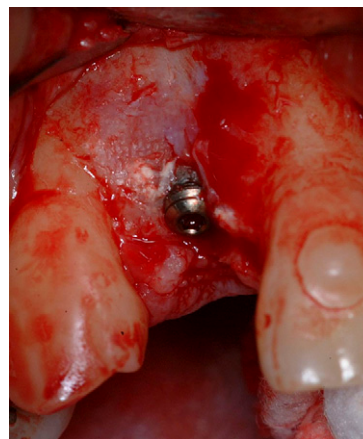
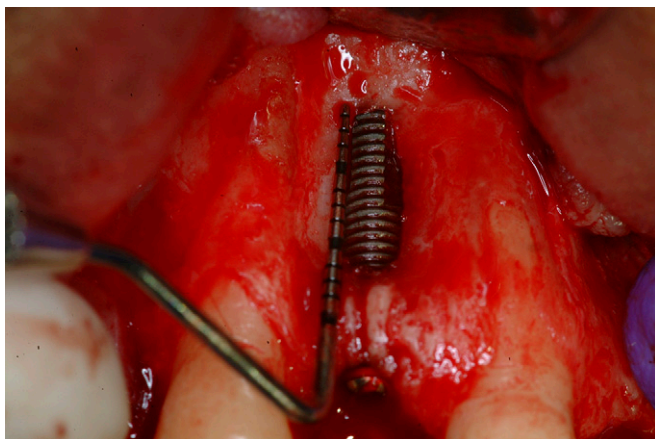


## Evaluation of Premature Membrane Exposure and Early Healing in Guided Bone Regeneration of Peri-Implant Dehiscence and Fenestration Defects With a Slowly Resorbing Porcine Collagen Ribose Cross-Linked Membrane: A Consecutive Case Series

E. Todd Scheyer\* and Michael K. McGuire\*



**Introduction:** Guided bone regeneration (GBR) is a well-known and accepted procedure for effective treatment of oral bony defects that is dependent on sustained barrier membrane function for adequate new bone formation. Cross-linking between collagen fibrils with various agents has proven to be 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 that appears to reduce the risk of cross-linking-associated membrane exposure.

**Case Series:** Seven patients with nine sites having 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 5 to 10 mm (mean of  $\approx 6.3$  mm). After 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 6-month reentry surgery, all dehiscence and fenestration defects were eliminated with newly regenerated bone covering previously exposed implant threads. No membrane exposure occurred during this study.

