Guided bone regeneration using collagen membranes simultaneous to implant placement at compromised sites leads to reproducible results and high success rates

Bastian Wessing¹, Istvan Urban²,³, Eduardo Montero⁴, Werner Zechner⁵, Markus Hof⁶, Javier Alándež⁷, Nuria Alándež⁷, Giovanni Polizzi⁸, Silvio Meloni⁹, Mariano Sanz⁴

¹Dental Practice Clinic, Luisenhospital, Aachen, 52064 Germany
²School of Dentistry, Loma Linda University, Loma Linda, CA 92350, USA
³Urban Regeneration Institute, Budapest, 1025 Hungary
⁴Section of Graduate Periodontology, Faculty of Odontology, Complutense University of Madrid, Madrid, 28040 Spain
⁵Department of Oral Surgery, University Clinic of Dentistry, Medical University of Vienna, Vienna, 1090 Austria
⁶Department of Oral Surgery & Division of Dental Student Training and Patient Care, University Clinic of Dentistry, Medical University of Vienna, Vienna, 1090 Austria
⁷Plénido Dental, Madrid, 28003 Spain
⁸BSC Verona, Verona, 37138 Italy
⁹Department of Surgical, Microsurgical, and Medical Sciences, Dentistry Unit, University Hospital of Sassari, Sassari, 07100 Italy

Correspondence: Bastian Wessing
E-mail: bastian.wessing@googlemail.com
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An implant-supported prosthesis can restore masticatory function to patients with missing teeth. A prerequisite for success is to position the implant inserted within sufficient bone to be stably osseointegrated, whilst also allowing the restoration to meet functional and esthetic needs. Unfortunately, prosthesis-driven implant sites are not always characterized by adequate bone dimensions. Furthermore, following tooth extraction, severe bone resorption often occurs. Though an array of surgical techniques are available for bone augmentation, guided bone regeneration (GBR) is one that can produce both functional and esthetic results reproducibly with high success rates, whether performed prior to or simultaneous with implant placement. Given the relevance of barrier membrane material and its individual properties to the success of GBR and, consequently, implant-supported restorations, we compared the clinical performance of a new resorbable non-crosslinked collagen membrane, creos xenoprotect (CXP), with a reference membrane Bio-Gide (BG), for GBR at dehisced implant sites. Results from a prospective, randomized clinical trial (NCT02373787) on 49 patients receiving simultaneous GBR and implant insertion demonstrated that both collagen membranes result in safe bone augmentation of dehiscence defects. Implant survival rate at reentry surgery, 6 months after implant insertion, was 100%. The new CXP membrane was statistically non-inferior to the reference BG membrane with respect to mean difference in bone defect height between implant insertion and reentry surgery (p <0.001). Moreover, there was no difference in patient pain or quality of life between the two treatment arms. However, there were trends in improved outcomes, namely higher bone gain and lower membrane exposure rates, when CXP was used compared with BG, though not statistically significant. Together, the study confirms that, even using a simultaneous surgical approach, the CXP collagen membrane supports bone regeneration at dehisced implant sites with few complications. This demonstrates that new barrier membrane materials with improved properties, such as CXP, can provide clinical benefits to patients.

Keywords: Guided bone regeneration; collagen membrane; randomized clinical trial; simultaneous implant placement; dehisced implant sites; esthetic zone
Implant-supported restorations are an established treatment option for full or partial edentulism [1-9]. A successful outcome, that is fulfilling the functional and esthetic needs of the patient, requires implant placement in sufficient alveolar bone at the correct three-dimensional position. Historically, implant position was largely driven by the available amount of the pristine alveolar bone, though this sometimes led to restoration challenges. Thus, there has been a move toward restoration-driven, backward-planning in determining the location for an implant.

