# Evaluation of Premature Membrane Exposure and Early Healing in Guided Bone Regeneration Peri-Implant Dehiscence and Fenestration Defects With a Slowly Resorbing Porcine Collagen Ribose Cross-Linked Membrane: A Consecutive Case Series

E. Todd Scheyer, D.D.S., M.S., Michael K. McGuire, D.D.S.[1]

[1] Private Practice, Houston, TX.

**Introduction:** Guided Bone Regeneration (GBR) is a well-known and accepted procedure for effective treatment of oral bony defects that is dependent upon sustained barrier membrane function for adequate new bone formation. Cross-linking between collagen fibrils with various agents has proven effective in prolonging membrane integrity and function, both critical to positive bone regenerative outcomes. Overlying mucosal dehiscence with membrane exposure, may, lead to less than adequate new bone formation. The current case series examines guided bone regenerative outcomes for peri-implant defects using a ribose cross-linked porcine collagen membrane which appears to reduce the risk of cross-linked associated membrane exposure.

**Case Series:** Nine patients with peri-implant dehiscence and fenestration defects were enrolled in this consecutive case series pilot study. At surgery the linear range of implant thread exposure was between 5 mm – 10 mm (mean of ~6.3 mm). Following implant insertion, grafting with mineralized allograft, and placement of a ribose cross-linked collagen membrane, patients were followed for a minimum of 6 months. At six-month reentry surgery all dehiscence and fenestration defects had been eliminated with newly regenerated bone covering previously exposed implant threads. No membrane exposure occurred during this study.

**Conclusion:** Successful GBR outcomes may be enhanced by avoiding premature membrane exposure. Although collagen cross-linking may be associated with increased mucosal dehiscence, the ribose cross-linked membrane examined in the current study may help promote positive regenerative outcomes by sustained functional and structural integrity and a reduction in membrane exposure incidence.

### Key Words:

**Guided bone regeneration; collagen; membranes, barrier; membranes, cross-linked.**

## Background

Time tested Guided Bone Regeneration (GBR) continues to play an important role in clinical bone regenerative procedures. Critical to that role are well-functioning barrier membranes with properties essential to positive regenerative outcomes. Such properties include the ability to exclude unwanted, non-osteogenic cell-lines from areas to be regenerated, space creation and maintenance, protection of the underlying blood clot, and wound stabilization.[1-3]

Although both non-resorbable and resorbable membranes are used, today's GBR procedures depend primarily on well-designed resorbable porcine or bovine derived collagen membranes that may or may not be cross-linked. Importantly, membranes must maintain their integrity for durations long enough to allow clinically sufficient amounts of new bone to form.[1,3,5-7] Crosslinking between collagen fibrils has become an important method of slowing collagen membrane resorption times in order to maintain membrane protected spaces critical to successful bone regeneration.[5-10] A number of crosslinking agents have been used to modify GBR membranes, including formaldehyde, glutaraldehyde, and the sugar, D-ribose.[6,7,11,12,13] Although successful in slowing resorption times, a number of studies suggest that cross-linked membranes may be more prone to premature membrane exposure than non-cross linked membranes[9,14,15] Although in the majority of cases overlying soft tissue dehiscences will heal,

premature membrane exposure may nevertheless compromise new bone formation during GBR procedures.[13,15,16] In a comprehensive meta-analysis, Machtei demonstrated significant differences in quantities of bone regeneration between intact and prematurely exposed collagen membranes during GBR procedures.[16] Sites with no membrane exposure yielded almost six times more new bone regeneration during GBR procedures than sites that became exposed, a finding both statistically and clinically significant.

In an effort to increase membrane biocompatibility, reduce the risk of premature membrane exposure, and maintain collagen fiber resorption rates compatible with effective GBR procedures, even in the face of overlying soft tissue dehiscence, various membranes cross-linked with a variety of agents continue to be examined. GLYM membrane[2], a porcine-derived collagen membrane cross-linked with ribose and expected to re-enter the marketplace, is one such membrane. This membrane has shown to have sufficient permeability to sustain osteoblast – like cells invitro[4].

The purpose of this prospective, consecutive case series pilot study was to examine the biocompatibility and membrane integrity characteristics of GLYM ribose cross-linked collagen membrane during GBR procedures designed to correct significant peri-implant dehiscence and fenestration defects present at implant placement and to evaluate the GBR outcomes at 6 months post grafting.

## Clinical Presentation

The current prospective consecutive case series was performed over a period of 14 months within a single clinical setting (Study time January 23, 2008 to October 21, 2008). Five males and 2 females between the ages of 39 and 64, all healthy and on no medications, were enrolled in this study. All patients reviewed and signed an informed consent. The study and consent forms were approved by the Essex Institutional Review Board, Lebanon, New Jersey. Of the seven patients, six were non-smokers and the seventh smoked approximately 4 cigarettes per day. Except for two patients who required the insertion of two implants, a single implant was placed into either an existing edentulous site or immediately following tooth extraction. Inclusion into this study required each proposed implant site to be dimensionally compromised, resulting in significant dehiscence or fenestration mediated implant thread exposures needing GBR intervention. (Figure 1a 1b, 1c) Of the nine sites, five had dehiscence defects ranging from 5 to 9 mm (mean: 6.4 mm) and four had fenestration defects ranging from 5 to 10 mm (mean: 6.25 mm). Three of the implant placement sites were in the maxilla and six in the mandible.

## Case Management

At the initial appointment all patients received comprehensive oral and radiographic examinations, including Cone Beam Computerized Tomography (CBCT). (Figure 1a) Study goals and procedures were thoroughly reviewed with each patient and informed consents obtained. Final entry into the study, which required a minimum of three implant threads exposed, was determined at surgery.

At surgery 2% xylocaine with 1:100,000 epinephrine, as well as small amounts of 2% xylocaine with 1:50,000 epinephrine for hemostasis, were administered, followed by full-thickness mucoperiosteal flap reflection. In most cases releasing incisions were required for adequate site exposure. If present, test site teeth were removed and residual sockets thoroughly

debrided of all inflamed tissue. Implants[3] were then placed at each test site in the usual manner, confirming the presence of significant peri-implant dehiscence or fenestration defects at all nine sites. (Figure 1b, 2a) Test sites were then grafted with mineralized freeze-dried bone allograft particulate grafts (FDBA)[4] in an attempt to restore normal alveolar ridge morphology and to cover all exposed implant threads. (Figure 1d, 2b) GLYM cross-linked membranes were then trimmed to extend 2 to 3 mm beyond the defect margins, rehydrated with sterile saline, and placed over the grafted sites without additional screw, tack or suture fixation. (Figure 1e, 2c) The soft tissue flaps were then closed primarily without tension using interrupted non resorbable[5] sutures. (Figure 2d)

Postoperatively, patients were placed on either Amoxicillin 500 mg tid or Doxycycline 100 mg bid for 10 days as well as on 0.12% chlorhexidine gluconate antibacterial rinses. Nonsteroidal anti-inflammatory analgesics were prescribed for pain control.

All patients received post-operative follow-up examinations at weeks 1, 3, 4 and months 2, 4 and 6. Reentry and second-stage implant surgery occurred six months following implant and graft placement.

