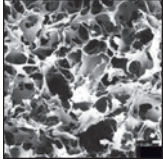


# Novel Collagen Matrix to Increase Tissue Thickness Simultaneous with Guided Bone Regeneration and Implant Placement in Esthetic Implant Sites: A Feasibility Study



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*The purpose of this case series was to assess safety and feasibility of a novel resorbable collagen matrix (CMX) to enhance tissue thickness simultaneous with implant placement and guided bone regeneration (GBR) in esthetic sites over an 8-week healing period. Soft tissue thickness at implant sites and adjacent teeth was monitored with an ultrasonic device. Overall tissue contour changes were assessed by sequential digital surface model superimpositions. Periodontal parameters and patient-related outcomes revealed no significant changes. Combining a novel CMX and GBR revealed a significant soft tissue thickness increase of 1.56 mm at implant sites after 8 weeks, with no significant decrease between 4 and 8 weeks. The overall tissue contour increase was most significant at a distance of 5 mm from the mucosal margin, corresponding to a tissue increase at the implant shoulder area. No effect was observed at adjacent teeth after 8 weeks.*

Int J Periodontics Restorative Dent 2018;38:575–582. doi: 10.11607/prd.3700

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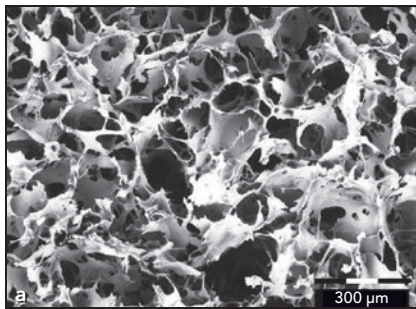
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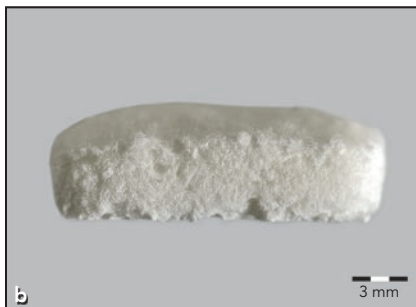
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Current dental research aims to better understand the biologic processes underlying alveolar bone healing and tissue regeneration, with the ultimate goal of improving patient care.<sup>1</sup> Although the facial soft tissue morphology plays a pivotal role in achieving esthetic success in the anterior maxilla,<sup>2</sup> the impact of dimensional soft tissue alterations in postextraction sites has received little attention in clinical research.<sup>3,4</sup> The integrity of the hard and soft tissue dimensions is jeopardized by physiologic and structural changes following tooth loss.<sup>5–7</sup> Although knowledge of soft tissue augmentation procedures in esthetic sites is limited,<sup>8</sup> a number of surgical techniques may indicate potential benefit for soft tissue enhancements around implants to improve color and texture.<sup>9–14</sup> Autogenous connective tissue grafts (CTG) remain the gold standard for soft tissue augmentation.<sup>10</sup> Drawbacks of autogenous CTGs include potential volume shrinkage, the morbidity associated with graft harvesting, and the limited availability of autogenous graft tissue.

To overcome the limitations of autogenous CTG, research has focused on the development of soft tissue substitutes.<sup>15,16</sup> Recently, a new resorbable collagen matrix (CMX) (Geistlich Fibro-Gide, Geistlich Pharma) was developed



**Fig 1** (a) Scanning electron microscopic image of resorbable collagen matrix showing its three-dimensional structure due to weak cross-linking through a chemical agent to improve mechanical properties and space-making capabilities. (b, c) Macroscopic structure of the resorbable collagen matrix (CMX) from a lateral view (b) and an axial view (c).



