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Bone reconstruction after surgical treatment of experimental peri-implantitis defects at a sandblasted/acid-etched hydroxyapatite-coated implant: an experimental study in the dog

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Abstract

Objectives: The objective of this study was to evaluate bone formation/osseointegration following surgical treatment of experimental peri-implantitis at dental implants with different surface characteristics exposed to ligature-induced breakdown conditions.

Methods: Ten turned (control), 10 sandblasted/acid-etched (SA), and 10 SA/hydroxyapatite nanocoated (HA) implants were installed into the edentulated posterior mandible in five Beagle dogs and allowed to osseointegrate for 12 weeks. Ligature-induced breakdown defects were then induced over 23 weeks using stainless steel wire ligatures. The ligatures were removed and soft tissues were allowed to heal for 3 weeks. Next, exposed implant surfaces were decontaminated followed by guided bone regeneration using a collagen membrane and submerged wound healing. The animals were euthanized for histometric analysis at 12 weeks post-surgery.

Results: The radiographic analysis showed vertical bone loss following ligature-induced breakdown without statistically significant differences among implant technologies. The histometric analysis showed significantly enhanced bone formation (height) at SA and SA/HA compared with turned implants ($p = 0.028$) following reconstructive surgery. Bone formation area was greater at SA/HA compared with turned implants, however the difference did not reach statistical significance.

Key words: acid-etched surface; animal study; dental implants; guided bone regeneration; hydroxyapatite; ligature-induced breakdown

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Conflict of interest and source of funding statement

The authors declare no conflict of interest related to this study. The study was supported by a grant from Osstem Implant Inc., Busan, Korea.

Conclusions: While ligature-induced defect progression does not appear implant surface dependent in this animal model, bone formation at the decontaminated implant surfaces appears more favourable at SA and SA/HA over turned implants following reconstructive surgery.

Factors recognized to influence dental implant osseointegration include implant macro-structure and surface characteristics. Moderately rough and rough surfaces appear to provide enhanced osseointegration compared with smooth or minimally rough surfaces (Lang & Jepsen 2009). Rough surface implants are produced modifying the implant surface by means of anodizing, plasma spraying, acid etching, sandblasting, or combinations thereof. In perspective, sandblasted/acid-etched (SA) surfaces demonstrate significantly enhanced osseointegration compared with turned surfaces (Grassi et al. 2006). Sandblasting apparently achieves preferred roughness for mechanical fixation, additional acid etching smoothing sharp surface peaks to add a high-frequency component to the surface of potential significance for protein adhesion (Wennerberg & Albrektsson 2009). Comparing SA with turned and acid-etched implants using a porcine model, significantly increased removal torque appeared required for SA implants following a 10-week healing interval (Szmukler-Moncler et al. 2004).

Surface characteristics including hydrophilicity, chemical bonding, and nanostructures have been developed with the intent to enhance/accelerate osseointegration (Wennerberg & Albrektsson 2010). A hydrophilic SA surface submerged in NaCl showed increased bone-implant contact compared with a hydrophobic SA surface (Buser et al. 2004). Calcium-phosphate-coated implants demonstrate higher disruption resistance and increased bone-implant contact compared with non-coated implants in a rat femur model (Mendes et al. 2007). Few studies have investigated the significance of dental implant surface nanostructures for osseointegration (Meirelles et al. 2007). Nanostructures attained through hydroxyapatite (HA) coating have been shown to enhance bone formation (Meirelles et al. 2008a, b, c). HA-coated SA titanium dental implant surfaces show significantly enhanced mesenchymal stem cell adherence, increased alkaline phosphatase activity, osteocalcin content, and osteopontin mRNA expression compared with control SA surfaces in vitro (Wang et al. 2008).

Although favourable outcomes have been noted in preclinical and clinical settings for micro- and nanostructured implant technologies, their susceptibility to biofilm-induced inflammatory processes has caused concern and their potential to support bone formation/re-osseointegration following regenerative treatment remains uncertain (Berglundh et al. 2007, Albouy et al. 2011). The objective of this study was to evaluate bone formation and osseointegration following surgical treatment of experimental peri-implantitis at dental implants with different surface characteristics exposed to peri-implantitis conditions.