## Clinical Outcomes

### *Soft Tissue Outcomes*

At all points in time peri-implant mucosal soft tissue healing proceeded uneventfully for all 9 grafted sites without evidence of localized infection. Immediate post-operative swelling and inflammation were mild through week one. (Figure 2d) By the third post-operative week, swelling and evidence of mucosal gingival inflammation had all but disappeared. (Table 1) (Figure 3a) At six months, peri-implant mucosa for all sites was healthy, without signs of swelling or inflammation. (Figure 3b)

### *Hard Tissue Outcomes*

Reentry procedures for second stage implant surgery at 6 months revealed significant bone regenerative responses at all nine test sites. In each case dehiscence or fenestrated thread exposures were either completely or almost completely eliminated by newly regenerated bone.

(Figures 4a, 4b, 4c)

### *Membrane Related Outcomes*

Immediately following GLYM membrane placement subjective assessments were made for membrane composition and handling characteristics. (Tables 2 & 3) Independent assessments by each investigator rated GLYM membrane as “soft and loose in place” and “placed easily and conformed well”.

At all study time points the overlying mucosa covering GLYM membrane remained intact. No membrane exposures occurred at any of the 9 treated sites from initial placement through the six month follow-up examination. Importantly, at the sixth month second stage reentry surgery GLYM membrane appeared (6/9) often to remain physically intact. (Figure 5)

## Discussion

Advances in tissue engineering and recombinant growth factor technologies are profoundly affecting clinicians' approaches to regenerative medicine and will no doubt lead to major paradigm shifts in soft and hard tissue regenerative protocols. The current case series, however, may serve as a reminder that established technologies may continue to be profoundly effective in regenerating vital tissues, are well understood by clinicians, and are cost efficient to our patients.

The 7 patients in this small case series presented with severe peri-implant dehiscence and fenestration bony defects and were all treated successfully by time tested evidence-based Guided Bone Regeneration. Multiple factors may have contributed to the successful outcomes of this study, including the overall good health of this patient pool, meticulous attention to surgical detail, effective graft matrices, and perhaps most importantly, a highly biocompatible cross-linked membrane. Significantly, this membrane continued to function for the entire 6-month duration of this case series without inducing overlying mucosal dehiscence with all its associated potential complications.

Several characteristics of GLYM cross-linked membrane should be briefly mentioned. 1) The membrane is highly biocompatible, allowing cross-membrane nutrient diffusion into the underlying protected space, thus aiding osteoblastic cellular viability.[17] 2) The nature of its cross-linking by natural occurring ribose molecules (glycation) not only significantly delays resorption time necessary for effective GBR, but also leads to nontoxic metabolic breakdown products that do not contaminate the surrounding local environment.[8,18,19,] and 3) If prematurely exposed via soft tissue dehiscence, ribose cross-linking appears to enhance the capacity to withstand bacterial collagenolytic degradation, allowing soft tissue healing and dehiscence closure.[14]

However, given that soft tissue dehiscence did not occur at any time point in this study seems to suggest that the ribose based cross-linking found in the current membrane may not increase the incidence of premature membrane exposure during GBR procedures, a finding that differs from previous studies of various cross-linked membranes. Larger, randomized controlled studies, with long-term follow-up, however, will be needed to verify the results of this current case series.

## Summary

### *Why are These Cases New Information?*

The membrane used in this case series has not been commercially available for more than three year but may soon return to the marketplace. The findings of no membrane exposure with favorable resolution of implant fenestrations make this resorbable membrane an attractive option for the clinician.

### *What are the Keys to Successful Management of These Cases?*

Proper diagnosis and treatments planning for a simultaneous implant placement and GBR technique.

Patient selection regarding their health status and compliance with the post-operative regiment.

Meticulous attention to surgical detail including flap management.

The use of effective graft matrices and a highly biocompatible cross-linked membrane.

### *What are the Primary Limitations to the Success of These Cases?*

Clinician inexperience with flap management, membrane/wound stability and other intricacies of the GBR technique. Due to the challenges of GBR, patient selection is a key factor for success.

## REFERENCES


1) Kay SA, Wisner-Lynch L, Marxer M, Lynch SE. Guided bone regeneration: Integration of a resorbable membrane and a bone graft material. Practical Periodontics and Aesthetic Dentistry 1997;9(2):185-194.

2) Moses O, Vitrial D, Aboodi G, et al. Biodegradation of three different collagen membranes in the rat calvarium: A comparative study. J Periodontol 2008;79:905-911.

3) Hutmacher D, Hurzeler MB, Schliephake H. A review of material properties of biodegradable and bioresorbable polymers and devices for GTR and GBR applications. Int J Oral Maxillofac Implants 1996;11:667-678.

4) Friedmann A, Dehnhardt J, Kleber BM, Bernimoulin JP. Cytobiocompatibility of collagen and ePTFE membranes on osteoblast-like cells *in vitro*. Journal of Biomedical Materials Research Part A 2007;935-941.

5) Zubery Y, Goldlust A, Alves A, Nir E. Ossification of a novel cross-linked porcine collagen barrier in guided bone regeneration in dogs. J Periodontol 2007;78:112-121.

6) Zubery Y, Nir E, Goldlust A. Ossification of a collagen membrane cross-linked by surgar: A human case series. J Periodontol 2008;79:1101-1107.

7) Neiva R, Pagni G, Duarte F et al. Analysis of tissue neogenesis in extraction sockets treated with guided bone regeneration: Clinical, histologic and micro-ct results. Int J Periodontics Restorative Dent 2011;31:457-469.

8) Rothamel D, Schwarz F, Sager M et al. Biodegradation of differently cross-linked collagen membranes: An experimental study in the rat. Clin Oral Implants Res 2005;16:369-378.

9) Friedmann A, Strietzel FP, Maretzki B, et al. Histological assessment of augmented jaw bone utilizing a new collagen barrier membrane compared to a standard barrier membrane to protect a granular bone substitute material. Clin Oral Implants Res 2002;13:587-594.

10) Lee CK, Koo KT, Kim TI et al. Biological effects of a porcine-derived collagen membrane on intrabony defects. J Periodontal Implant Sci 2010;40(5):232-238.

11) Tal H, Moses O, Kozlovsky, Nemcovsky C. (2012) Bioresorbable collagen membranes for Guided Bone Regeneration, Bone Regeneration, Prof. Haim Tal (ED.), ISBN: 978-953-51-0487-2. In Tech. Available from: http://www.intechopen.com/books/bone-regeneration/bioresorbable-collagen-membranes-for-guided bone regeneration.

12) Goissis G, Marcantonio E Jr., Maracantonio RA et al. Biocompatibility studies of anionic collagen membranes with different degree of glutaraldehyde cross-linking. Biomaterials 1999;20:27-34.

13) Klinger A, Asad R, Shapira L, Zubery Y. In vivo degradation of collagen barrier membranes exposed to the oral cavity. Clin Oral Impl Res 2010;8:873-876.

14) Moses O, Pitaru S, Artzi Z, Nemcovsky CE.Healing dehiscence-type defect in implants placed together with different barrier membranes: A comparative clinical study. Clin Oral Implants Res 2005;16:210-219.

15) Oh TJ, Meraw SJ, Lee EJ et al. Comparative analysis of collagen membranes for the treatment of implant dehiscence defects. Clin Oral Implants Res 2003;14(1):80-90.

16) Machtei EE. The effect of membrane exposure on the outcome of regenerative procedures in humans: a meta-analysis. J Periodontol 2001;72:512-516.

17) Friedmann A, Dehnhardt J, Kleber B-M, Bernimoulin J-P. Cytocompatibility of collagen and ePTFE memranes on osteoblast-like cells in vitro. Journal Biomed Mater Res A 2008;86(4)935-941.

18) Bailey AJ, Sims TJ, Avery NC, Halligan EP. Non-enzymatic glycation of fibrous collagen: Reaction products of glucose and ribose. Biochem J 1995;305:385-390.