(Fig 1). It is weakly cross linked through a chemical agent to improve its mechanical properties. This feature enhances the space-making effect of CMX compared to non-cross-linked collagen matrices, improving the stabilization of the blood clot and providing sufficient space for the ingrowth of host cells during wound healing.<sup>17</sup> Preclinical experiments in mice revealed favorable tissue integration and promotion of angiogenesis.<sup>18</sup> Currently, no clinical data is available for the use of CMX in combination with simultaneous implant placement and guided bone regeneration (GBR). This approach may not only have synergistic effects on soft tissue and bone regeneration in a single surgical intervention, it may also reduce morbidity for patients in need of an implant-supported restoration in the esthetic zone.

The primary objective of this study was to assess the safety and feasibility of using CMX to enhance soft tissue thickness in esthetic sites. The secondary objective was to visualize and quantify the overall tissue contour changes by sequential digital surface model superimpositions.

## Materials and Methods

### Study Design

The study was designed as a single-arm, single-center pilot study. Patients in need of single-tooth replacement of a maxillary central incisor and exhibiting insufficient facial bone wall anatomy, allowing the concept of early implant placement with simultaneous GBR and soft tissue grafting by CMX, were

admitted to the study. The study was approved by the standing ethical committee of Switzerland (KEK-BE-Nr 071/13).

Patients were consecutively recruited according to the following inclusion criteria (Fig 2): (1) healthy periodontal conditions and a full-mouth plaque score < 25%<sup>19</sup>; (2) implant sites allowing the concept of early implant placement postextraction and GBR<sup>20</sup>; (3) absence of significant medical conditions; and (4) aged 18 years or older. Exclusion criteria were as follows: (1) systemic diseases altering tissue healing; (2) smoking; (3) intake of immunosuppressants, bisphosphonates, or high-dose corticosteroids; (4) history of malignancy within the past 5 years; and (5) pregnant or lactating.

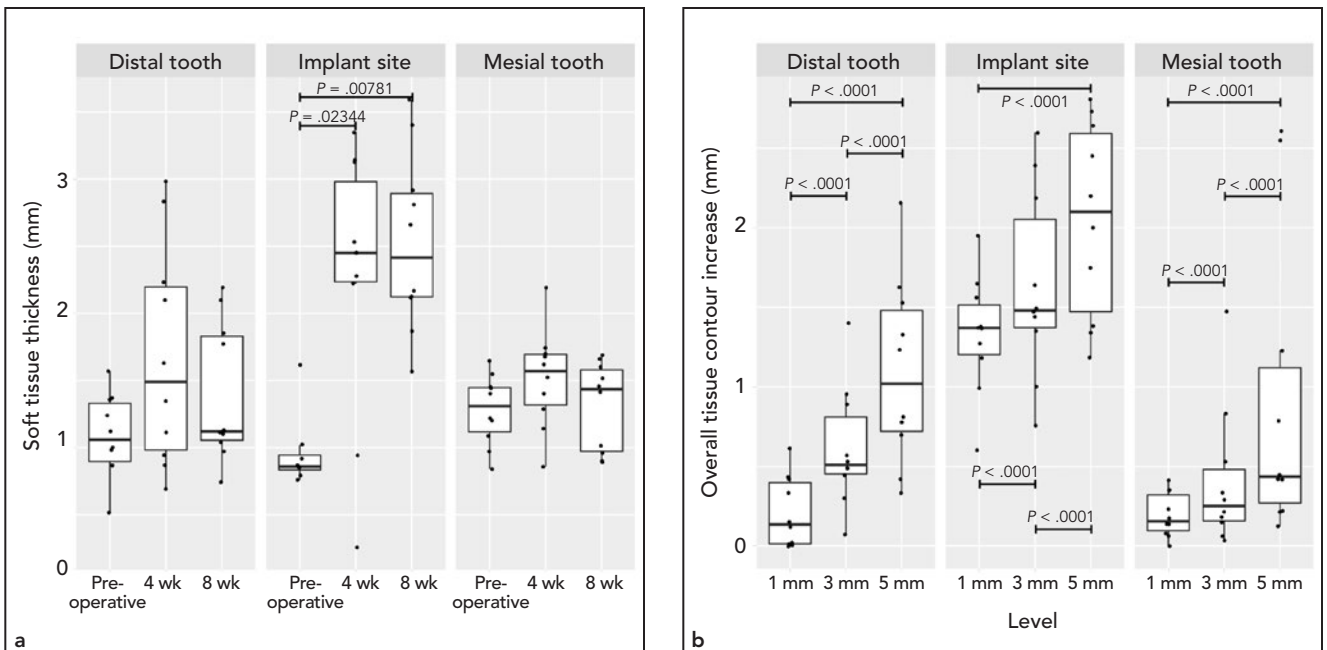
### Clinical and Radiographic Examinations

