Influence of Microtextured Implant Surfaces on Peri-implantitis and Its Treatment: A Preclinical Trial

Juan C. Rodriguez, DDS, MS[1]/Tapan Koticha, BDS, MDS[2]/Diana L. Eubanks, DVM, MS[3]/
Ivan Rudek, DDS[4]/Fred J. Molz, PhD[5]/Ludovica Chiavaccini, DVM, MSCS[6]/
Andrew Claude, DVM, Dipl ACVAA[7]/Steven Elder, PhD[8]/Hom-Lay Wang, DDS, MSD, PhD[9]

Purpose: *The prevalence of peri-implantitis has increased significantly, forcing clinicians to search for ways to prevent it. Laser-microtextured surfaces promote soft tissue attachment and provide a tight seal around implants. Hence, the aim of this study was to examine the clinical, radiographic, and histologic features of ligature-induced peri-implantitis, as well as the effect of surgical treatment of these induced peri-implantitis lesions on laser-microtextured implants in a controlled animal model.* ***Materials and Methods:*** *Six mini-pigs (three males/three females) received 6 implants each (3 resorbable blast textured [RBT] implants and 3 laser-microtextured [LM] implants) in mandibular premolar sites, for a total of 36 implants. Two groups were identified based on the time point of sample analysis. After osseointegration was achieved, metal wire ligatures were placed and left for 12 weeks. Group 1 samples were then obtained, and group 2 samples received rescue therapy following a guided bone regeneration (GBR) protocol. Sample collection in group 2 was completed 12 weeks after the samples were submerged and treated. All samples were analyzed histologically and measurements were taken.* ***Results:*** *Four implants (three RBT, one LM) were lost at early time points because of implant instability. Interimplant distances and soft tissue thicknesses varied subtly between groups. More notable was the mean (± standard error of the mean) crestal bone loss (group 1: 1.860 ± 1.618 mm [LM] and 2.440 ± 2.691 mm [RBT]; group 2: 2.04 ± 1.613 mm [LM] and 3.00 ± 2.196 mm [RBT]) ($P < .05$), as demonstrated by a paired t test. Histologic pocket depth was also greater at RBT sites than at LM sites (4.448 ± 2.839 mm and 4.121 ± 2.251 mm, respectively, in group 1; and 3.537 ± 2.719 mm and 2.339 ± 1.852 mm, respectively [$P < .005$] in group 2).* ***Conclusion:*** *LM implants had less crestal bone loss and shallower histologic pocket depth compared with their RBT counterparts. Also, LM implants had higher bone fill when a rescue therapy (GBR) was performed.* Int J Oral Maxillofac Implants 2017 (7 pages). doi: 10.11607/jomi.5599

Keywords: *implant surface, microtextured implant surface, peri-implantitis*

[1]Adjunct Clinical Assistant Professor, Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, Michigan, USA.
[2]Clinical Assistant Professor, Department of Periodontics, College of Dentistry, The University of Oklahoma, Oklahoma City, Oklahoma, USA. Formerly, Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, Michigan, USA.
[3]Associate Clinical Professor Service Chief, Community Veterinary Services, Department of Clinical Sciences, Mississippi State University, Mississippi State, Mississippi, USA.
[4]Private practice, Itajei, Brazil. Formerly, Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, Michigan, USA.
[5]Vice President, Research and Development, BioHorizons, Birmingham, Alabama, USA.
[6]Assistant Professor, Clinical Anesthesia, University of Pennsylvania, School of Veterinary Medicine. Formerly, Community Veterinary Services, Department of Clinical Sciences, Mississippi State University, Mississippi State, Mississippi, USA.
[7]Assoc. Professor and Section Chief, Anesthesiology, Michigan State University, College of Veterinary Medicine, East Lansing, Michigan, USA.
[8]Professor, Department of Agricultural and Biological Engineering, Mississippi State University, Mississippi State, Mississippi, USA.
[9]Professor and Director of Graduate Periodontics, Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, Ann Arbor, Michigan, USA.