19) Rothamel D, Schwarz F, Sculean A et al. Biocompatibility of various collagen membranes in cultures of human PDL fibroblasts and human osteoblast-like cells. Clin Oral Implants Res 2004;15(4):443-449.

Corresponding Author:

E. Todd Scheyer, D.D.S., M.S.

Perio Health Professionals, PLLC

3400 S. Gessner Road, Suite 102

Houston, Texas 77063

etsperio@swbell.net

Submitted September 17, 2013; accepted for publication January 6, 2014.

***Figure 1a:***

*Typical cross sectional case presentation with significantly narrowed alveolar ridge which one would anticipate a buccal fenestration.*

***Figure 1b:***

*A representative fenestration defect at surgery. In this case, 10 mm of threads were exposed.*

***Figure 1c:***

*Occlusal view demonstrates extreme buccal bone deficit with resulting exposed implant threads.*

***Figure 1d:***

*Particulate FDBA graft in place to cover all exposed threads and to restore normal ridge anatomy.*

***Figure 1e:***

*Ribose cross-linked collagen membrane placed to cover the FDBA grafted site.*

***Figure 2a:***

*At implant placement 5 mm of implant threads are exposed in this representative case.*

***Figure 2b:***

*Particulate FDBA grafts placed to restore ridge anatomy and to cover all exposed implant threads.*

***Figure 2c:***

*Resorbable collagen ribose cross-linked membranes placed to cover the grafted sites.*

***Figure 2d:***

*Flaps closed primarily without tension. At the end of one week post-op 8 sites were rated with mild inflammation and 1 site with none.*

***Figure 3a:***

*A representative sample with little to no gingival inflammation 3 weeks following GBR surgery.*

***Figure 3b:***

*At 6 months soft tissues at all sites were healthy and without signs of inflammation.*

***Figure 4a:***

*At 6-month reentry surgery, all 5 mm of exposed implant threads are now covered with vital, newly formed bone.*

***Figure 4b:***

*The 10 mm fenestrated defect seen in Figure 1b is no longer present. At 6 months all prior exposed threads are covered with regenerated bone.*

***Figure 4c:***

*Buccal crestal ridge anatomy restored to normal, eliminating the 10 mm fenestration defect.*

***Figure 5:***

*At 6 month second stage surgery a large portion of the ribose cross-linked membrane remains intact.*

**TABLE 1:**

**GINGIVAL INFLAMMATION RATINGS (N = 9)[6]**

| Follow up time | NONE | MILD | MODERATE | SEVERE |
|---|---|---|---|---|
| WEEK 1 | **1** | **8** | **0** | **0** |
| WEEK 3 | **7** | **2** | **0** | **0** |
| WEEK 4 | **8** | **1** | **0** | **0** |
| MONTH 2 | **0** | **0** | **0** | **0** |
| MONTH 4 | **0** | **0** | **0** | **0** |
| MONTH 6 | **0** | **0** | **0** | **0** |

*Inflammation Ratings

None

Mild (color change without edema)

Moderate (glazing, redness, edema and/or hypertrophy)

Severe (marked redness, edema/hypertrophy, and spontaneous bleeding or ulceration)

**TABLE 2:**

**Initial Composition After Placement**

| |
|---|
| The membrane is hard and fixed in place |
| The membrane is firm and fixed in place |
| The membrane is firm and loose in place |
| The membrane is soft and fixed in place |
| The membrane is soft and loose in place |

**TABLE 3:**

| **Membrane Handling** |
| --- |
| The membrane was placed easily and conformed well |
| The membrane was placed easily but was difficult to conform |
| The membrane required effort to place throughout |

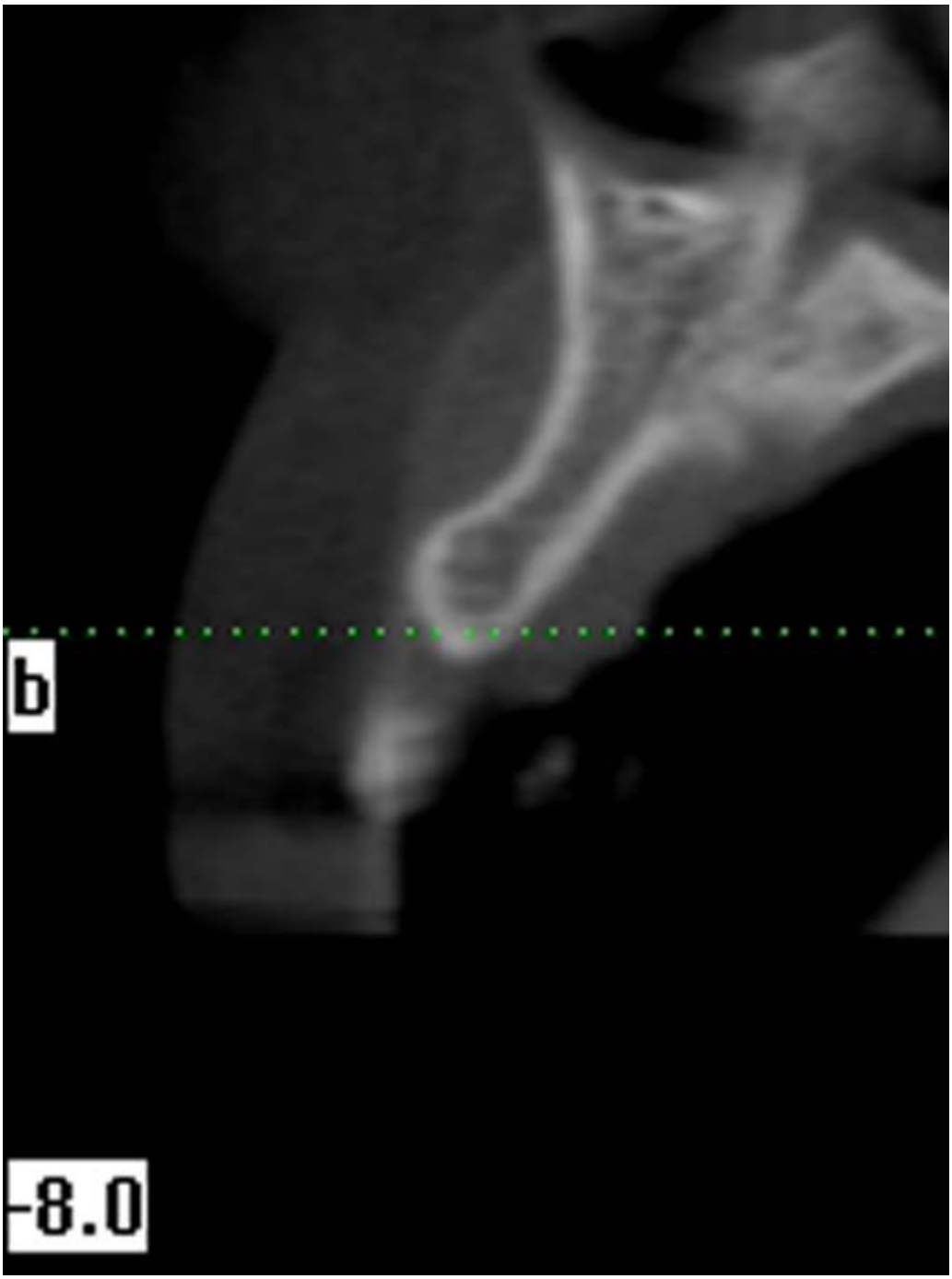
[2] Glymatrix, OSSIX® PLUS distributed by OraPharma, Warminster, PA; produced by ColBar LifeScience, Herzliya, Israel. Glymatrix technology is a proprietary glycation based collagen cross-linking technology using ribose as a natural cross-linking agent.