The following clinical parameters were assessed at teeth adjacent to the target implant site in four positions: supuration, plaque index (PI), sulcus bleeding index (SBI), bleeding on probing (BoP), probing depth (PD), attachment loss (AL), and the band of keratinized mucosa on the facial aspect (KT) (Fig 3).

The radiographic analysis in the screening phase was based on three-dimensional (3D) cone beam computed tomography (CBCT) with a field of view of 4 × 4 cm (3D Accutomo 170, Morita), which was used to assess the local bone anatomy and the feasibility of early implant placement.<sup>4,6</sup>

Screening	Preoperative (visit 1)	Surgery (visit 2)	4 wk (visit 3)	8 wk (visit 4)
Information	-2 wk ± 3 d	Day 0	4 wk ± 3 d	8 wk ± 3 d
Inclusion criteria	Informed consent			
Exclusion criteria	Full-mouth plaque score			
Type 2/3 early implant placement	Photographs	Photographs	Photographs	Photographs
2D or 3D radiograph	PIROP	PIROP	PIROP	PIROP
Understanding the aim of the study	Impression		Impression	Impression
	Periodontal parameters			Periodontal parameters
	OHIP questionnaire			OHIP questionnaire

**Fig 2** Study screening and enrollment: visits, timeline, and parameters examined.



**Fig 3** (a) Soft tissue thickness analysis using PIROP. A significant increase in soft tissue thickness was observed at implant sites over time compared to mesial and distal sites. At implant sites, significant thickening of 1.56 mm was observed at 8 weeks ( $P = .00781$ ). The soft tissue thickness revealed no significant increase between 4 weeks and 8 weeks of healing ( $P = .54055$ ). Distal sites, covered by collagen membranes and CMX, showed an increase of 0.06 mm ( $P = .22097$ ). Mesial sites, covered by a collagen membrane only, increased by 0.13 mm ( $P = .84570$ ). (b) Overall tissue contour increase over 8 weeks of healing: The greatest effect on bone and soft tissue increase was found at a distance of 5 mm from the gingival margin for all sites: At implant sites, the increase amounted to 2.1 mm; at the distal tooth grafted with CMX, 1.0 mm; and at mesial tooth grafted with no CMX, 0.4 mm.