Prosthodontically-driven positioning of implants for optimal functional and cosmetic results may, however, indicate an implant insertion site without the minimum amount of bone width and height needed for implant stability and osseointegration. In addition, severe bone resorption may occur following tooth extraction, with most resorption occurring in the first three months [10] and approximately 50% of the resorption in the buccolingual direction within the first year [11]. Therefore, bone augmentation procedures are necessary when the pristine alveolar ridge does not present the adequate dimensions for implant placement, especially in the esthetic zone [7, 12].

Several surgical alveolar ridge augmentation procedures have been developed. These include ridge splitting and expansion, bone block transplantation from intra- or extra-oral donor sites, osteodistraction, sandwich osteoplasty and guided bone regeneration (GBR) [13], which may be conducted alone or in conjunction with grafting procedures [14, 15] utilizing various sources of graft material i.e. autografts, allografts, xenografts and other bone substitutes. These augmentation techniques may be performed simultaneous with or prior to implant placement. The simultaneous approach, if possible, is beneficial for both patient and surgeon, due to fewer surgeries, reduced costs, and a lower risk of comorbidities. Several studies have shown that GBR results in high long-term implant survival rates [13, 16] that are similar to placement in pristine bone [17]. Moreover, it has been demonstrated that these rates are achieved whether GBR is applied in a simultaneous or staged approach [16].

GBR uses a membrane and graft materials beneath the periosteum to create and maintain a space around the bony defect where new bone can grow (Figure 1). Since osteoprogenitor cells grow relatively slowly, the membrane separates the maintained space from rapidly proliferating epithelial and connective tissue cells, preventing their migration into the defect. Originally developed based on tissue engineering principles by Karring and Nyman in 1979 [18], GBR has since been extensively successfully applied to lateral alveolar ridge augmentation with several high-quality studies demonstrating reproducible results [19-23].

The membranes used in GBR should ideally exhibit several properties: biocompatibility, tissue integration, cell occlusivity, nutrition transfer, mechanical properties that allow the membrane to create and maintain the space needed for GBR, as well as good handling properties. Early studies primarily used polytetrafluorethylene (PTFE) membranes as the barrier. Whilst this stable, rigid material enabled investigators to achieve horizontal and vertical bone gains of up to 9 and 12 mm, respectively [24-27], several studies also reported this material had a high membrane exposure rate of 30-40% [22, 28, 29], though others reported good results [26, 27, 30]. Nevertheless, PTFE is a non-resorbable material that ultimately requires removal, necessitating an extensive reentry procedure [22, 28, 29].

To avoid the need for membrane removal surgeries, alternative resorbable materials were developed, including collagen membranes, and their use in tissue regeneration and GBR has also been extensively studied [31-35]. Two decades of research has shown that the amount of bone gain with resorbable collagen membranes to be comparable to that obtained with non-resorbable membranes [16, 28, 36]. Furthermore, resorbable membranes exhibited lower membrane exposure rates [26, 28, 37, 38], of particular importance given that wound dehiscence with membrane exposure often reduces bone regeneration [39].

There is a postulated relationship between membrane degradation time, bone gain and membrane exposure rate – the longer the degradation time, the greater the bone gain but the greater the dehiscence and membrane exposure rate. Certainly non-crosslinked collagen membranes have good
tissue and cell compatibility, and lower dehiscence rates, compared with their chemically cross-linked counterparts and PTFE membranes, but they are also less stable [40-42]. It should be noted that definitive evidence confirming longer membrane degradation times leads to higher regenerated bone quality or quantity is lacking. Nevertheless, there is no reason to suggest that newer materials will not be able to achieve all desired GBR membrane properties, including optimum bone gain/membrane degradation time and biocompatibility, along with ease-of-use.

Indeed, a newly developed non-crosslinked collagen membrane, creos xenoprotect (CXP; Nobel Biocare AG, Göteborg, Sweden), has been shown to exhibit significantly longer degradation times and improved mechanical properties, both in vitro and in a rat model, than another commonly-used non-crosslinked collagen barrier membrane, Bio-Gide (BG; Geistlich, Wolhusen, Switzerland) [43]. A retrospective analysis of 36 patients with GBR at 49 sites with 103 implants placed with either a simultaneous or staged approach found a low CXP membrane exposure rate of 12% [44], demonstrating excellent potential of the new membrane. However, the clinical relevance of the difference in properties observed between CXP and the reference membrane BG was unknown.