[3] Dentsply Molndal Sweden and Straumann Andover, MA

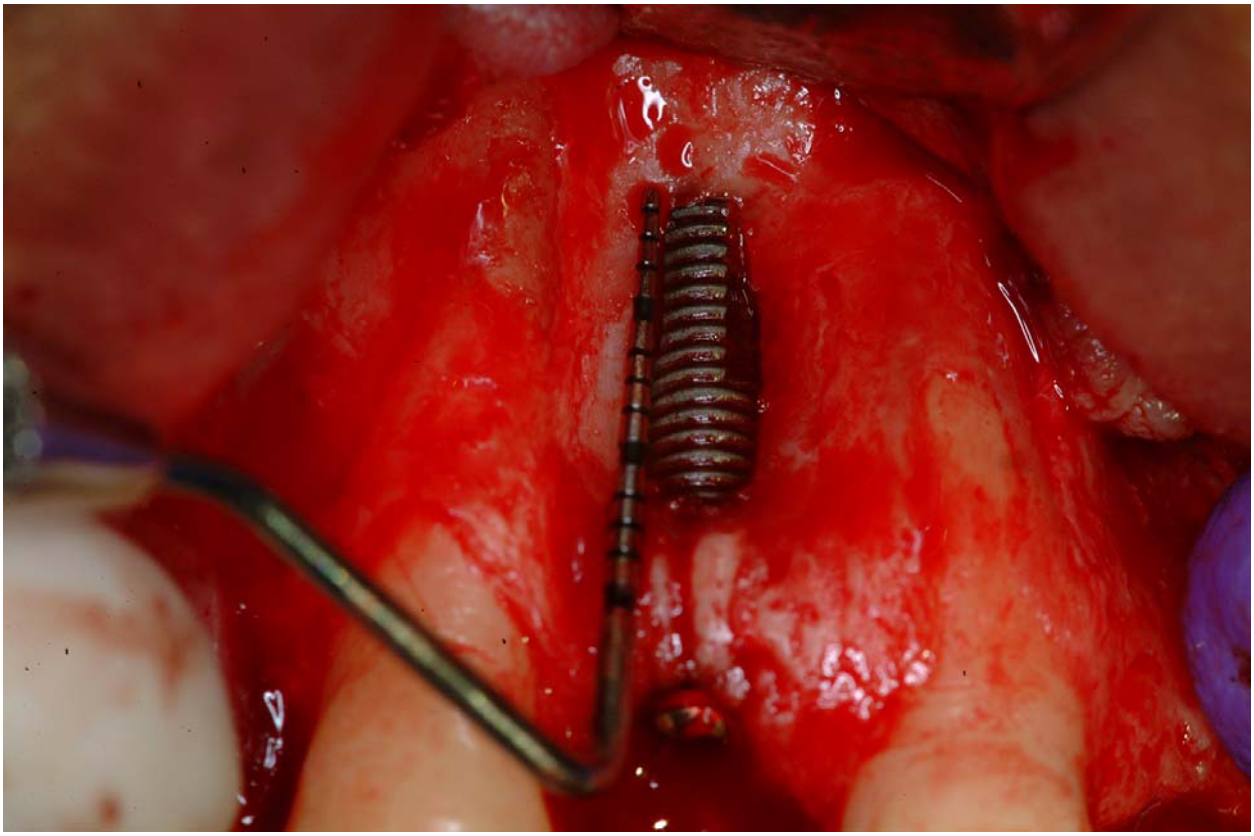
[4] LifeNet Virginia Beach, VA

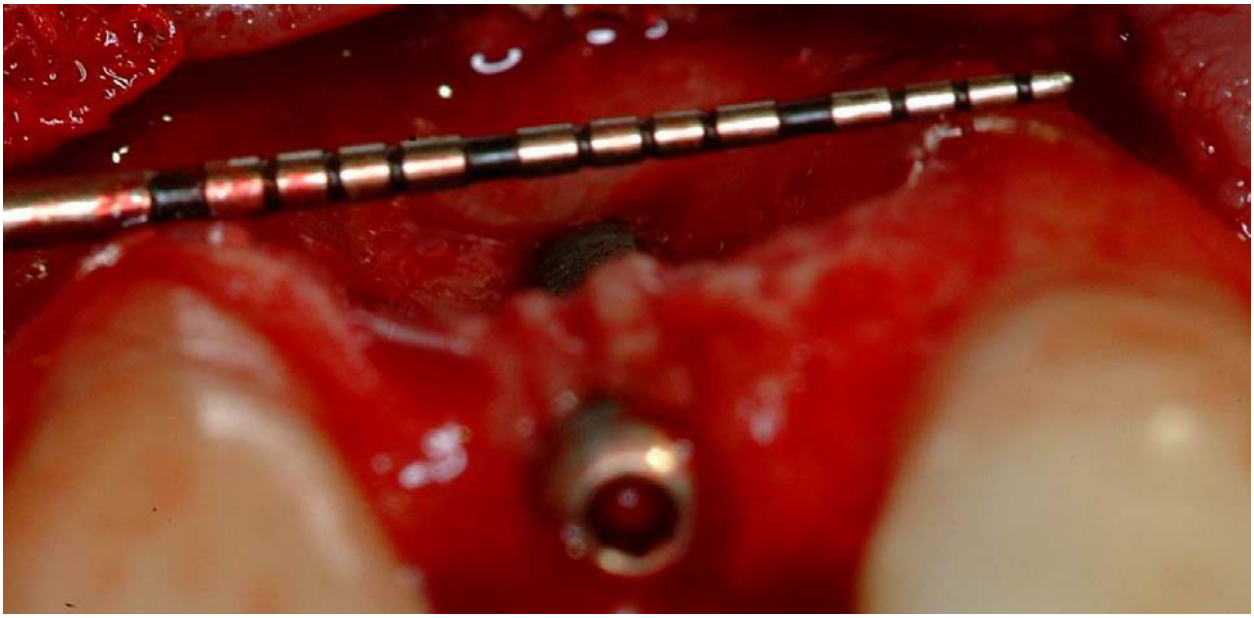
[5] W.L. Gore & Associates, Inc Flagstaff, AZ