Correspondence to: Dr Hom-Lay Wang, Department of Periodontics and Oral Medicine, University of Michigan School of Dentistry, 1011 N. University Ave, Ann Arbor, MI 48109-1078, USA. Fax: (734) 936-0374. Email: homlay@umich.edu

Osseointegrated endosseous dental implants for replacement of lost dentition have been in use for more than 30 years with widely reported success.[1–4] However, this journey has not been without complications. The increasing numbers of dental implants placed have led to more implant-related complications, which create a challenging and an unpredictable burden for patients and dentists alike. Several attempts have been made to define the diseases associated with dental implants, and two main entities have emerged: peri-implant mucositis and peri-implantitis.[2,5–7] Peri-implant mucositis is the presence of inflammation in the mucosa at an implant site with no signs of loss of supporting bone beyond the initial physiologic bone remodeling.[8] In addition to inflammation in the mucosa, peri-implantitis is characterized by loss of supporting bone beyond the initial biologic bone remodeling.[8] Derks et al[4] reported a peri-implantitis prevalence ranging from 28% to 56% of subjects and 12% to 43% of implant sites, which ultimately leads to a total implant loss of 7.6%. This variation in prevalence could be due largely to the lack of uniformity in criteria used to define peri-implantitis, as well as to the variables inherent in the diagnosis of disease.[9,10] Because of the high incidence of peri-implant complications, practitioners have tried several surgical and nonsurgical treatments, concluding that peri-implant mucositis is treatable with nonsurgical therapy; however, peri-implantitis seems to respond better to surgery, but the results are unpredictable.[5,11,12] In the absence of a safe and predictable treatment for peri-implantitis, the focus on prevention has become even more important.

Several factors influence the incidence of peri-implantitis; patient-based risk indicators include, but are not limited to, poor-oral hygiene, smoking, alcohol consumption, history of periodontitis, diabetes mellitus, and genetic traits. Factors leading to early implant loss include smoking, history of periodontitis, implant length less than 10 mm, and certain implant surface characteristics, with the last factor being especially relevant to late implant loss.[4] Other determining factors for crestal bone loss and peri-implantitis are implant macrodesign and surface treatments.[4,7] The Seventh European Workshop on Periodontology examined whether implant surfaces play a role in the etiology of peri-implant diseases.[5] A review by Renvert et al[13] revealed that while clinical evidence was lacking with regard to the effect of implant surfaces on the initiation of peri-implantitis, limited experimental evidence showed that surface characteristics may have an effect on the progression of established peri-implantitis.

Recent animal studies have shown that a difference exists in the extent of experimentally induced peri-implantitis between different rough surfaces.[14–16] The researchers found that certain rough surfaces were associated with greater bone loss with spontaneous progression of peri-implantitis. This disease progression is likely to occur if an invasion of pathogenic bacteria and chronic inflammation occur through the gingival sulcus due to failure of the soft tissue seal. Consequently, there has been a growing focus on optimizing the transmucosal component of dental implants in hopes of promoting mucosal and connective tissue (CT) attachment and, hence, creating a resistant seal to the oral cavity. To accomplish this, laser-etched microgrooved titanium surfaces have been used to promote the contact guidance phenomenon, which refers to the tendency of a cell to be oriented and guided in its direction of motion by the shape of the surface with which it is in contact.[17]

Depending on the groove characteristics (depth, width, pitch), the cell response may vary from a focal adhesion to just the groove ridge to the entire cell's adhering to the groove floor or wall. In vitro and in vivo studies seem to suggest that horizontal grooves on transmucosal components of implants encourage formation of a wider zone of CT attachment[18] and prevent epithelial downgrowth.[19,20]

Laser-microtextured titanium surfaces (Laser-Lok, BioHorizons) that promote soft tissue attachment to implant structures are a promising advancement in the field of implant dentistry. Animal and human evidence of CT attachment to laser-microtextured titanium surfaces has been demonstrated at the histologic level after a healing period of 3 and 6 months, respectively.[21,22] To test the endurance of the CT attachment observed around laser-microtextured titanium implants, the authors aimed to study the clinical, radiographic, and histologic features of ligature-induced peri-implantitis at dental implant sites with similar geometry but different surface characteristics of the implant collar. A secondary aim was to evaluate the effect of surgical treatment of experimentally induced peri-implantitis using guided bone regeneration (GBR) on two implant surfaces in a controlled animal model.