Therefore, we recently conducted a prospective, randomized controlled clinical trial to evaluate the efficacy and non-inferiority of CXP, compared with the reference membrane BG, when used in a GBR procedure performed simultaneously with implant placement [45]. This multicenter clinical investigation was performed at seven university clinics and private practices in Europe, with all patients in need of single-tooth implant-supported restoration(s) in the anterior and premolar areas of the maxilla or the mandible. The primary outcome in this study was to evaluate the amount of newly regenerated bone after GBR procedure with simultaneous implant placement at sites with a buccal dehiscence. The 49 patients meeting inclusion criteria for defect size at the time of surgery were randomized into two treatment arms, with 24 patients in the CXP arm and 25 patients in the BG arm. Two patients, one from each arm, were lost to reentry surgery after a 6-month healing period through attending a different restoration clinic. To enhance healing, we complemented the GBR procedure by making decortication holes in the planned bone area to draw blood from the cancellous bone into the graft site. We also applied the so called “sandwich augmentation” technique [46], in which autologous bone chips are placed directly on the implant surface and were covered with anorganic bovine bone mineral (Figure 1). The bone graft was then covered by the randomized collagen membrane which was either fixed to the underlying bone by cortical titanium pins or a periosteal vertical mattress suture to immobilize the graft material at the desired position. To achieve tension-free primary wound closure, a closed healing procedure using a mucoperiosteal flap with periosteal release incision was performed. We evaluated bone augmentation results at the reentry procedure by raising a full flap. Other outcomes evaluated were soft tissue healing and implant survival.

We adopted a comprehensive strategy to assess the extent of GBR, quantifying the size of bone defect at implant placement and at reentry surgery with four parameters (Figure 2): (1) defect height (DH), the primary outcome, measured from the top of the implant shoulder to the first bone-to-implant contact perpendicular to the long implant axis; (2) defect width (DW), the distance between the mesial

![Figure 1. Schematic representation of a simultaneous approach implant insertion and guided bone regeneration (GBR) procedure. (A) Implants are placed into the defect, the size of which is measured. (B) In some cases, the defect is filled with particulate graft material, such as autologous bone chips on the implant surface and anorganic bone matrix on top. (C) The implant site and defect is covered with a barrier membrane, to maintain the space for bone regeneration and prevent soft tissue encroachment. Reprinted with permission [45].](http://www.smartsicetch.com/index.php/mr)
Table 1. Bone gain in defect from implant insertion to reentry surgery after a 6-month healing period

<table>
<thead>
<tr>
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<th>Bone gain from implant insertion to reentry</th>
<th>% Bone gain from implant insertion to reentry</th>
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<tr>
<td></td>
<td>Defect height</td>
<td>Defect width</td>
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<tr>
<td><strong>Total</strong></td>
<td>Mean±SD (mm)</td>
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<tr>
<td></td>
<td>3.7±2.5</td>
<td>1.1±2.3</td>
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<tr>
<td>N</td>
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<td>47</td>
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<tr>
<td><strong>CXP</strong></td>
<td>Mean±SD (mm)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.1±2.2</td>
<td>1.5±2.3</td>
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<tr>
<td>N</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td><strong>BG</strong></td>
<td>Mean±SD (mm)</td>
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<tr>
<td></td>
<td>3.3±2.8</td>
<td>0.6±2.2</td>
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<tr>
<td>N</td>
<td>24</td>
<td>24</td>
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<tr>
<td>p-value CXP vs. BG (two-sided t tests)</td>
<td>0.459</td>
<td>0.140</td>
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CXP, creos xenoprotect membrane; BG, reference membrane; SD, standard deviation. Reprinted with permission [45].

and distal bone crest, at the level of the implant shoulder; (3) defect depth (DD), the distance from the bone crest to the implant surface, perpendicular to the long implant axis; and, (4) infrabony defect (ID), the distance from the bone crest to the first bone-to-implant contact parallel to the implant axis.