[6] Lobene et al., 1986; J Periodontol

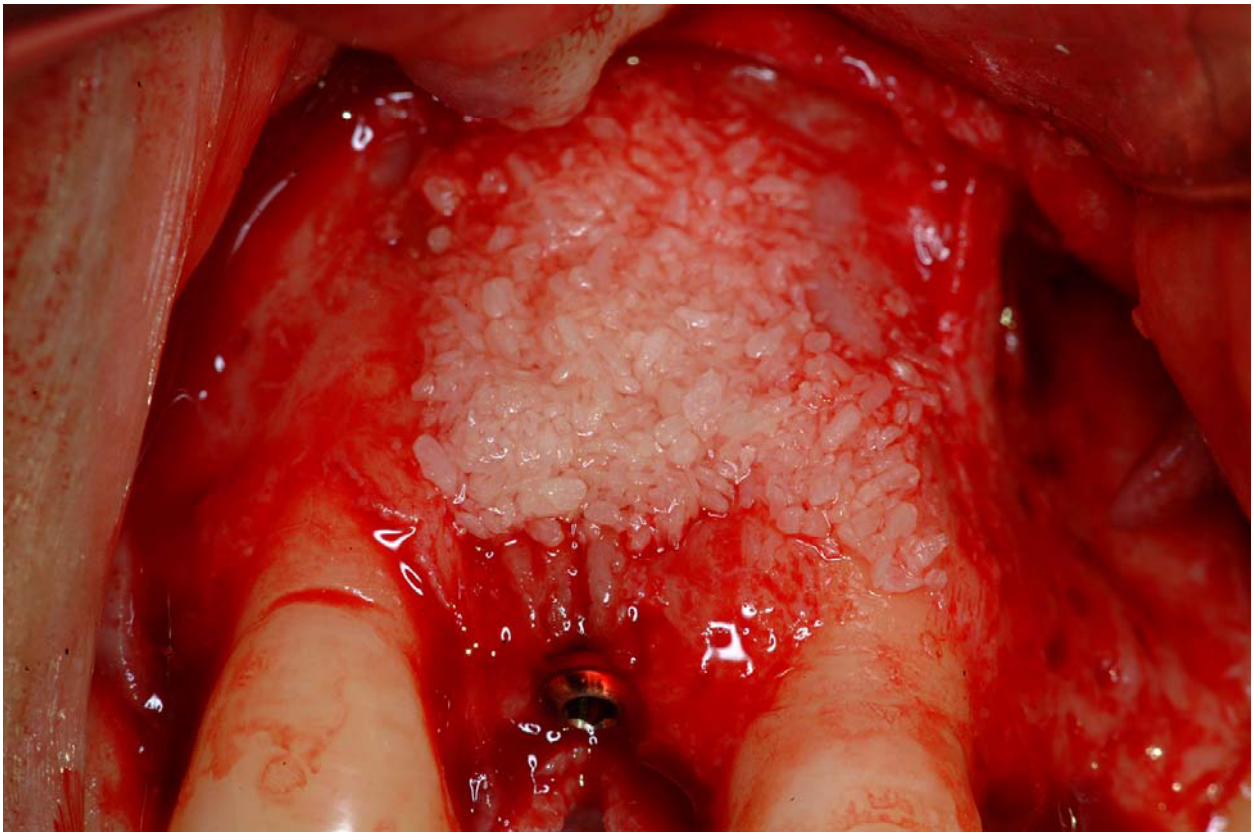

b
-8.0

 DOI: 10.1902/cap.2014.130080

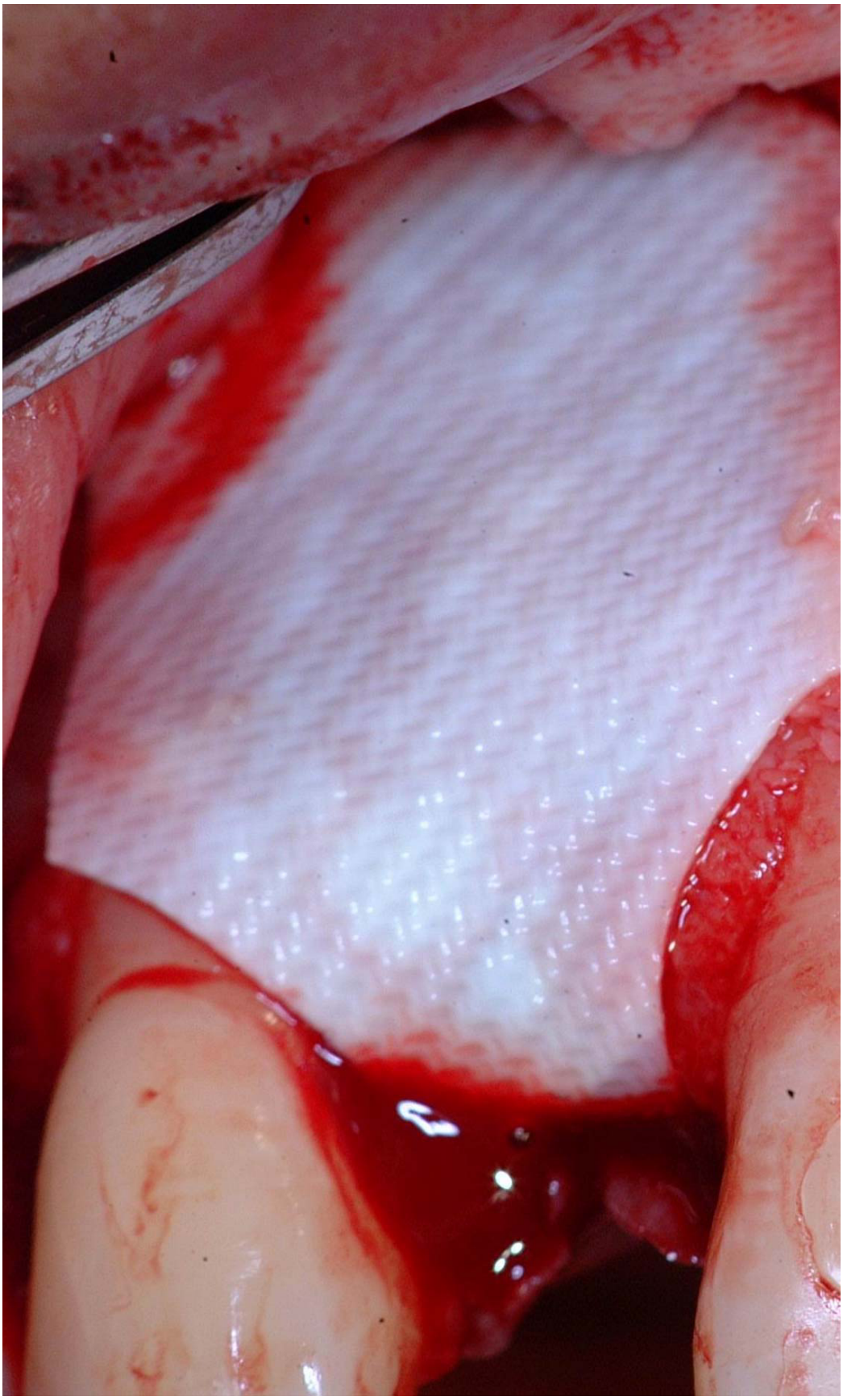


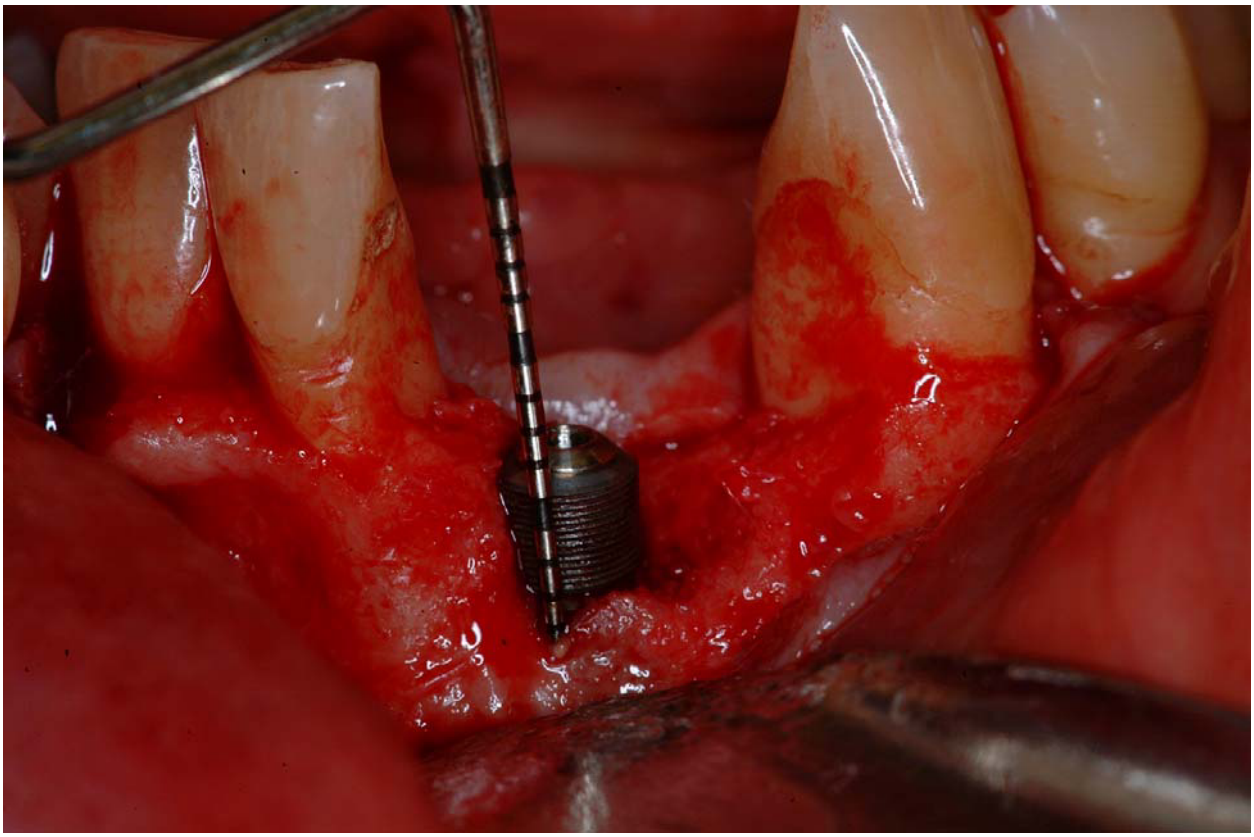