**Conclusions:** 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. *Clin Adv Periodontics* 2015;5:165-170.

**Key Words:** Bone regeneration; collagen; dental implantation; dental implants; membranes; osseointegration.

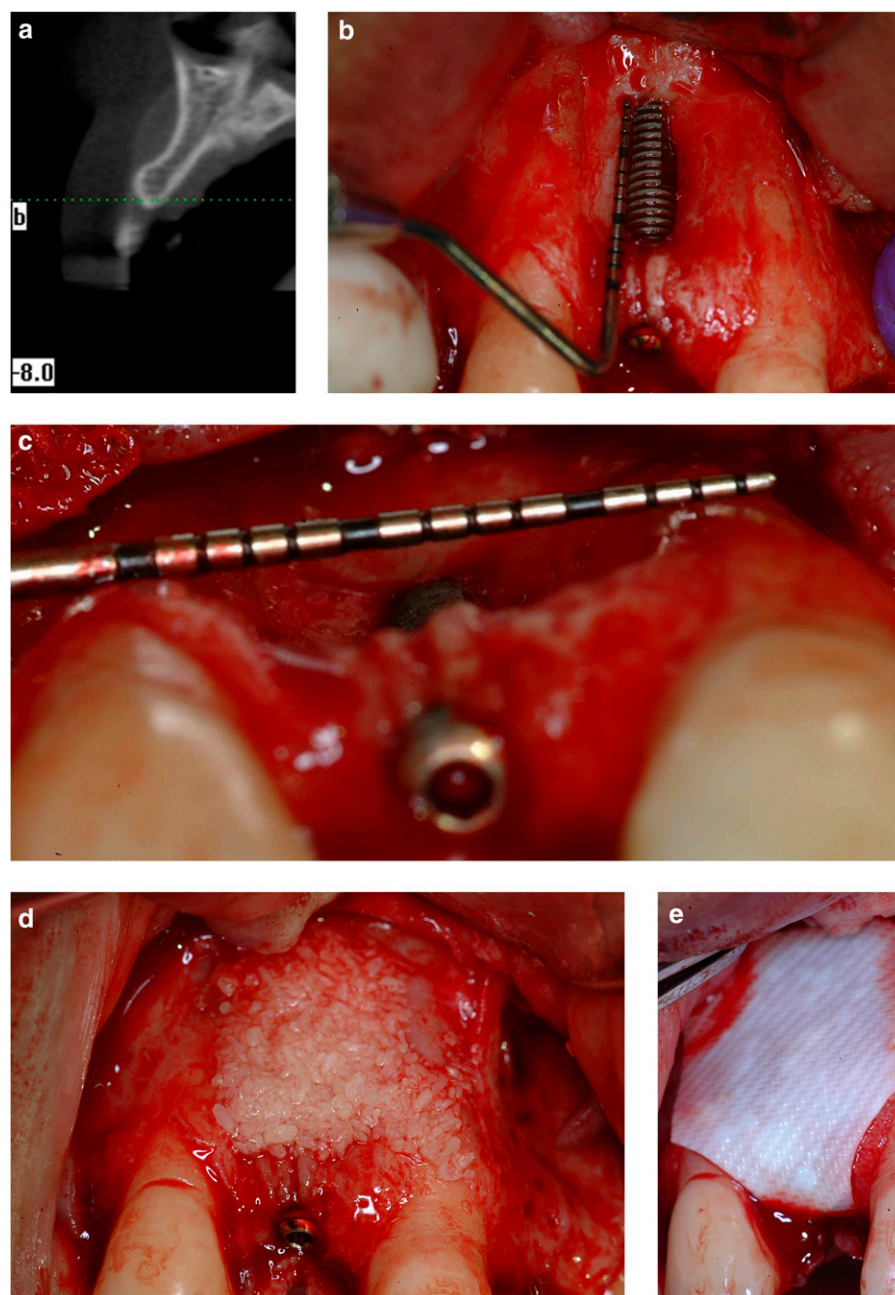
### Background

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: 1) the ability to exclude

unwanted, non-osteogenic cell lines from areas to be regenerated; 2) space creation and maintenance; 3) protection of the underlying blood clot; and 4) wound stabilization.<sup>1-3</sup>

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.<sup>1,3-6</sup> Cross-linking among collagen fibrils has become an important method of slowing collagen membrane

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**FIGURE 1** Representative case 1. **1a** Typical cross-sectional presentation with significantly narrowed alveolar ridge in which one would anticipate a buccal fenestration (b). **1b** Fenestration defect at surgery. In this case, 10 mm of threads were exposed. **1c** Occlusal view demonstrating extreme buccal bone deficit with resulting exposed implant threads. **1d** Particulate FDBA graft in place to cover all exposed threads and to restore normal ridge anatomy. **1e** GLYM placed to cover the FDBA-grafted site.

resorption times to maintain membrane-protected spaces critical to successful bone regeneration.<sup>4-9</sup> A number of cross-linking agents have been used to modify GBR membranes, including formaldehyde, glutaraldehyde, and the sugar D-ribose.<sup>4-6,10-12</sup> 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.<sup>8,13,14</sup> Although in the majority of cases overlying soft tissue dehiscences will heal, premature membrane exposure may nevertheless compromise new bone formation during GBR procedures.<sup>12,14,15</sup>

In a comprehensive meta-analysis, Machtei<sup>15</sup> demonstrated significant differences in quantities of bone regeneration between intact and prematurely exposed collagen membranes during GBR procedures. Sites with no membrane exposure yielded almost six times more new bone regeneration during GBR procedures than sites that became exposed, a finding that was 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. A porcine-derived collagen membrane cross-linked by a proprietary glycation-based collagen cross-linking technology using ribose as a natural cross-linking agent (GLYM)<sup>†</sup> provides the ability to control biodegradability of the barrier membrane for 4 to 6 months. This membrane was shown to have sufficient permeability to sustain osteoblast-like cells *in vitro*.<sup>16</sup>

The purpose of this prospective, consecutive case series pilot study is to examine the biocompatibility and membrane integrity characteristics of GLYM 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 after grafting.