Defects eligible for GBR in the study had one or two walls missing and a defect height of 3-7 mm, or up to 10 mm if the defect width did not exceed 2 mm. Though a range of defect heights at implant insertion were present in both CXP (5.1±2.1 mm) and BG (4.9±1.9 mm) treatment arms, they were very similar between the two groups (p = 0.832). Defect height reduced by 4.1±2.2 mm (81±24%) in the CXP arm from implant insertion to reentry, compared with 3.3±2.8 mm (62±61%) in the BG arm (Table 1). Using a non-parametric two-sided 95% confidence interval, the CXP arm is therefore statistically non-inferior to the BG arm at the one-sided 2.5% level of significance (p <0.001). Indeed, accounting for all four defect size parameters, there was overall higher mean bone gain from implant insertion to reentry in the CXP arm than the BG arm, though this did not reach statistical significance (Table 1). The bone gain observed with both membranes was similar to a value of 3.491 mm, recently reported in a systematic review and meta-analysis as the mean defect height gain in bone augmentation using particulate autologous bone, xenograft and a bioabsorbable membrane [16], confirming that a simultaneous procedure can lead to bone augmentation of dehiscence defects.

Favorable soft tissue outcomes were observed with both membranes. Though some patients reported pain one-week post-surgery, with a mean score of 2.3/10, this rapidly reduced to 0.3 by week 3, and had ceased altogether in all patients by week 12. There were no significant differences between the CXP and BG arms regarding pain or quality of life (p >0.05), the latter evaluated with the OHIP-14 questionnaire. However, the membrane exposure rate from implant insertion to reentry was almost two-fold lower in the CXP arm (2 patients, 8.7%) than the BG arm (4 patients, 16.7%), consistent with the low rate reported for CXP previously [44], though the difference between membranes was not statistically significant. Overall, our simultaneous GBR and implant insertion procedure resulted in low dehiscence and membrane exposure rates, which likely

Figure 2. Schematic representation of the measurements quantifying the peri-implant bone defect. (A) Defect height, measured from the top of the implant shoulder to the first bone-to-implant contact perpendicular to the long implant axis. (B) Defect width (DW), the distance between the mesial and distal bone crest, at the level of the implant shoulder. (C) Defect depth (DD), the distance from the bone crest to the implant surface, perpendicular to the long implant axis. (D) Infrabony defect (ID), the distance from the bone crest to the first bone-to-implant contact parallel to the implant axis. Reprinted with permission [45].
contributed to the observed high implant survival rate at reentry of 100%

In summary, our recent randomized controlled trial confirmed that successful bone augmentation and implant survival at reentry can be achieved when performing a simultaneous implant placement procedure with GBR using a new resorbable, non-crosslinked collagen membrane at single-tooth sites.\(^{[45]}\) Though this study was restricted to bone augmentation of dehiscence defects, we could confirm that the new CXP membrane, which exhibits improved mechanical properties to the reference membrane BG\(^{[43]}\), is statistically non-inferior in a clinical setting. Moreover, CXP displayed trends toward increased bone gain (20% greater defect fill for CXP than BG) and reduced dehiscence rates that should be further investigated. These findings support that treatment approaches employing fewer surgeries and cutting-edge materials can lead to clinically-relevant benefits for patients.

**Conflicting interests**

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**Authors’ contributions**

B.W. made substantial contributions to the study conception and design, acquisition, analysis and interpretation of data, as well as drafted and critically reviewed this research highlight article. I.U. made substantial contributions to the study conception and design, acquisition, analysis and interpretation of data, as well as critically reviewed this article. W.Z., G.P. and M.S. made substantial contributions to data acquisition and critically reviewed the article. All authors approved the final version of the article.

**Abbreviations**


**References**


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