 DOI: 10.1902/cap.2014.130080

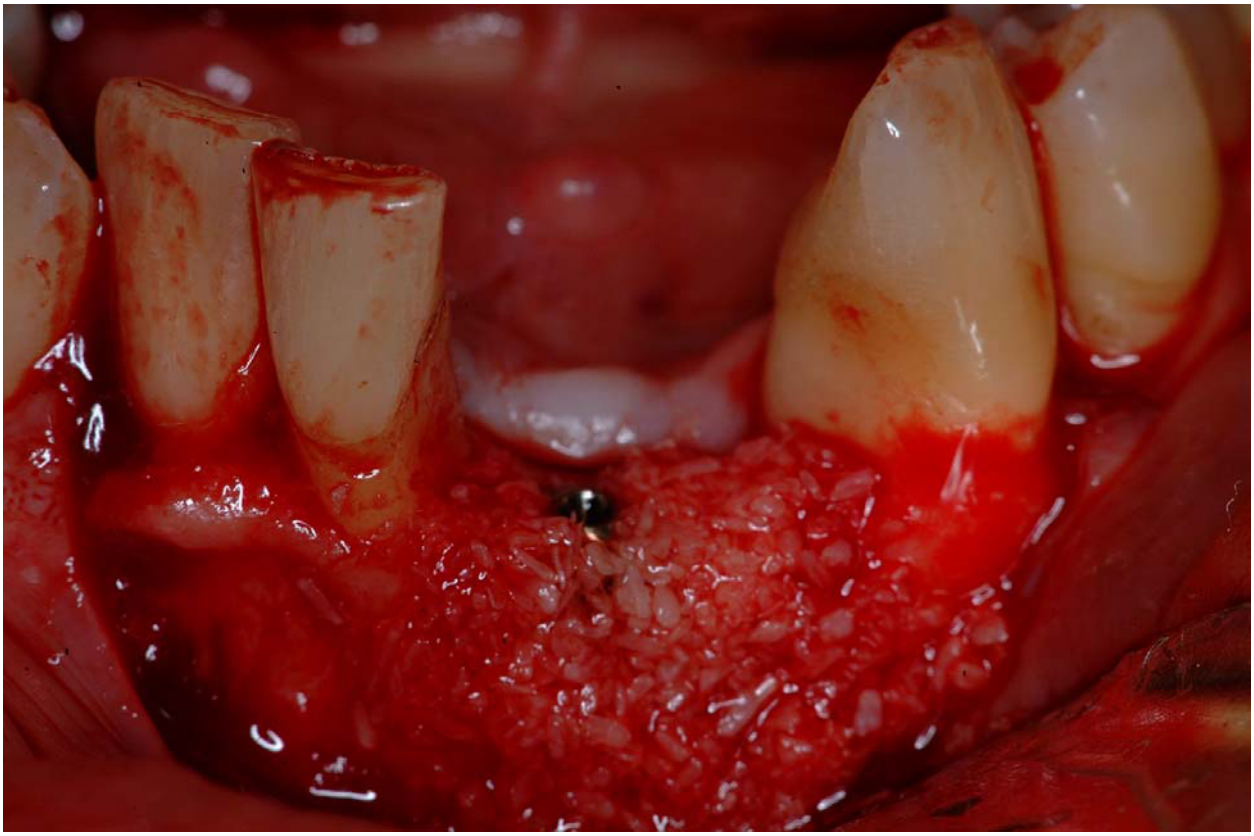


 DOI: 10.1902/cap.2014.130080

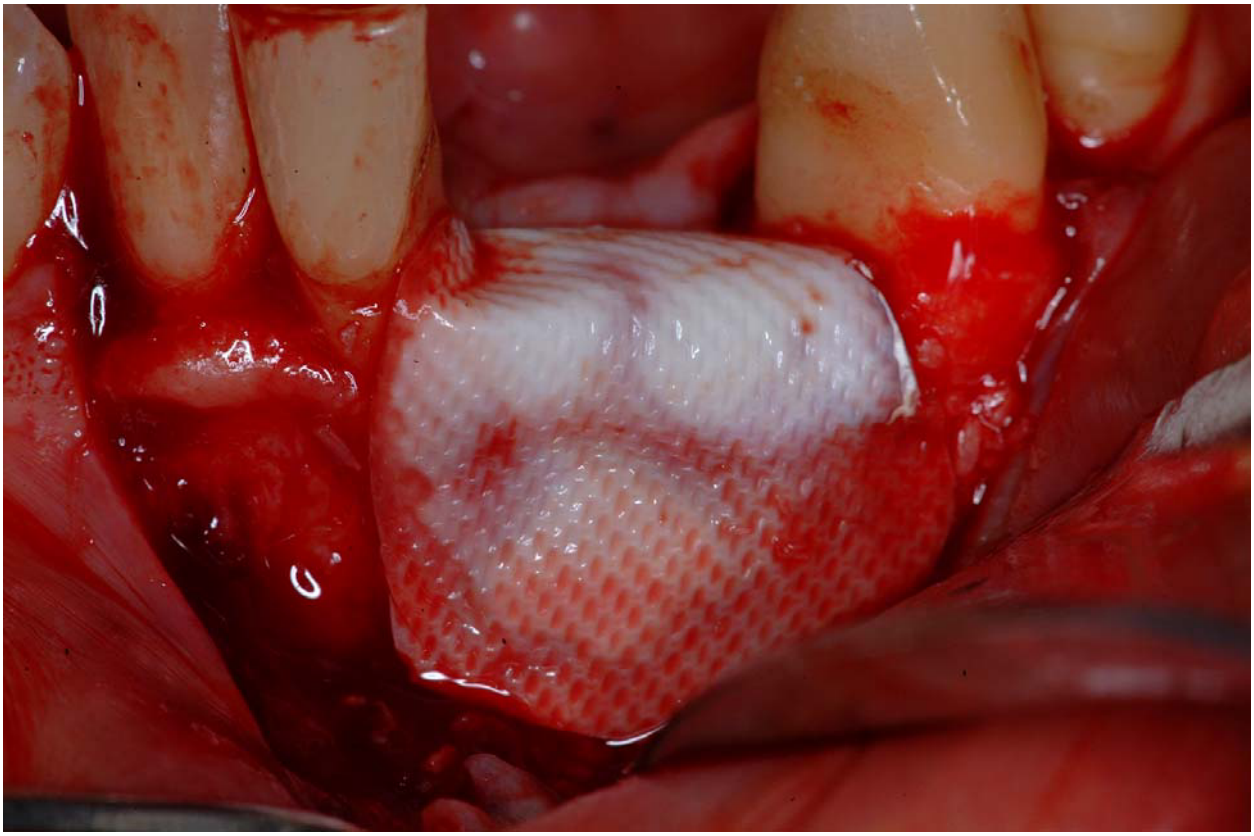