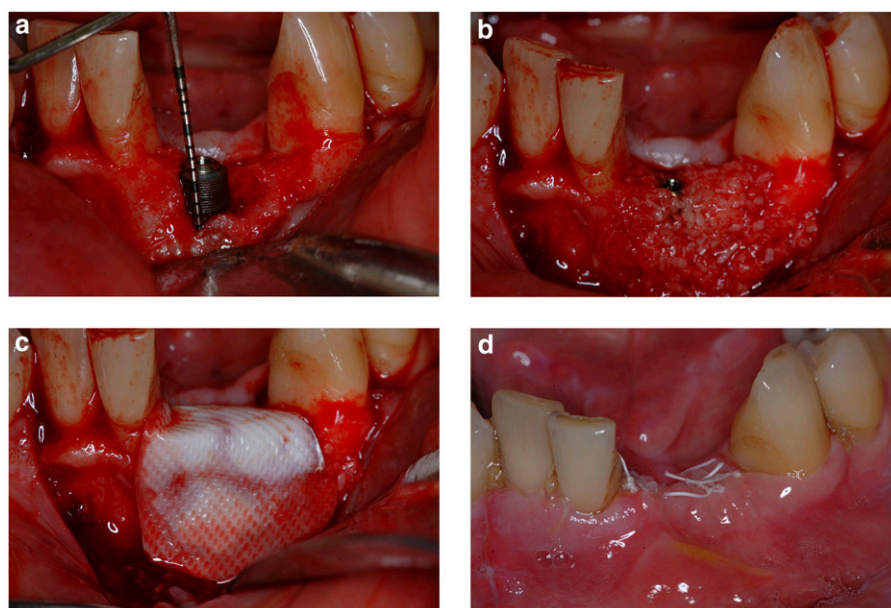
## Clinical Presentation

The current prospective consecutive case series was performed over a period of 9 months (January 28, 2008 to October 27, 2008) within a single clinical setting in Houston, Texas. All participants enrolled in the study were healthy and on no medications (five males and two females, aged 39 to 64 years; mean age:

53 years). All patients reviewed and signed an informed consent. The study and consent forms were approved by the Essex Institutional Review Board, Lebanon, New Jersey. Six patients were non-smokers, and one patient smoked approximately four cigarettes daily. Except for two patients who required the insertion of two implants, a single implant was placed into either an existing edentulous site or immediately after tooth extraction.

<sup>†</sup> GLYMATRIX, Ossix Plus, Datum Biotech, Lod, Israel.





**FIGURE 2** Representative case 2. **2a** At implant placement, 5 mm of implant threads were exposed. **2b** Particulate FDBA grafts placed to restore ridge anatomy and to cover all exposed implant threads. **2c** Resorbable GLYMs placed to cover the grafted sites. **2d** Flaps closed primarily without tension.

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 (Figs. 1a through 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 computed tomography (Fig. 1a). Study goals and procedures were thoroughly reviewed with each patient, and informed consents were 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 were thoroughly debrided of all inflamed tissue. Implants<sup>‡</sup> 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 (Fig. 1b). Test sites were then grafted with mineralized freeze-dried bone allograft (FDBA)<sup>§</sup> particulate grafts in an attempt to restore normal alveolar ridge morphology and to cover all exposed implant threads (Fig. 1d). 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 (Fig. 1e). The soft-tissue flaps were then closed primarily without tension using interrupted non-resorbable sutures.<sup>¶</sup> A second representative case is shown in Figure 2.

Postoperatively, patients were placed on either 500 mg amoxicillin three times per day or 100 mg doxycycline twice per day for 10 days, as well as 0.12% chlorhexidine gluconate antibacterial rinses. Non-steroidal anti-inflammatory analgesics were prescribed for pain control.