MATERIALS AND METHODS

The Institutional Animal Care and Use Committee of Mississippi State University approved all animal experiments (approval no. 12-050). Six mini-pigs (three male, three female), weighing between 70.3 and 89.4 kg, bred exclusively for biomedical research purposes, were obtained from a licensed vendor and used for the experiments. The authors determined the sample size by performing a power sample size calculation and by considering previous studies with similar sample sizes.[14–16] All surgical procedures were carried out under general anesthesia induced with intravenous propofol (10 mg/mL, 0.6 mL/kg) and sustained with nitrous oxide:oxygen (1:1.5–2) and isoflurane in conjunction with endotracheal intubation.

Endosseous solid screw–type implants (tapered internal system, BioHorizons) were used in this research. Two configurations (resorbable blast textured [RBT] and laser-microtextured [LM]) were used based on the surface texture of the implants. All implants were internal hex, 3.4 mm in diameter and 9 mm in length. RBT implants received standard narrow-profile abutments and LM implants received microtextured narrow-profile abutments.

The study was divided into three phases: *(1)* preparatory phase, *(2)* active breakdown phase, and *(3)* treatment phase (Fig 1). Samples in group 1 were obtained after the active breakdown phase, and samples in group 2 were obtained after the treatment phase. During phase 1, mandibular premolars (P2, P3, P4) were extracted and the sites were left to heal under secondary intention for 12 weeks. After the 12-week healing period, a second surgical procedure was performed to place the implants. A mucoperiosteal flap was raised on each lower quadrant, and three RBT or LM implants were placed in an alternating manner according to a randomization code. Hence, each animal received six implants. The healing abutments were placed over each implant, and the flaps were approximated around the abutments and sutured without tension. Sutures were removed at 2 weeks, and animals were switched to a soft-food diet. Phase 2 began 12 weeks after implant surgery; at

 doi: 10.11607/jomi.5599

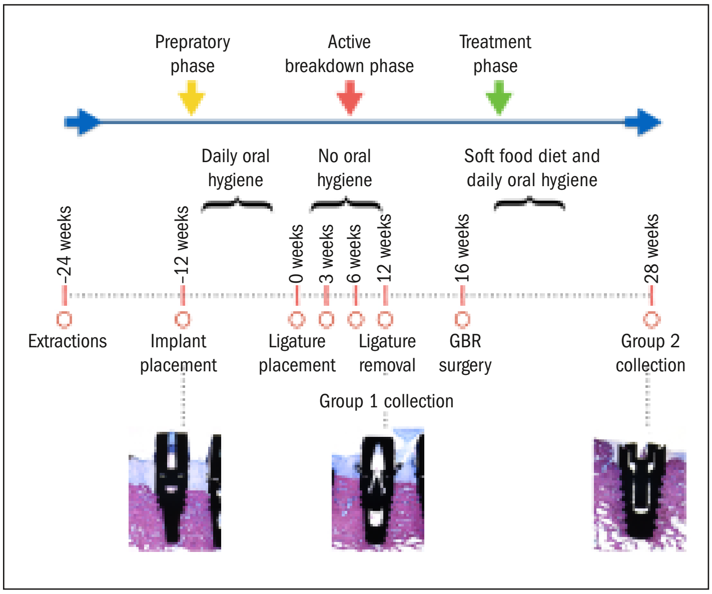


Fig 1 Study timeline depicting the preparatory phase, active breakdown phase, and treatment phase. Oral hygiene protocols and diet are also shown, as well as the sample collection time points and treatment provided.

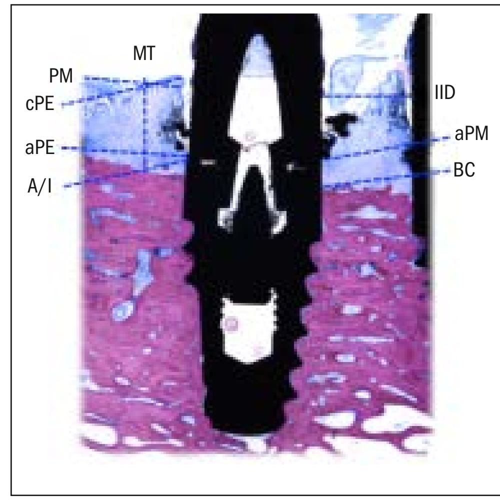


Fig 2 Demarcation of anatomical landmarks used for measurements on the implant histologic sample: PM = marginal peri-implant mucosa; aPM = apical plaque margin; MT = mucosa thickness; A/I = abutment-implant junction; cPE = coronal pocket epithelium; aPE = apical pocket epithelium; IID = interimplant distance; BC = bone crest.