Material and Methods

Animals

Five adult male Beagle dogs, approximate weight 10 kg, acquired from licensed breeder (OrientBio, Seoul, Korea), were used. The study protocol was approved by the Animal Research Committee, Seoul National University (approval number: SNU-100629-3). All experiments were performed in accordance with Institute of Laboratory Animal Resources, Seoul National University guidelines. ARRIVE guidelines (Kilkenny et al. 2011) were consulted in reporting this research. The study outline is shown in Fig. 1. The experiments were performed March 12, 2010 through September 2, 2011. The animals were individually housed in W900 × D800 × H800 indoor runs, ambient temperature 23 ± 2°C, relative humidity 50 ± 10%, air-condition 12–18 air changes/h, light/dark cycle 12/12, and they were fed a standard pellet dog-food diet (HappyRang, Seoulfeed Company, Seoul, Korea) throughout the study and had ad libitum access to water.

Dental implants

Custom ø3.0 × 8.5 mm implants (Osstem, Busan, Korea) manufactured to fit the narrow edentulated alveolar ridge were used. For the experimental group, 10 SA (Ra = 2.5 μm) and 10 SA/HA-coated (Ra = 2.5 μm) implants were used. The HA surface was processed through thermal acid etching and HA growth of less than 20 nm (mean 10 nm) thickness. The type of interface was a single interface disjointed surface with less than 10 μm thickness. Single crystalline HA covered almost 50% of the implant surface. For the control group, 10 turned implants (Ra = 0.2 μm) were used.

Surgical protocol

The animals were anaesthetized using xylazine (15 mg/kg IV) and tiletamine/zolazepam (10 mg/kg IV). All mandibular premolars and first molars were extracted and the edentulated alveolar ridges were allowed to heal for 12 weeks. Next, dental implant installation was performed. Turned, SA/HA and SA implants were randomized to contra-lateral jaw quadrants in subsequent animals using the 3 × 3 Latin Square Design. The implants were installed 1 mm subcrestally. Plaque control using a toothbrush was performed twice weekly for 12 weeks following implant installation. Healing abutments were then connected and healing allowed to progress for another 2 weeks. Next, stainless steel wire ligatures were applied at the implant neck to induce peri-implant bone loss (Fig. 2). Plaque control was not

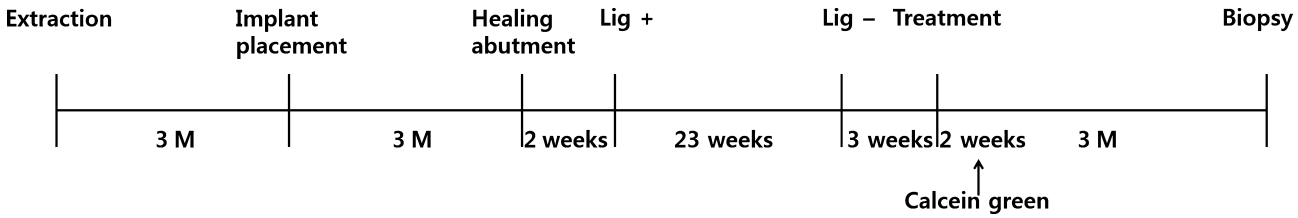

Fig. 1. Study outline: Placement (Lig+) and removal (Lig−) of ligatures 23 weeks later. Administration of calcein 2 weeks following guided bone regeneration surgery. Animals were sacrificed and biopsies collected at 12 weeks following surgery.