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

## Clinical Outcomes

### Soft Tissue Outcomes

At all points in time, peri-implant mucosal soft-tissue healing proceeded uneventfully for all nine grafted sites without evidence of localized infection. Immediate postoperative swelling and inflammation were minimal through week 1, with eight sites rated as having mild inflammation and one site as having none (Fig. 2d). By postoperative week 3, swelling and evidence of mucosal gingival inflammation had all but disappeared (Fig. 3a, Table 1).<sup>17</sup> At 6 months, peri-implant mucosa for all sites was healthy, without signs of swelling or inflammation (Fig. 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 (Fig. 4).

### Membrane-Related Outcomes

Immediately after GLYM placement, subjective assessments were made for membrane composition (hard and fixed in place, firm and fixed in place, firm and loose in place, soft and fixed in place, or soft and loose in place) and handling characteristics (placed easily and conformed well, placed easily but was difficult to conform, or required effort to place throughout). Independent assessments by each investigator rated GLYMs as “soft and loose in place” and “placed easily and conformed well.”

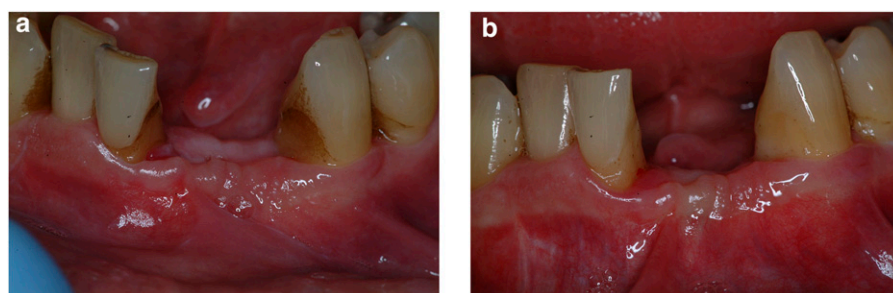
At all study time points, the overlying mucosa covering the GLYM remained intact. No membrane exposures occurred at any of the nine treated sites from initial placement

<sup>‡</sup> DENTSPLY, Mölndal, Sweden.

<sup>§</sup> Straumann, Andover, MA.

<sup>||</sup> LifeNet Health, Virginia Beach, VA.

<sup>¶</sup> W. L. Gore & Associates, Flagstaff, AZ.



**FIGURE 3** Representative case 2. **3a** Little to no gingival inflammation was present 3 weeks after GBR surgery. **3b** At 6 months, soft tissues at all sites were healthy and without signs of inflammation.

**TABLE 1** Gingival Inflammation Ratings (N = 9)<sup>17</sup>

Follow-Up Time	None	Mild	Moderate	Severe
Week 1	1	7	1	0
Week 3	6	3	0	0
Week 4	8	1	0	0
Month 2	9	0	0	0
Month 4	9	0	0	0
Month 6	9	0	0	0

None = no inflammation; mild = color change without edema; moderate = glazing, redness, edema, and/or hypertrophy; severe = marked redness, edema/hypertrophy, and spontaneous bleeding or ulceration.

through the 6-month follow-up examination. Importantly, at the 6-month second-stage reentry surgery, the GLYM appeared often (six of nine) to remain physically intact (Fig. 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. However, the current case series may serve as a reminder that established technologies

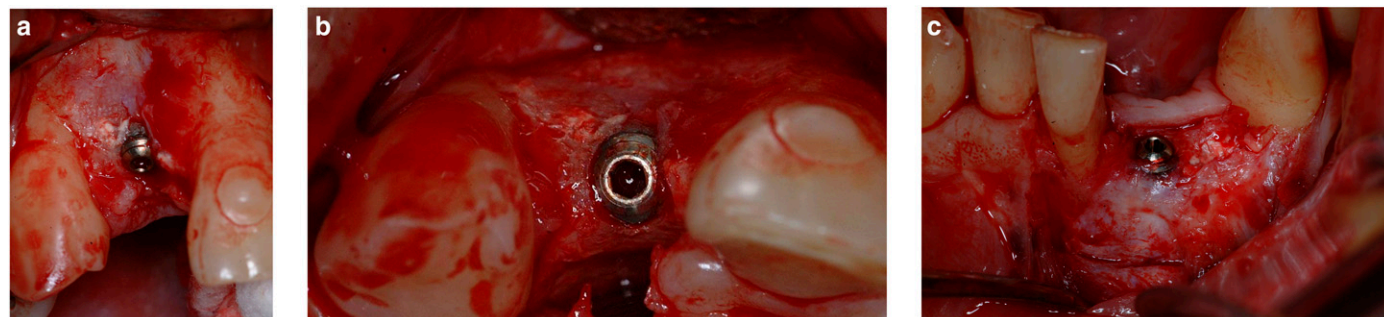
may continue to be profoundly effective in regenerating vital tissues, are well understood by clinicians, and are cost effective for patients.