this point, laser-microtextured healing abutments together with metal ligatures were placed in the peri-implant sulcus of each implant. This step coincided with the end of all oral hygiene procedures to allow for the induction of experimental peri-implantitis. At week 12, animals in group 1 were euthanized using a lethal dose of sodium pentothal. Bone blocks containing the implants were obtained and subjected to histologic analyses. For phase 3 experiments in the remaining three animals (group 2), the ligatures were removed and oral hygiene procedures were reestablished. Four weeks later, surgery was performed; mucoperiosteal flaps were raised to provide access following degranulation and debridement. The implant surfaces were then cleaned with cotton saturated with a tetracycline solution (250 mg diluted with 2.5 mL sterile saline solution). Areas were then irrigated with normal saline. A GBR procedure was performed in which a combination of xenogenic bovine bone (Laddec, BioHorizons) and a collagen membrane (Mem-Lok RCM, BioHorizons) was used to repair the peri-implant defects. Submerged healing took place for 12 weeks, after which the animals were euthanized and the specimens were subjected to histologic analysis. After euthanasia, the jaws were retrieved and placed in the fixative solution; tissue blocks containing the implant and surrounding soft and hard tissues were dissected using a diamond saw (Exakt, Kulzer) and processed for ground sectioning according to standard protocol.[23] Sections were stained with hematoxylin-eosin and toluidine-azure II and examined using both stereomicroscopy and light microscopy.

Figure 2 shows the landmarks identified and used for the linear measurements (ImageJ software, National Institutes of Health). A masked examiner (JCR) made all linear measurements by setting known parameters and performing triplicate measurements on the mesial and distal aspects of each implant. Measurements were based on the marginal position of the peri-implant mucosa (PM), the abutment-fixture (A/F) junction, the bone crest (BC), the most coronal and apical extension of the pocket epithelium (cPE and aPE, respectively), and the interimplant distance for all sites.

Table 1 Bone Loss (mm) from the Abutment-Fixture Junction to the Bone Crest[a]

	Group 1		Group 2	
	LM	RBT	LM	RBT
	1.509	2.463	2.421	3.104
	1.434	1.565	1.614	2.520
	2.244	0.984	1.614	2.370
	2.561	1.122	1.242	2.524
	2.446	2.764	0.535	2.667
	1.839	2.201	1.524	3.275
	2.133	2.183	3.260	1.180
	1.949	2.684	2.187	1.211
	0.989	0.750	1.040	2.088
	1.529	1.283	2.586	2.459
	0.242	5.131	1.559	2.677
	0.348	4.210	2.179	3.766
	2.801	3.939	2.508	3.897
	3.047	2.750	2.486	4.027
	2.140	2.987	3.653	5.196
	2.554	2.037	2.237	5.048
Mean	1.86	2.44	2.04	3.00

[a]Pooled data for mesial and distal implant sites.
LM = laser microtextured; RBT = resorbable blast textured.

Table 2 Total Soft Tissue Thickness (mm), Determined in the Interimplant Area with Linear Measurements from Marginal Peri-Implant Mucosa to Bone Crest

	Group 1[a]						Group 2[b]					
Measurement	**9086-left**	**9086-right**	**9102-left**	**9102-right**	**9138-left**	**9138-right**	**9089-left**	**9089-right**	**9090-left**	**9090-right**	**9091-left**	**9091-right**
1	4.263	3.247	2.830	2.693	1.881	3.168	1.657	1.630	0.835	0.657	2.476	1.690
2	4.787	3.591	4.540	2.692	3.282	6.410	0.288	1.139	0.786	1.262	2.157	5.188
3	4.316	3.678	1.489	4.136	3.080	2.960	0.734	0.204	2.719	1.055	2.551	3.610
4	3.542	4.482	4.601	6.624	5.376	3.699	NA	NA	2.526	2.886	3.113	3.084
Mean	4.22	3.74	3.36	4.03	3.40	4.05	0.89	0.99	1.71	1.46	2.57	3.39

[a]Total mean thickness = 3.806 mm.
[b]Total mean thickness = 1.838 mm.