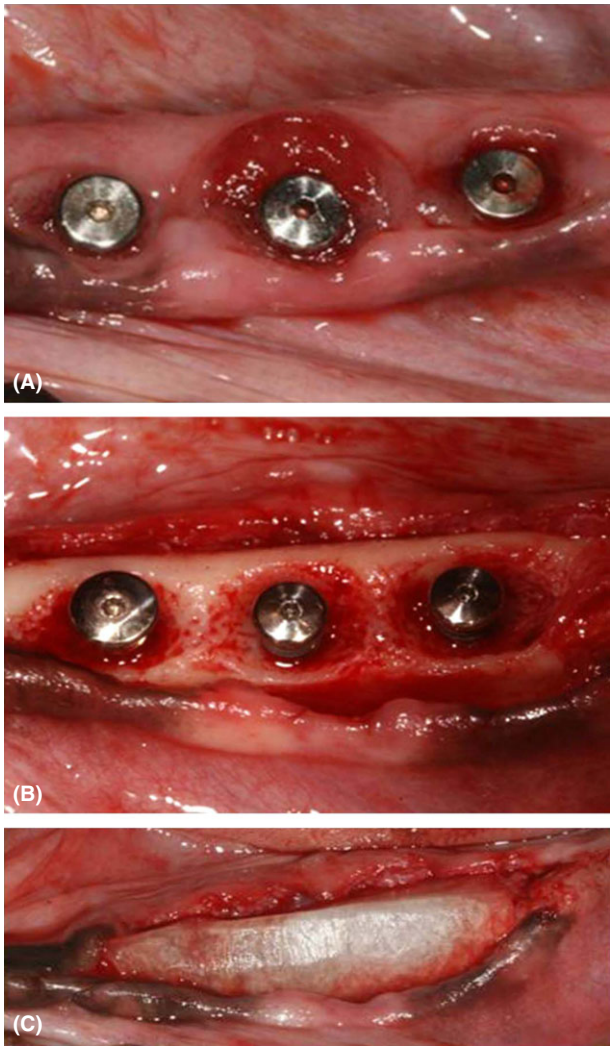

Fig. 2. Ligature-induced peri-implantitis (A), peri-implantitis defects following flap surgery and debridement (B), and following application of a collagen membrane for guided bone regeneration (C).

pursued during this period. Intra-oral radiographs were obtained at weeks 5, 8, 12, 18, and 23 to monitor bone level changes. The wire ligatures were removed at week 23 and healing abutments replaced with cover screws. Next, the implant sites were accessed elevating buccal and lingual mucoperiosteal flaps following a 3-week healing interval. Plastic curettes (Hu-Friedy, Chicago, IL, USA) were used to remove the granulation tissue. The implant surfaces were cleaned using a cotton pellet alternately soaked in 0.12% chlorhexidine and saline. In following, a resorbable collagen membrane (Cytoplast®, Sybron Implant Solutions, Orange, CA, USA) was applied over the implants to provide for guided bone regeneration and the wounds closed for primary intention healing. Graft materials were not used.

Post-surgery procedures

The animals received daily enrofloxacin 10 mg/kg for infection control and meloxicam 0.04 mg/kg for pain control for 7 days. They also received daily a 0.05% chlorhexidine mouth rinse to support oral hygiene for 7 days. Calcein fluorescent label (Sigma-Aldrich, St. Louis, MO, USA; 30 mg/kg IM) was administered at 2 weeks following surgical intervention (Nkenke et al. 2002). Intra-oral radiographs were obtained at 4, 8, and at 12 weeks post-surgery when the animals were euthanized and block biopsies harvested for histological analysis.

Histological processing

The tissue blocks were fixed in 10% neutral buffered formalin for 6 days, dehydrated, and then embedded in methacrylate-based resin. The specimens were sectioned in buccal-lingual plane, processed to approximately 40–50 μm thickness, and stained using haematoxylin and eosin. One sample per implant closest to the mid-section was analysed and the unit of analysis was the animal.

Radiographic analysis

One calibrated experienced masked examiner (HNG) performed the radiographic analysis using an image-analysis software (Tomoro Scope Eye 3.5 Image Analyzer, Techsan Digital Imaging, Seoul, Korea) and standardized images

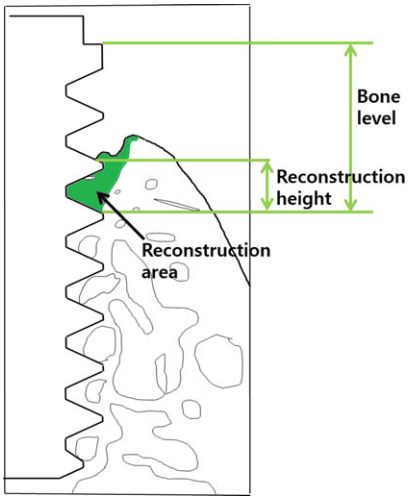

Fig. 3. Schematic representation of the histometric analysis.

obtained using a dental radiographic unit (ADX4000AT, Dexcowin, Seoul, Korea). Bone levels from the implant shoulder to the most coronal extent of bone along the mesial and distal surface of the implant were recorded.