The seven 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 GBR. Multiple factors may have contributed to the successful outcomes of this study, including: 1) the overall good health of this patient pool; 2) meticulous attention to surgical

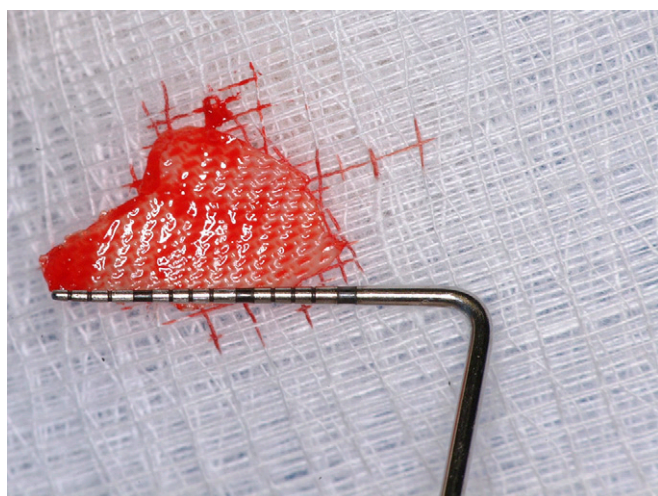
detail; 3) effective graft matrices; and, perhaps most importantly, 4) a highly biocompatible cross-linked membrane. Significantly, this membrane continued to function for the entire 6-month duration of this case series without inducing overlying mucosal dehiscence with all its associated potential complications.

Several characteristics of GLYM should be mentioned briefly. 1) The membrane is highly biocompatible, allowing cross-membrane nutrient diffusion into the underlying protected space, thus aiding osteoblastic cellular viability.<sup>16</sup> 2) The nature of its cross-linking by naturally occurring ribose molecules (glycation) not only significantly delays resorption time necessary for effective GBR but also leads to non-toxic metabolic breakdown products that do not contaminate the surrounding local environment.<sup>7,18,19</sup> 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.<sup>13</sup>

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. However, larger, randomized controlled studies, with long-term follow-up, will be needed to verify the results of this current case series. ■



**FIGURE 4** Representative cases 1 and 2 reentry. **4a** Case 1. The 10-mm fenestrated defect seen in Figure 1b is no longer present. At 6 months, all previously exposed threads are covered with regenerated bone. **4b** Case 1. Buccal crestal ridge anatomy was restored to normal, eliminating the 10-mm fenestration defect. **4c** Case 2. At the 6-month reentry surgery, all 5 mm of exposed implant threads are now covered with vital, newly formed bone.



**FIGURE 5** Representative case 1. At the 6-month second-stage surgery, a large portion of the GLYM remained intact.

## Summary

### Why are these cases new information?

- Potential return of membrane used in this case series to the marketplace after >3 years of being commercially unavailable
- Findings of no membrane exposure with favorable resolution of implant fenestrations, which make this resorbable membrane an attractive option for clinicians

### What are the keys to successful management of these cases?

- Proper diagnosis and treatment planning for a simultaneous implant placement and GBR technique
- Patient selection regarding their health status and compliance with the postoperative regimen
- 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 in these cases?

- Clinician inexperience with flap management, membrane/wound stability, and other intricacies of the GBR technique
- The challenges of GBR, which make patient selection a key factor for success

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○ indicates key references.