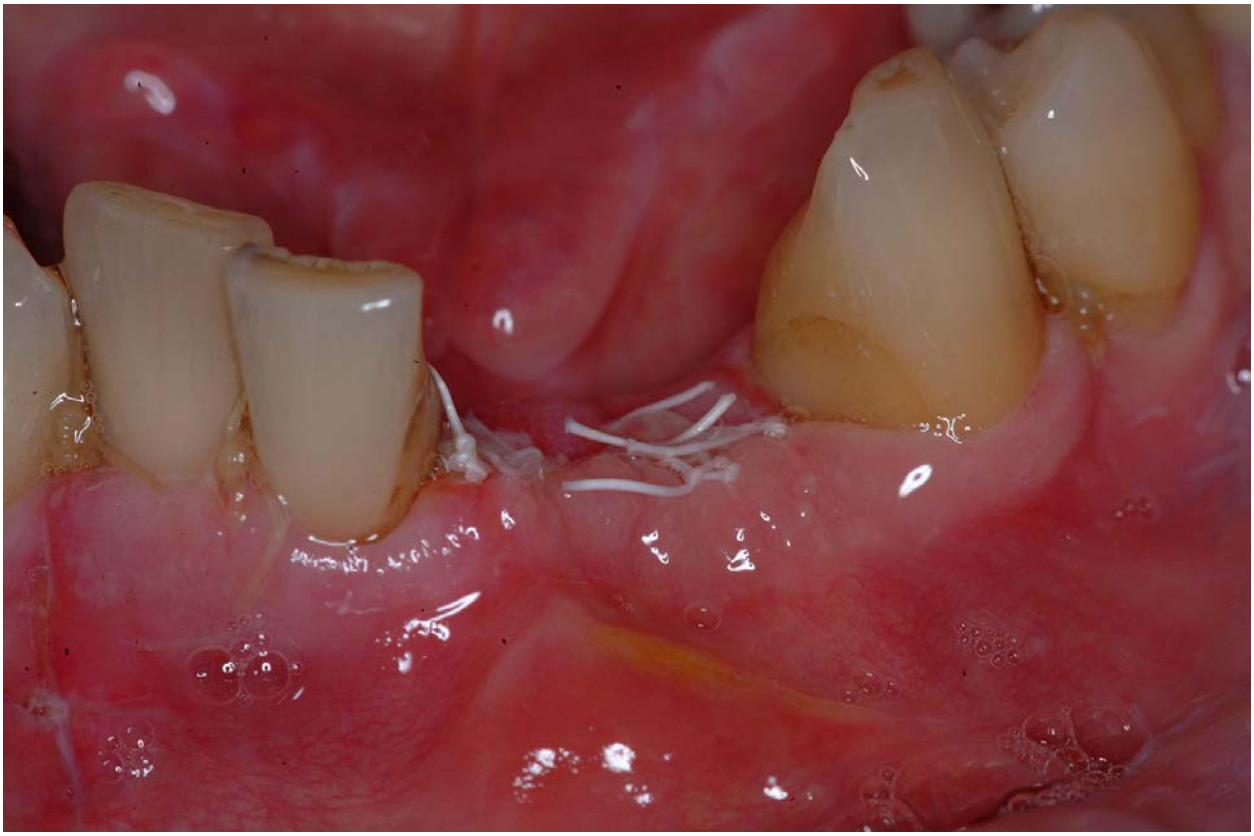
 DOI: 10.1902/cap.2014.130080



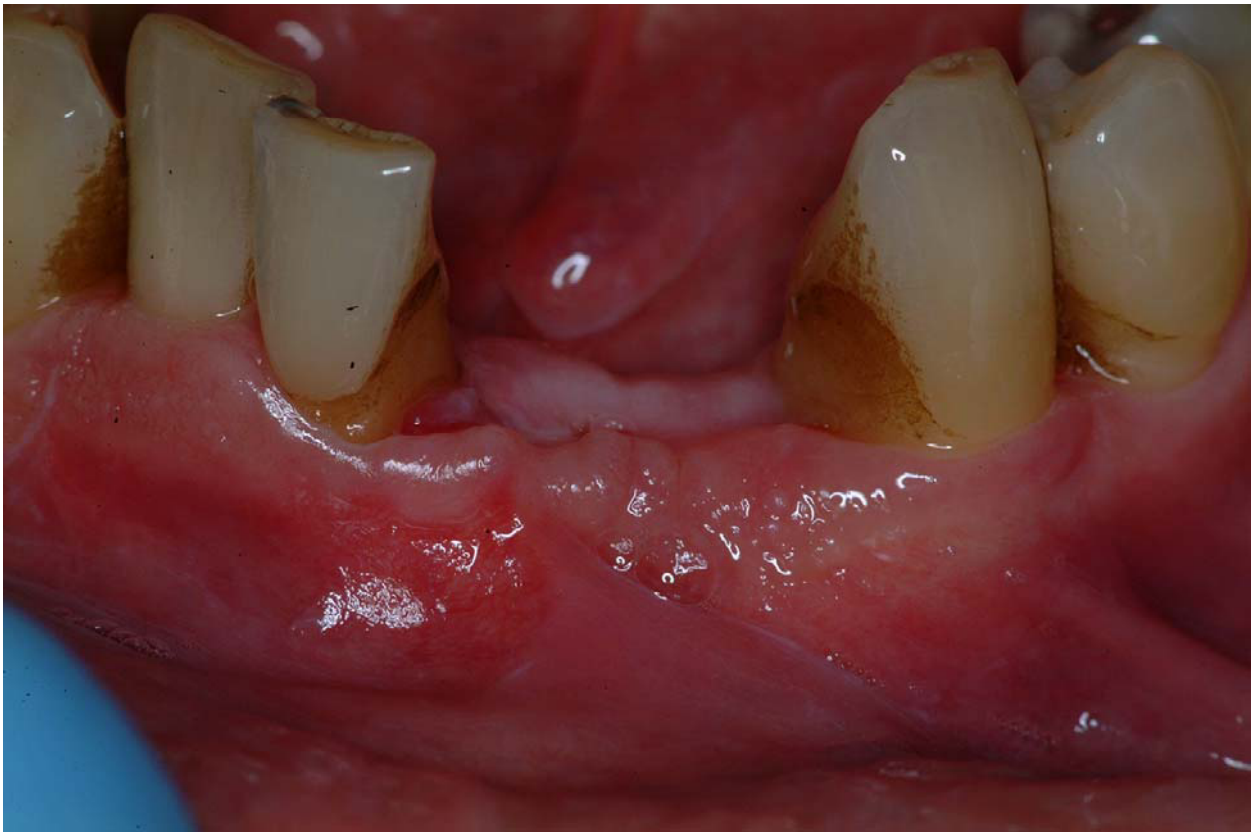
 DOI: 10.1902/cap.2014.130080



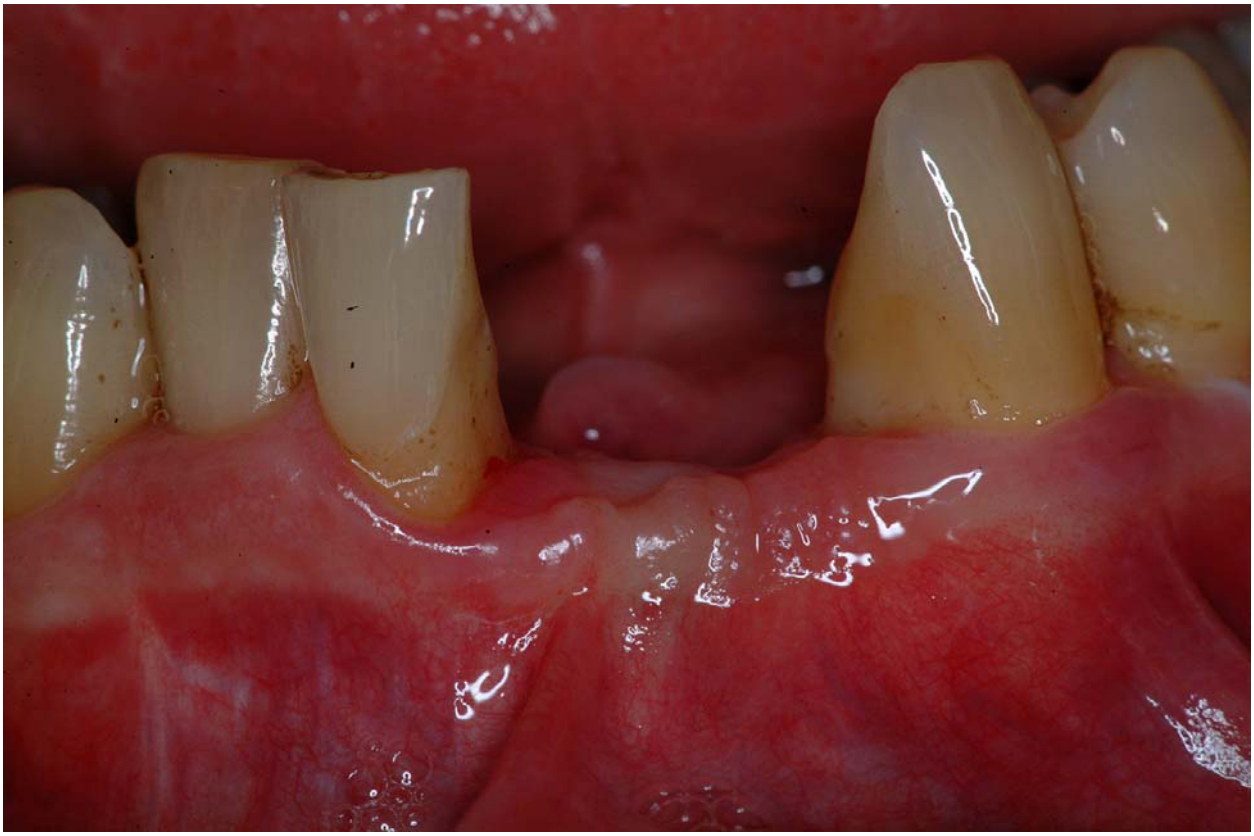