Histometric analysis

The same calibrated experienced masked examiner (HNG) performed the histometric evaluation twice using a light microscope and the image-analysis software (Tomoro Scope Eye 3.5 Image Analyzer, Techsan Digital Imaging). The following parameters were evaluated for the buccal and lingual surfaces of each implant (Fig. 3):

- Peri-implant defect depth: distance from the most apical aspect of the induced peri-implant defect to the implant shoulder;
- Bone reconstruction height: distance from the most apical aspect of the induced peri-implant defect to the most coronal new bone-implant contact;
- Bone reconstruction area: area of newly formed bone within the induced peri-implant defect; and
- Bone-implant contact: fraction bone-implant contact within reconstructed bone.

Statistical analysis

Statistical analysis was performed using SPSS v.18 (SPSS, Chicago, IL, USA). Summary statistics is presented as group means ± SD ($N = 5$). Differences between groups were analysed using analysis of variance (ANOVA) and post hoc comparisons using the least significant difference (LSD) test. The significance level was set at $p < 0.05$. Primary outcome parameter was bone reconstruction height ($N = 5$), while bone reconstruction area and bone-implant contact served as secondary outcome parameters. Intra-examiner reliability was determined using the intra-class correlation coefficient. The intra-class correlation coefficient was 0.976 with a 95% confidence interval of 0.948–0.989.

Results

Radiographic analysis

Peri-implant bone levels gradually decreased over the sequence of experimental peri-implantitis until ligature removal week 23 (Fig. 4). Average bone levels at week 26 comprised 2.4 ± 1.0 mm for turned, 2.7 ± 0.6 mm for SA/HA, and 2.3 ± 1.0 mm for SA implants without significant differences among surface technologies ($p = 0.773$). Twelve weeks following guided bone regeneration surgery bone levels averaged 2.2 ± 0.8 mm for turned, 2.3 ± 0.7 mm for SA/HA, and 2.0 ± 0.8 mm for SA implants without significant differences among surface technologies ($p = 0.700$); bone level changes averaging 0.1 ± 0.4, 0.4 ± 0.7, and 0.3 ± 0.6 mm, respectively (Table 1).

Histometric analysis

Mean crestal bone level from the implant shoulder to the most apical aspect of the ligature-induced defect amounted to 2.7 ± 1.2 mm for turned, 3.5 ± 1.2 mm for SA/HA, and 3.2 ± 1.4 mm for SA implants without significant differences among implant technologies ($p = 0.823$). Bone fill ($N = 5$) from the fundus of the defect to the most coronal bone-implant contact of the induced ligature-induced defect comprised 0.1 ± 0.2 mm for turned, 0.5 ± 0.6 mm for SA/HA, and 0.5 ± 0.7 mm for SA implants; SA/HA and SA implants showing enhanced bone formation compared with turned implants ($p = 0.025$), however, without significant differences between SA/HA and SA implants. Bone reconstruction area averaged 0.2 ± 0.2 mm^2 for turned compared with 0.5 ± 0.6 mm^2 for SA/HA implants and 0.3 ± 0.4 mm^2 for SA implants without significant differences between implant technologies (Fig. 5). Bone-implant contact within regenerated bone comprised 40.3% for turned compared with 60.9% for SA/HA implants, and 49.8% for SA implants without a significant difference differences between implant technologies (Table 2).