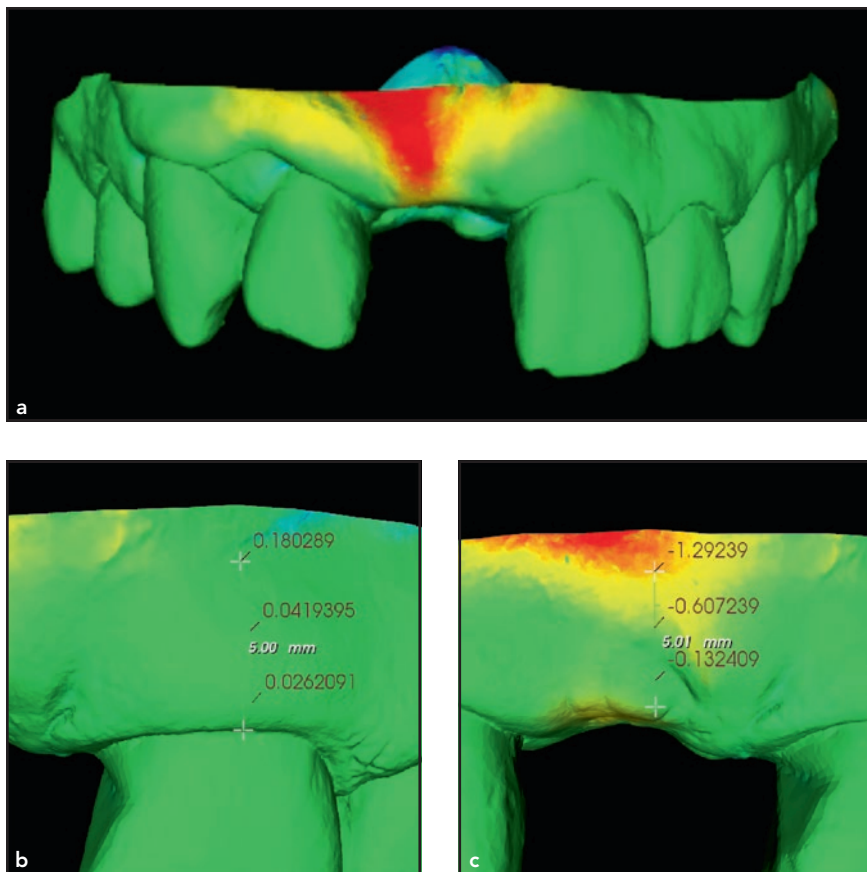
**Soft Tissue Thickness Analysis and Patient-Reported Outcomes**

The facial soft tissue thickness was analyzed at the mesial and distal adjacent tooth and at the target implant site using an ultrasonic biometer (PIROP, Echo-Son).<sup>21</sup> Soft tissue

thickness was assessed prior to surgery and at 4 and 8 weeks of healing. Photographs were taken at all visits to document soft tissue healing and integration. Patient-reported outcome measures (PROMS) were assessed using the Oral Health Impact Profile (OHIP) to evaluate the oral health-related quality of life.<sup>22</sup>

**Overall Tissue Contour Increase by Sequential Digital Surface Model Superimpositions**

The dimensional changes of the facial tissues were documented as overall tissue contour alterations between surgery and 8 weeks of healing. Impressions were taken, and



**Fig 4** Visualization of dimensional changes over time. (a) Surface mesh models were rigidly aligned using anatomical landmarks and Di2Mesh software as described previously.<sup>4</sup> (b, c) Distances between the surface meshes were presented as color-coded figures to visualize facial tissue increase and analyzed at 1, 3, and 5 mm from the gingival margin at the adjacent teeth (b) and the target site (c).

surface mesh models were created. Surface mesh models were rigidly aligned using anatomical landmarks by Di2Mesh software as described previously<sup>4</sup> (Fig 4).

#### *Surgical Procedure with Simultaneous Hard and Soft Tissue Augmentation*

A sulcular incision was made along the adjacent teeth, with one vertical releasing incision distal to the canine. A bone-level implant with

a platform-switching interface and a hydrophilic implant surface was placed (Figs 5a to 5d) (Bone Level SLActive, Straumann). The integrity of the facial bone wall was characterized by the defect width, height, and depth, using the implant shoulder as a reference (Figs 5e and 5f). Simultaneous GBR was performed with a two-layer composite graft with locally harvested autogenous bone chips to cover the exposed implant surface, combined with a superficial layer of deproteinized bovine bone mineral (Bio-Oss,

Geistlich) and double-layered non-cross-linked collagen membrane (CM) (Bio-Gide, Geistlich).<sup>23</sup> Subsequently, the CMX was inserted dry on the implant site and extended to the distal tooth site on the facial aspect on top of the collagen membrane (Figs 5g to 5i) followed by a tension-free wound closure (Figs 5j and 5k). Patients received analgesics and antibiotic prophylaxis for 3 days and were advised to rinse with a 0.2% chlorhexidine solution for 2 weeks. Sutures were removed 2 weeks after surgery (Figs 5l to 5o), and the tissue changes were documented after 4 and 8 weeks (Figs 5p to 5s).