 DOI: 10.1902/cap.2014.130080



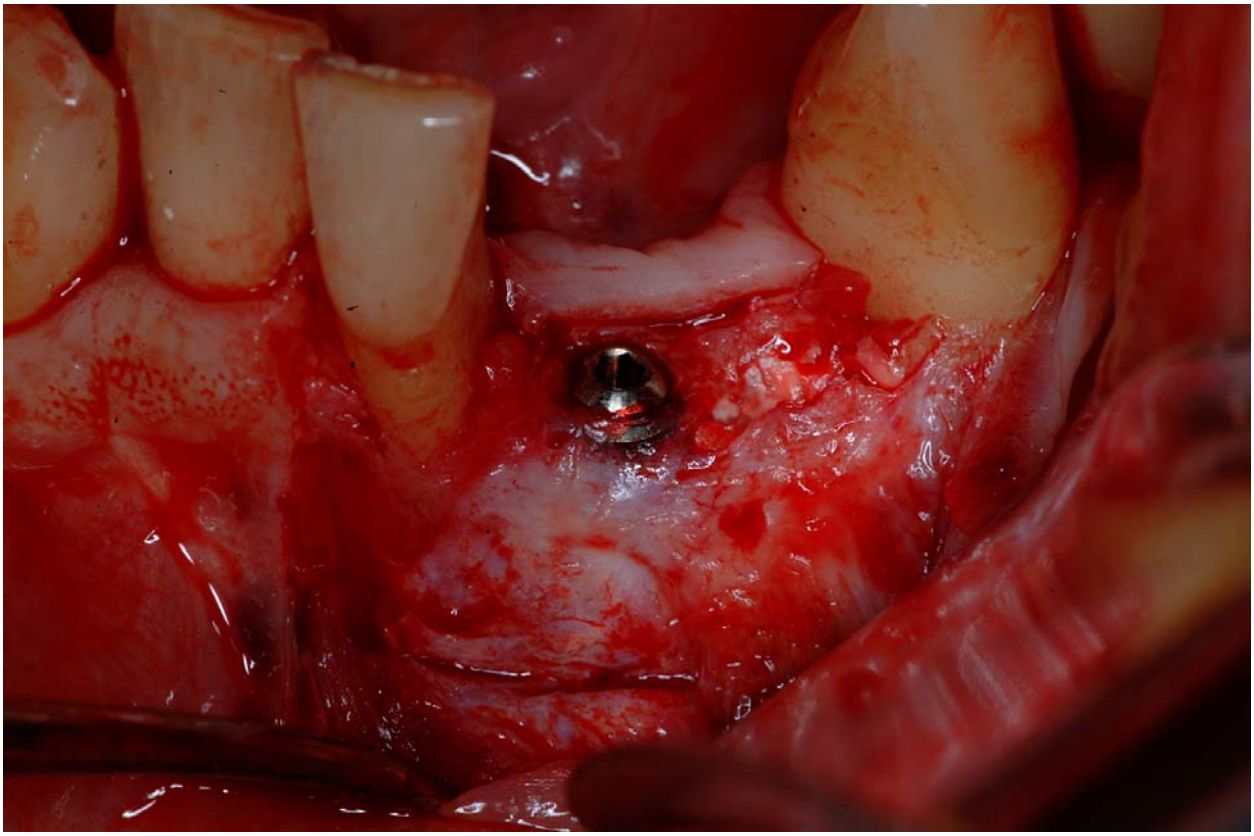
 DOI: 10.1902/cap.2014.130080



 DOI: 10.1902/cap.2014.130080



 DOI: 10.1902/cap.2014.130080



 DOI: 10.1902/cap.2014.130080