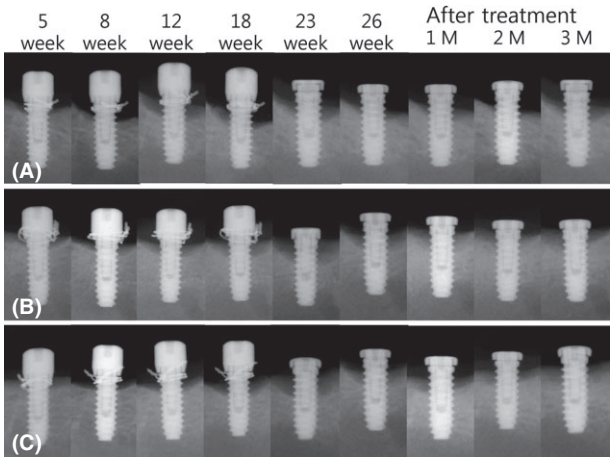

Fig. 4. Representative radiographs showing crestal bone levels at weeks 5, 8, 12, 18, 23, and 26 of peri-implantitis defect induction, and at 4, 8, and 12 weeks following guided bone regeneration for turned (A), SA/HA (B), and SA (C) implants.

Table 1. Radiographic analysis (means ± SD in mm; 95% CI, $n = 5$)

	Week 5	Week 8	Week 12	Week 18	Week 23	Treatment (Week 26)	Week 4	Week 8	3Week 12
Turned	0.7 ± 0.5	1.6 ± 0.8	1.9 ± 0.9	2.5 ± 0.9	2.4 ± 0.9	2.4 ± 1.0	2.2 ± 0.8	2.1 ± 0.8	2.2 ± 0.8
SA/HA	0.8 ± 0.5	1.8 ± 0.4	2.1 ± 0.5	2.5 ± 0.5	2.6 ± 0.5	2.7 ± 0.6	2.4 ± 0.6	2.3 ± 0.6	2.3 ± 0.7
SA	0.7 ± 0.5	1.6 ± 0.7	1.8 ± 0.7	2.4 ± 0.7	2.3 ± 0.9	2.3 ± 1.0	2.2 ± 0.8	2.0 ± 0.8	2.0 ± 0.8
p-value	0.956	0.796	0.772	0.939	0.773	0.746	0.812	0.697	0.700