#### *Statistical Analysis*

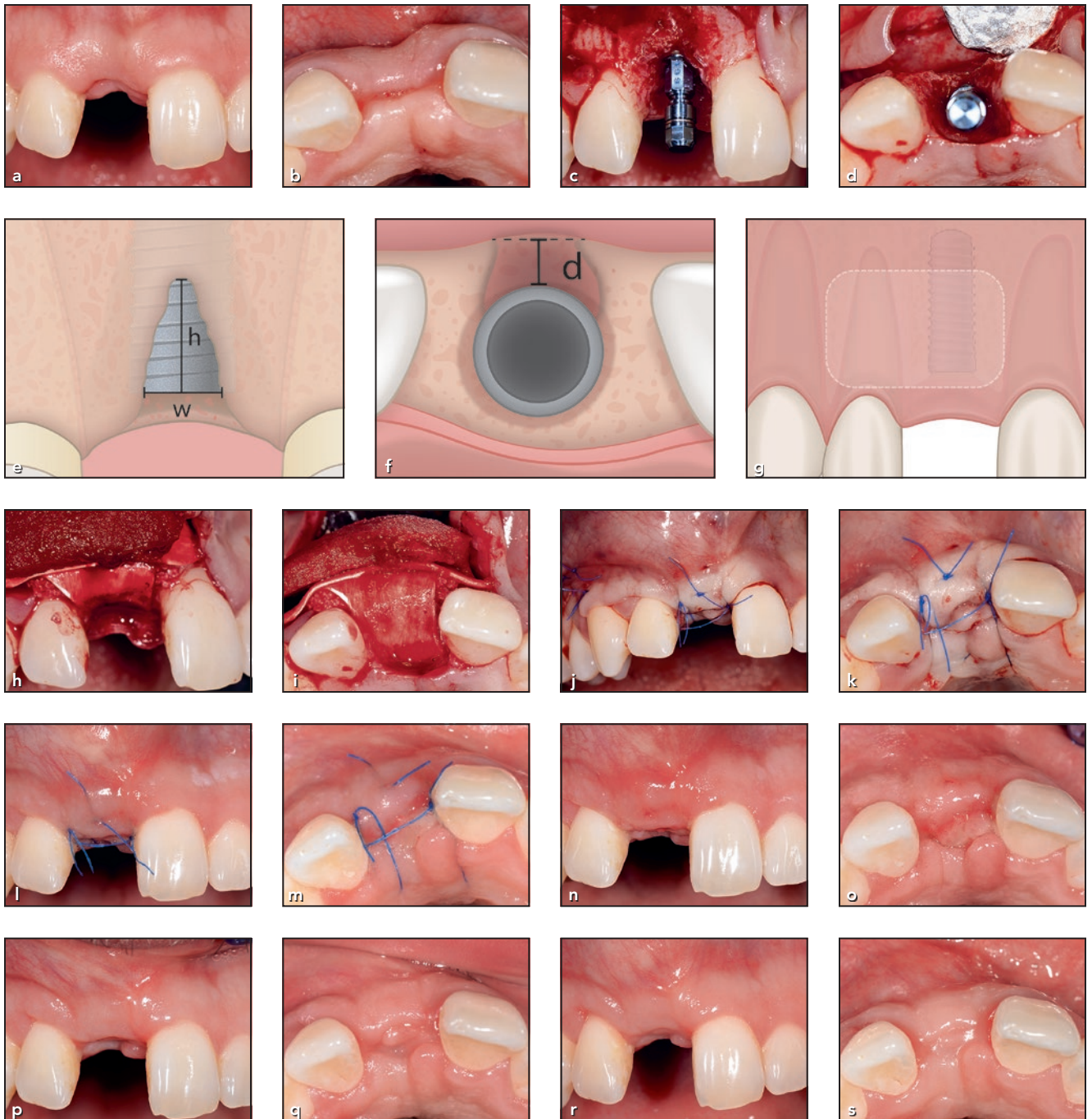
Paired two-sample comparisons were done with Wilcoxon signed rank test, and independent two-sample comparisons were performed with Mann-Whitney-Wilcoxon test. Two-way repeated measure analysis of variance (ANOVA) was calculated using nonparametric Brunner-Langer model for longitudinal data in factorial experiments.  $P < .05$  was considered statistically significant except for pairwise post hoc comparisons, which were adjusted by the simple Bonferroni correction.