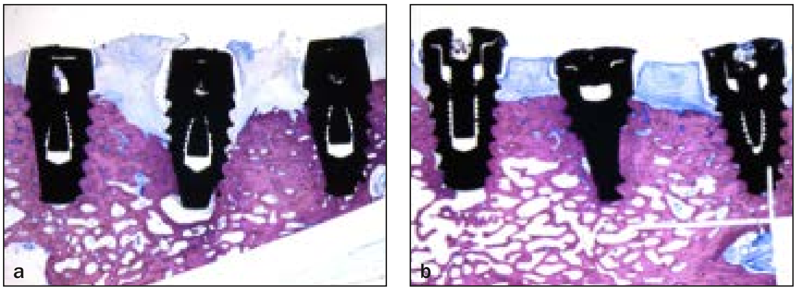


Fig 3a Histologic samples in group 1. The mesial and distal implants have a laser-microgrooved (LM) texture, and the middle implant has a resorbable blast textured (RBT) surface. Note the extent of bone loss associated with the middle implant but the higher bone crest level on the mesial and distal sites. Sections were stained with hematoxylin-eosin and toluidine-azure II and examined by means of stereomicroscopy and light microscopy.

Fig 3b Histologic samples in group 2. The mesial and distal implants have an RBT surface, while the middle implant has an LM surface. The middle implant has a higher bone crest level than the mesial and distal sites. Sections were stained with hematoxylin-eosin and toluidine-azure II and examined by means of stereomicroscopy and light microscopy.

The measurements included bone loss (A/F to BC), soft tissue thickness at the crestal level (PM to highest BC), histologic sulcus depth (cPE to lowest aPE), and interimplant distance. A paired *t* test was performed as appropriate. Differences were considered significant at $P < .05$. Data are presented as mean ± standard error of the mean.

RESULTS

Clinical Observations

Healing proceeded uneventfully for 32 surgical implant sites during the 12 weeks after extraction of all mandibular premolars and implant placement; 3 RBT and 1 LM implants (9102 middle left, 9089 middle right, 9089 distal left, and 9138 middle right) were lost because of instability at abutment placement. The failures may have been related to premature loading (such as biting the cage). The second phase of the study, after initiation of ligature-induced peri-implantitis, proved uneventful for 12 weeks. The assigned time points were completed for all animals, and all remaining implants performed well, with no loss or compromised stability.

Histologic Observations

To ensure that unwanted variables were not encountered in the experiments, the authors performed standard measurements of interimplant distances and soft tissue thickness for both groups and implant types. The interimplant distance in both groups was similar (group 1, 3.451 ± 1.03 mm; group 2, 3.385 ± 1.445 mm). This implant location accuracy helped minimize the effect of bone loss in neighboring implant sites (Table 1).

Mean soft tissue thickness in group 1 was 3.806 ± 0.441 mm and in group 2 was 1.838 ± 1.501 mm ($P < .005$) (Table 2). This discrepancy between groups could be attributed to the fact that group 1 had no bone loss at baseline. Similarly, the reduction in soft tissue thickness in group 2 may have been caused by recession and bone loss at the time of treatment and placement of a cover screw.

Group 1. Histologic samples are shown in Figs 3 to 5. Both implant systems are shown with ligatures

 doi: 10.11607/jomi.5599

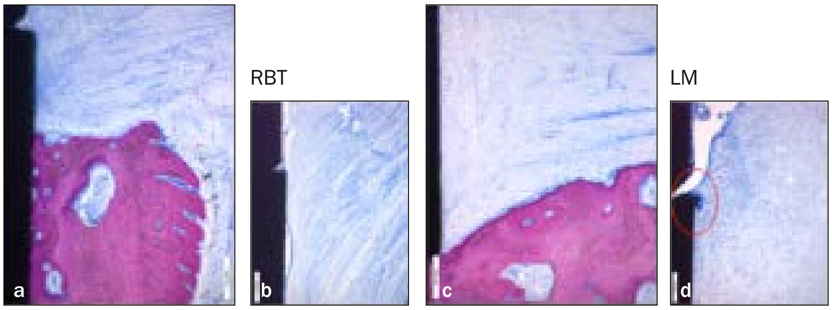
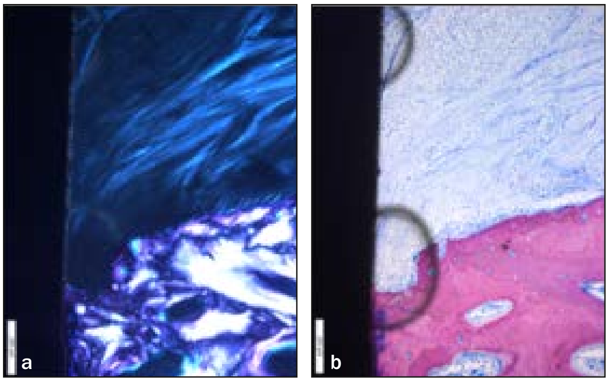