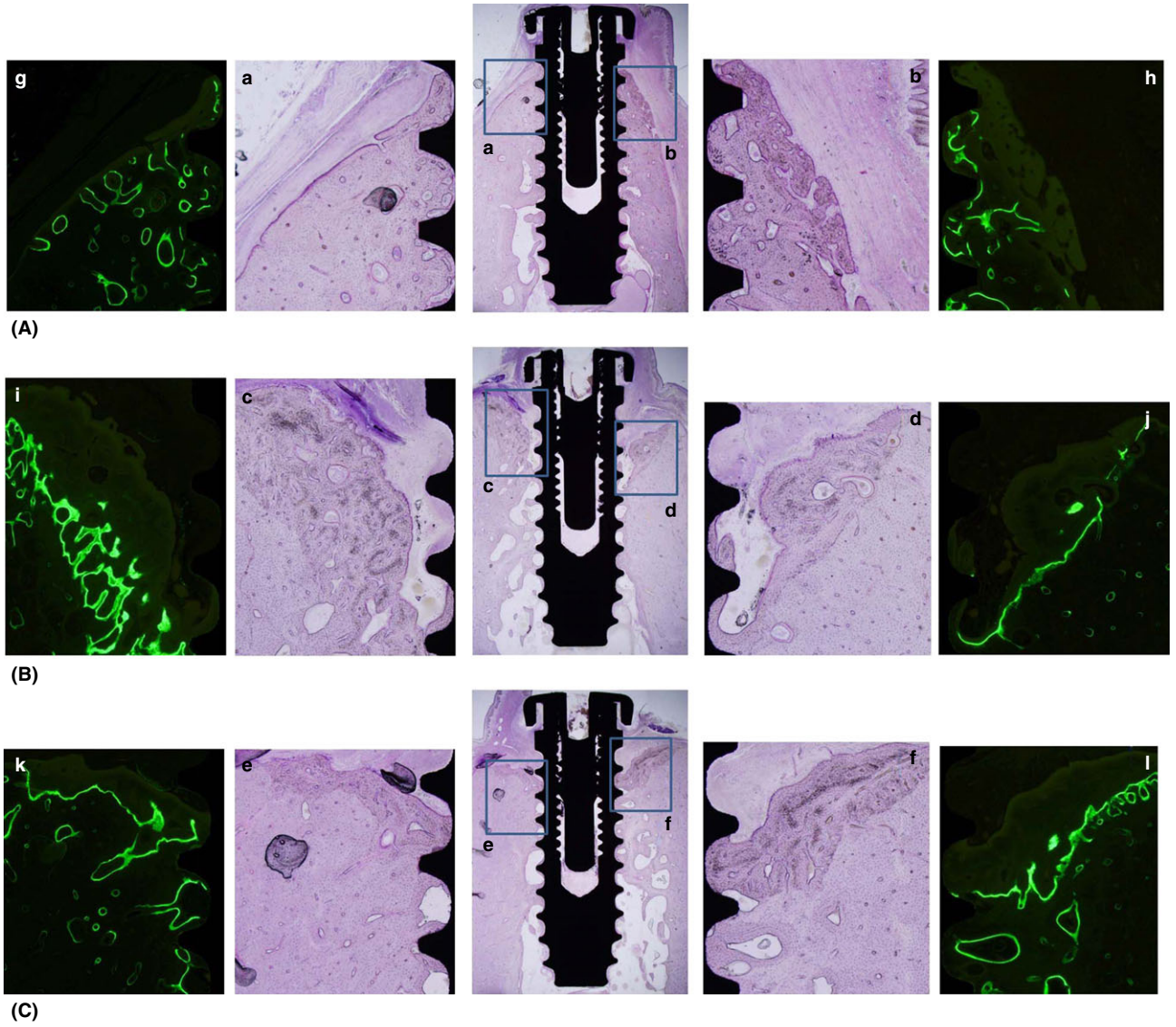

Fig. 5. Representative photomicrographs showing overviews (×12.5) of turned (A), SA/HA (B), and SA (C) surface implants and magnification (inserts; ×40) of crestal bone levels (haematoxylin & eosin and calcein fluorescent marker).

Discussion

The objective of this study was to evaluate bone formation and osseointegration following surgical treatment of experimental peri-implantitis at dental implant surface technologies – turned, SA/HA, and SA – exposed to ligature-induced breakdown conditions over 23 weeks. The SA and SA/HA surfaces did not prove to be excessively susceptible to provoked ligature-induced breakdown compared with the turned control as judged from similar depth peri-implant bone defects for the three surface technologies. The implants were then subject to surface decontamination and guided bone regeneration surgery. Reconstructive surgery resulted in statistically significant increased vertical bone reconstruction at SA/HA and SA surfaces versus that at the control. Only numerical differences in favour of the SA/HA surface relative to bone reconstruction area and

Table 2. Histometric analysis (means ± SD in mm; 95% CI, $n = 5$)

	Peri-implantitis defect depth	Bone reconstruction height (mm)	Bone reconstruction area (mm^2)	Bone-implant contact (%)
Turned	2.7 ± 1.2	0.1 ± 0.2*†	0.2 ± 0.2	40.3 ± 44
SA/HA	3.5 ± 1.2	0.5 ± 0.6*	0.5 ± 0.6	60.9 ± 39
SA	3.2 ± 1.4	0.5 ± 0.7†	0.3 ± 0.4	49.8 ± 39
p-value	0.823	0.025	0.420	0.284

*$p = 0.014$.
†$p = 0.021$.

osseointegration were observed. In all, the results suggest that the SA and SA/HA nanostructured implant surface technologies may not present as a significant obstacle to bone formation following exposure to experimental peri-implantitis conditions.

Resolution of peri-implantitis defects has been shown influenced by implant surface characteristics in animal models. Albouy et al. (2011) showed improved bone levels following surgical treatment including mechanical cleaning at turned, titanium plasma-sprayed, and SA implants, while mucosal swelling/redness and bone loss characterized healing at titanium implants with an anodized surface. Parlar et al. (2009) reported that resolution of peri-implantitis defects at turned, SA, and titanium plasma-sprayed implants varied with the surface decontamination approach, comparatively favourable bone formation being observed at SA over that at titanium plasma-sprayed and turned implants, differences between implant surface technologies also observed in the preset study. However, studies in clinical settings have not been able to confirm preferred implant surface characteristics or decontamination protocols in the management of advanced peri-implantitis lesions, only limited effects have been reported irrespective of approach (Schwarz et al. 2011, 2012, 2013). Also, the local use of chlorhexidine has been reported to have minor influence on surgical resolution of peri-implantitis (Carcuac et al. 2015). Clearly, preclinical/clinical studies, today limited to surface technologies or decontamination protocols, also need to consider addition of osteoconductive/osteoinductive technologies to approach clinical significance.