## **Results**

#### *Surgical Procedure*

The study population consisted of three women and seven men with a mean age of 46 years ( $\pm 17$  years).





**Fig 5** Surgical procedure. After 8 weeks of healing (a, b), a mucoperiosteal flap was raised and a bone-level implant with a platform-switching interface and a hydrophilic implant surface was placed (c, d) (Bone Level SLActive, Straumann). (e, f) Defect analysis and CMX positioning. The integrity of the facial bone wall is characterized based on the defect width ( $w$ ), height ( $h$ ) and depth ( $d$ ) using the implant shoulder as a reference. (g) The CMX was placed at the target site and extended to the distal tooth site. Thus, three test sites were obtained: the mesial tooth site with no CMX grafting; the target site with implant placement, GBR, and CMX grafting; and the distal tooth site with CMX grafting. Facial defects were grafted using locally harvested autogenous bone chips to cover the exposed implant surface, followed by a superficial layer of deproteinized bovine bone mineral (Bio-Oss, Geistlich). The augmented site was covered with a double-layered non-cross-linked collagen membrane (Bio-Gide, Geistlich). Subsequently, the CMX was adapted in a dry state using scissors or a scalpel. The CMX was inserted dry on the facial aspect on top of the collagen membrane and subsequently soaked with the patient's blood (h, i). After release of the periosteum, tension-free wound closure was obtained (j, k). The sutures were removed 2 weeks after surgery (l–o). Soft tissue healing was assessed at 4 weeks (p, q) and 8 weeks (r, s) of healing.

Oral hygiene reached a mean full-mouth plaque score of  $14\% \pm 3.89\%$ . A deficient facial bone wall was present in all sites, requiring simultaneous GBR, with defect dimensions of  $3.00 \pm 1.59$  mm in width,  $3.40 \pm 3.53$  mm in height, and  $2.70 \pm 1.89$  mm in depth (Figs 5e and 5f). The defects were grafted with a first layer of locally harvested autogenous bone chips exhibiting a mean weight of  $191.1 \pm 62.78$  mg. DBBM was applied in a mean amount of  $384.6 \pm 129.62$  mg. Trimming of the CMX was performed to a mean length of 18.8 mm, a thickness of 3 mm, and a height of 10.45 mm. Postoperative healing was uneventful in all but two patients showing a small dehiscence without exposure of CMX. Overall, no serious adverse events and no device-related adverse events were observed. The periodontal parameters did not show significant changes over the follow-up period. The mean OHIP score was 4.9 at visit 1 and 2.9 at visit 4, showing good oral health status in all patients. The CMX revealed no significant increase in keratinized mucosa at implant ( $P = 1.0000$ ) and distal tooth sites ( $P = .3125$ ).

#### *Soft Tissue Thickness Analysis Using PIROP*

Implant sites yielded a median thickening of 1.56 mm at 8 weeks ( $P = .00781$ ) (Fig 3a). The soft tissue thickness remained unchanged between 4 and 8 weeks ( $P = .54055$ ). Distal sites, covered by collagen membrane and CMX, showed a median increase of 0.06 mm

( $P = .22097$ ). Mesial sites, covered by a collagen membrane only, increased by 0.13 mm ( $P = .84570$ ). ANOVA comparisons revealed significant different soft tissue increase for implant sites compared to tooth sites ( $P = .00002$ ). No difference in soft tissue increase was observed between distal (CM + CMX) and mesial (CM) tooth sites ( $P = .52311$ ).