Fig 4 Implant-abutment interface area is shown. *(a)* Dense cellularity associated with resorbable blast textured (RBT) peri-implant tissues compared with *(c)* laser microgrooved (LM) surface. *(b)* and *(d)* Abutment-implant (A/I) junction at higher magnification shows surface characteristics on RBT-treated and LM-treated surfaces. Connective-tissue attachment is seen at the A/I junction on LM surfaces *(d)* but not on RBT surfaces *(b).*

in place; a dense biofilm is seen at the level of the ligatures and migrating apically to the abutment-implant interface. The authors observed a difference between the two implant surface treatments. CT fiber attachment was seen on laser-microgrooved areas in the LM implants, whereas the sulcus of RBT implants seemed to allow a deeper penetration of biofilm and exhibited a higher inflammatory infiltrate (Figs 4 and 5). Different rates of crestal bone loss were observed between samples and among the groups.

Group 2. The histologic analysis, performed after completion of regenerative therapy, showed a heterogeneous outcome. In certain cases, the bone-grafted sites experienced an overall reduction in soft tissue support and a greater sulcus depth (Table 3), as well as a slightly increased peri-implant bone loss.

Table 3 shows precise histologic measurements of crestal bone loss. Crestal bone loss in group 1 was 1.860 ± 1.618 mm for LM-treated implants and 2.440 ± 2.691 mm for RBT-treated implants. Slightly higher bone loss was found in both implant types in group 2 (LM implants, 2.04 ± 1.613 mm; RBT implants, 3.00 ± 2.196 mm) ($P < .005$). Histologic pockets were also deeper at RBT sites compared with LM sites (4.448 ± 2.839 mm and 4.121 ± 2.251 mm, respectively, in group 1; 3.537 ± 2.719 mm and 2.339 ± 1.852 mm, respectively ($P < .005$), in group 2, being statistically significantly different in laser-microtextured implants.



Figs 5a and 5b Higher-magnification slides show connective-tissue fiber attachment perpendicular to the laser-microgrooved implant surface in a sample from group 1.

Table 3 Histologic Pocket Depth (mm) Measured from the Most Coronal and Apical Extension of the Pocket Epithelium

	Group 1		Group 2	
	LM	RBT	LM	RBT
	4.589	5.161	2.474	5.952
	4.071	5.703	2.723	6.256
	2.881	5.523	4.191	3.324
	5.022	7.341	3.115	2.468
	2.799	4.008	2.223	3.358
	2.641	4.616	2.041	3.556
	4.755	3.099	1.624	2.008
	6.372	4.063	1.461	4.061
	1.777	2.360	2.795	3.571
	3.213	3.078	2.660	2.867
	3.947	4.303	2.288	3.426
	4.600	3.889	1.257	1.607
	4.415	6.082	2.634	—
	4.793	3.874	1.271	—
	5.130	4.643	—	—
	4.935	3.437		
Mean	4.121	4.448	2.339	3.537

LM = laser microtextured; RBT = resorbable blast textured.

DISCUSSION

The maintenance of soft tissue contour, characterized by adequate underlying bone, is critical for dental implants placed in esthetically demanding situations.[24,25] Crestal bone remodeling was once believed to be an inevitable process taking place during the first year of implant loading and continuing gradually at a lower scale.[1] Investigators have focused on reducing this remodeling. The introduction of platform switching and laser-modified microtexture at the cervical portion of dental implants has addressed this issue. However, studies have shown that in most scenarios in which these two modalities were tested and compared with one another, laser microtexture outperformed platform switching, even in cases involving a thin soft tissue profile.[26–28] In the present study, the LM-treated implants tended to exhibit more resistance to peri-implant tissue inflammation at the breakdown stage. Similarly, once the ligatures were removed, LM-treated implants exhibited less advanced disease progression. These results, based on histologic measurements, also reflect what was observed clinically at the time of sacrifice. Localized inflammation was present in all samples; however, inflammation seemed more severe at RBT implant sites than at LM implant sites, as shown in Fig 3a. Also found was attachment of dense CT fibers with vertical orientation to the implant-abutment interface in the LM-treated implant sites (Fig 3b). Interestingly, because of the study design, lateral sites (mesial or distal) with LM-treated implants tended to limit the amount of bone loss observed in the middle implant site; when LM implants were placed in the middle location, they tended to respond better than their lateral counterparts.