The adjunctive use of bone grafting, bone biomaterials, or growth factors was not considered in the present study. Only meticulous debridement adjunctive to a decontamination protocol using a chlorhexidine and saline-based protocol (Schou et al. 2003) followed by provisions for guided bone regeneration was used to focus on possible/relevant contributions of the decontaminated implant surface to resolution of the adjoining peri-implantitis defect. SA implants showed a tendency to support greater bone formation than turned implants, while SA/HA implants showed greater bone reconstruction than SA and turned implants although observed differences did not reach statistical significance for the SA/HA and HA implants. One point of discussion is the limited reconstruction of alveolar bone averaging 0.5 mm at the SA/HA and SA implants. Comparable vertical bone gain (0.7 mm) has been reported in previous work although following minor differences in experimental protocol (Persson et al. 1999). However, immediate comparisons between studies may not be meaningful due to differences in design, animal model, implant technologies, time allowed between peri-implantitis initiation, reconstruction and study termination, and analysis. One should also consider the limited regenerative potential of alveolar bone shown following guided bone regeneration in a supra-alveolar defect model (Caplanis et al. 1997, Wikesjö et al. 2004). Further, in intra-bony peri-implant defects, the regenerative potential is related to the depth of the intra-bony defect, shallow defects such as herein only allowing limited vertical bone gain. In perspective, mean peri-implant vertical bone gain in complex chronic peri-implantitis defects in nonhuman primates receiving a BMP-2 construct amounted to clinically relevant 2.6 mm or 77% of the partially intra-bony defect compared to 0.8 mm or 24% for the surgery control, BMP-2 induced bone providing robust evidence of re-osseointegration, bone-implant contact approximating 40% (Hanisch et al. 1997a, b).

In contrast to previous work evaluating re-osseointegration at various implant surface technologies following guided bone regeneration using a canine platform (Wetzel et al. 1999), re-osseointegration, although limited, was observed in the present study. The SA/HA surface yielded greater, although not statistically significant, re-osseointegration compared with SA and turned surfaces. These observations are in harmony with previous work where rough surfaces irrespective of the decontamination protocol showed enhanced re-osseointegration compared to turned controls (Persson et al. 2004). This observation intriguing in itself in the sense that biofilm formation is facilitated at rough surfaces (Teughels et al. 2006) and biofilm decontamination apparently more challenging (Dennison et al. 1994). However, the absolute difference between the surface technologies in the present study was too small to permit a definitive statement. Also, it should be noted that the turned implants used in the present study were considerably smoother than commercially available turned implants. Clearly a systematic study is needed to exploit the effects of existing and novel implant surface decontamination protocols to support much needed re-osseointegration in clinical settings.

In conclusion, while ligature-induced breakdown does not appear implant surface dependent in this animal model, bone formation and osseointegration at the decontaminated implants appears more favourable at SA and SA/HA surfaced over turned implants surfaces following surgical treatment.

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Clinical Relevance

Scientific rationale for the study: Dental implant surface technologies have been shown to significantly influence osseointegration. However, limited information is available relative to bone formation/re-osseointegration at surface technologies exposed to peri-implantitis. Hence, the objective of this study was to evaluate bone formation and osseointegration at dental implants with different surface characteristics exposed to experimental peri-implantitis conditions.
Principle findings: The histometric analysis showed significantly enhanced bone formation at decontaminated sandblasted/acid-etched (SA) and SA/hydroxyapatite (HA) nanostructured implants over turned implants subject to ligature-induced breakdown following guided bone regeneration surgery.
Practical implications: SA and SA/HA nanostructured implant surface technologies do not appear to provide a significant obstacle to alveolar reconstruction following exposure to ligature-induced breakdown.