned implant surfaces. Saddle-type and supra-alveolar defects have been used to evaluate guided bone regeneration.

Only a few such studies have attempted to evaluate the significance of implant surface modifications on osseointegration in newly formed regenerated bone. Conner et al[30] assessed BIC at TPS, HA-coated, and acid-etched titanium implants following guided bone regeneration using 3-wall saddle-type defects in the edentulous mandible in dogs. The HA implants exhibited significantly greater BIC compared to acid-etched and TPS implants. Similarly, Lima et al[31] evaluated BIC at TPS and turned implants following guided bone regeneration using saddle-type defects in the dog. BIC ranged from 12% to 32% for TPS, compared to 0% to 4% for turned implants. In general, studies in newly formed regenerated bone in a variety of experimental settings confirm that implant surface characteristics play a decisive role in osseointegration much like that observed for native bone.

In this study, rhBMP-2 (0.4 mg)/ACS was used to induce local bone formation. To the authors' knowledge, this was the first study to evaluate the effect of surface modifications in newly formed induced bone. The dual acid-etched implant surface and the corresponding turned control surface from the same manufacturer have been evaluated in previous studies. Lazarra et al[32] showed that the acid-etched implant surface exhibited significantly increased BIC compared to control in human bone (type 3 or 4). Veis et al[33] showed similar advantages for the acid-etched surface when implanted in conjunction with autograft in a dog model. Furthermore, Weng et al[23] showed that acid-etched implants exhibited superior BIC compared to turned equivalents inserted into poor-quality bone in the posterior edentulous canine mandible. The findings of the present study are consistent with these observations. New bone formation of considerably low density (approximately 20%) exhibited significantly increased BIC at acid-etched implants compared to turned controls following an 8-week healing interval. It appears from this and previous studies that surface modification may increase the osteoconductive potential of endosseous titanium implants in a variety of settings, including native, regenerated, and induced bone.

CONCLUSION

The results suggest that dual acid-etching of the surface of titanium implants has a positive effect on osseointegration in newly formed and native bone. Significant differences in bone density do not appear to influence this effect.

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