Regarding the study's secondary aim, the GBR procedure proved to be challenging. In all cases the osseous defect left by the ligature-induced experiment was not completely filled. The histologic appearance of the implant types was similar, except for evidence of perpendicular CT fiber attachment on LM surfaces. Consistent with other studies, it was found that application of bone graft and barrier membranes in the treatment of peri-implant defects remains a widely unpredictable approach; however, some level of bone fill was achieved. Similarly, surface treatment resulted in a 1-mm difference in bone gain between groups, favoring the LM surfaces, which, in some cases, reached a 0.5-mm distance from the BC to the implant neck. The results of this study—at both the disease induction phase and the regenerative phase—favored LM surfaces in terms of disease resistance and regenerative potential. The results also support findings in the literature showing multiple benefits of this type of surface modification in maintaining long-term health and esthetics around dental implants.[18,26–28]

Some limitations were also present in this study. Because implants were placed in an intercalated manner, the tissue inflammation from one area tended to extend to the neighboring surface, creating a cumulative inflammatory effect. This was evident histologically, where more crestal bone loss was seen on the implant side exposed to the worst of the three implants. Total bone loss was also reported based on pooled data from mesial and distal aspects to compensate for implant site bias. However, even when these details are taken into consideration, the results clearly favored the LM surface. Also, one must keep in mind that the examiner was masked to the groups.

CONCLUSIONS

Laser-microtextured implants showed less crestal bone loss after ligature-induced peri-implantitis. They also exhibited higher bone fill when a rescue therapy (GBR) was performed on all implants.

ACKNOWLEDGMENTS

The authors thank the animal care staff at Mississippi State University for their assistance in conducting this experiment. The study was sponsored by BioHorizons, Birmingham, Alabama. Dr Fred J. Molz is employed at BioHorizons as the vice president of research and development. Dr Hom-Lay Wang receives financial support as a lecturer for BioHorizons. None of the other authors has any financial interests, either directly or indirectly, in the products or information mentioned in the article.

REFERENCES

1. Albrektsson T, Brånemark PI, Hansson HA, Lindstrom J. Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man. Acta Orthop Scand 1981;52:155–170.
2. Berglundh T, Persson L, Klinge B. A systematic review of the incidence of biological and technical complications in implant dentistry reported in prospective longitudinal studies of at least 5 years. J Clin Periodontol 2002;29(suppl):s197–s212.
3. Naert I, Quirynen M, van Steenberghe D, Darius P. A study of 589 consecutive implants supporting complete fixed prostheses. Part II: Prosthetic aspects. J Prosthet Dent 1992;68:949–956.
4. Derks J, Schaller D, Håkansson J, Wennström JL, Tomasi C, Berglundh T. Effectiveness of implant therapy analyzed in a Swedish population: Prevalence of peri-implantitis. J Dent Res 2016;95:43–49.
5. Lang NP, Berglundh T, Working Group 4 of Seventh European Workshop on Periodontology. Periimplant diseases: Where are we now? Consensus of the Seventh European Workshop on Periodontology. J Clin Periodontol 2011;38(suppl):s178–s181.
6. Lindhe J, Meyle J, Group D of European Workshop on Periodontology. Peri-implant diseases: Consensus report of the Sixth European Workshop on Periodontology. J Clin Periodontol 2008;35(suppl): s282–s285.
7. Heitz-Mayfield LJ. Peri-implant diseases: Diagnosis and risk indicators. J Clin Periodontol 2008;35(suppl):s292–s304.
8. Zitzmann NU, Berglundh T. Definition and prevalence of peri-implant diseases. J Clin Periodontol 2008;35(suppl):s286–s291.
9. Fransson C, Lekholm U, Jemt T, Berglundh T. Prevalence of subjects with progressive bone loss at implants. Clin Oral Implants Res 2005;16:440–446.
10. Roos-Jansaker AM, Lindahl C, Renvert H, Renvert S. Nine- to fourteen-year follow-up of implant treatment. Part II: Presence of peri-implant lesions. J Clin Periodontol 2006;33:290–295.
11. Klinge B, Gustafsson A, Berglundh T. A systematic review of the effect of anti-infective therapy in the treatment of peri-implantitis. J Clin Periodontol 2002;29(suppl):s213–s225.
12. Abrahamsson I, Berglundh T, Glantz PO, Lindhe J. The mucosal attachment at different abutments. An experimental study in dogs. J Clin Periodontol 1998;25:721–727.
13. Renvert S, Polyzois I, Claffey N. How do implant surface characteristics influence peri-implant disease? J Clin Periodontol 2011; 38(suppl):s214–s222.
14. Albouy JP, Abrahamsson I, Persson LG, Berglundh T. Spontaneous progression of peri-implantitis at different types of implants. An experimental study in dogs. I: Clinical and radiographic observations. Clin Oral Implants Res 2008;19:997–1002.

15. Albouy JP, Abrahamsson I, Persson LG, Berglundh T. Spontaneous progression of ligatured induced peri-implantitis at implants with different surface characteristics. An experimental study in dogs II: Histological observations. Clin Oral Implants Res 2009;20:366–371.
16. Berglundh T, Gotfredsen K, Zitzmann NU, Lang NP, Lindhe J. Spontaneous progression of ligature induced peri-implantitis at implants with different surface roughness: An experimental study in dogs. Clin Oral Implants Res 2007;18:655–661.
17. Brunette DM, Chehroudi B. The effects of the surface topography of micromachined titanium substrata on cell behavior in vitro and in vivo. J Biomech Eng 1999;121:49–57.
18. Kim S, Oh KC, Han DH, et al. Influence of transmucosal designs of three one-piece implant systems on early tissue responses: A histometric study in beagle dogs. Int J Oral Maxillofac Implants 2010;25:309–314.
19. Chehroudi B, Gould TR, Brunette DM. Titanium-coated micromachined grooves of different dimensions affect epithelial and connective-tissue cells differently in vivo. J Biomed Mater Res 1990;24:1203–1219.
20. Chehroudi B, Gould TR, Brunette DM. The role of connective tissue in inhibiting epithelial downgrowth on titanium-coated percutaneous implants. J Biomed Mater Res 1992;26:493–515.
21. Nevins M, Kim DM, Jun SH, Guze K, Schupbach P, Nevins ML. Histologic evidence of a connective tissue attachment to laser microgrooved abutments: A canine study. Int J Periodontics Restorative Dent 2010;30:245–255.
22. Nevins M, Nevins ML, Camelo M, Boyesen JL, Kim DM. Human histologic evidence of a connective tissue attachment to a dental implant. Int J Periodontics Restorative Dent 2008;28:111–121.
23. Donath K, Breuner G. A method for the study of undecalcified bones and teeth with attached soft tissues. The Säge-Schliff (sawing and grinding) technique. J Oral Pathol 1982;11:318–326.
24. Elian N, Jalbout ZN, Cho SC, Froum S, Tarnow DP. Realities and limitations in the management of the interdental papilla between implants: Three case reports. Pract Proced Aesthet Dent 2003;15:737–744.
25. Tarnow D, Elian N, Fletcher P, et al. Vertical distance from the crest of bone to the height of the interproximal papilla between adjacent implants. J Periodontol 2003;74:1785–1788.
26. Iorio-Siciliano V, Matarasso R, Guarnieri R, Nicolò M, Farronato D, Matarasso S. Soft tissue conditions and marginal bone levels of implants with a laser-microtextured collar: A 5-year, retrospective, controlled study. Clin Oral Implants Res 2015;26:257–262.
27. Linkevicius T, Puisys A, Svediene O, Linkevicius R, Linkeviciene L. Radiological comparison of laser-microtextured and platform-switched implants in thin mucosal biotype. Clin Oral Implants Res 2015;26:599–605.
28. Guarnieri R, Grande M, Ippoliti S, Iorio-Siciliano V, Riccitiello F, Farronato D. Influence of a Laser-Lok surface on immediate functional loading of implants in single-tooth replacement: Three-year results of a prospective randomized clinical study on soft tissue response and esthetics. Int J Periodontics Restorative Dent 2015;35:865–875.