#### *Relationship Between Tissue Increase and Applied Materials*

To investigate the relationship between the overall tissue increase and the applied materials, a linear regression analysis was performed. First, the overall tissue gain was compared to the total amount of DBBM and autogenous bone chips applied. The least-squares slope revealed a nonsignificant effect ( $P = .7288$ ). Second, the soft tissue increase was compared to the thickness of the CMX. No significant relationship was found between the thickness of the applied CMX and the increase in soft tissue thickness ( $P = .2599$ ).

#### *Overall Tissue Contour Increase After an 8-Week Healing Period*

The overall bone and soft tissue alterations of the facial contour between surgery and 8 weeks of healing was analyzed to understand in which areas the tissue grafting was most efficient. The overall tissue contour increase was most significant at a distance of 5 mm from the gingival margin for all sites ( $P < .0001$ ).

It amounted to 2.1 mm for implant sites (CMX + GBR), 1.0 mm for the adjacent distal tooth site (CMX + CM), and 0.4 mm at the adjacent mesial tooth site (CM) (Fig 3b).

## **Discussion**

The present study revealed a significant increase in soft tissue thickness at implants of 1.56 mm for CMX in combination with simultaneous GBR in esthetic sites after 8 weeks using an early implant placement protocol. The soft tissue thickness remained unchanged between 4 and 8 weeks. The overall tissue contour increase was most significant at a distance of 5 mm from the gingival margin, corresponding to a tissue thickness increase at the implant shoulder area. The PROMS did not increase over the treatment period, showing good patient acceptance. These results support that soft tissue augmentation using CMX in combination with GBR was safe, showing a significant increase in soft tissue thickness and overall tissue contour in the early wound healing stage.

The resorbable CMX was designed to serve as a substitute for autogenous subepithelial CTG. The improved mechanical properties by a low degree of cross-linking should allow the matrix to better withstand mechanical stresses, mimic the biologic and mechanical environment in wound healing, and provide space for the ingrowth of host cells during wound healing.<sup>24</sup> The present study showed no relationship between the thickness of

the applied CMX and the effective soft tissue thickness. We can only hypothesize that the volume stability of the CMX is limited to a certain thickness and that the primary flap closure may provoke compression of the CMX. A certain stability of the CMX is observed, since no decrease in soft tissue thickness was detected between 4 and 8 weeks. However, long-term follow-up is needed to verify the present tissue stability. Since cross-linking has been shown to negatively affect transmembranous angiogenesis in a rat model,<sup>25</sup> other authors performed preclinical experiments of these CMX in vivo, showing an uneventful replacement of most of the matrix within 90 days.<sup>17,26</sup> The safety and feasibility of CMX simultaneous with GBR and implant placement is in line with the literature and provides a further application of CMX to reduce patient morbidity and operating times.<sup>26,27</sup>

In clinical studies, an increase in soft tissue thickness of between 0.35 and 3.2 mm using CTGs has been reported.<sup>12,28,29</sup> Acellular dermal matrix-derived allogenic membranes applied simultaneous with implant placement without GBR revealed a median increase in soft tissue thickness of 2.0 mm after 12 weeks.<sup>30</sup> In a recent study, the CMX was applied at abutment connection and compared to a CTG. After 90 days, the CMX revealed a mean soft tissue increase of 1.1 mm on the facial aspect, showing no significant difference compared to CTG.<sup>27</sup> These findings are in agreement with the present investigation exhibiting a soft tissue increase of

1.56 mm. In addition, the CMX demonstrated uneventful healing and periodontal health throughout the observation period except for two minor dehiscences related to patient compliance. The tissue thickness was slightly increased at the distal tooth with CMX + CM compared to the mesial tooth with CM only, without reaching statistical significance. This may be related to a tenting effect of the CMX in combination with GBR or to the triangular flap design, or it may be caused by the releasing incision. The slight decrease in the OHIP score from 4.9 to 2.9 in this study demonstrated good acceptability of the treatment, with minimal impairment of the quality of life.<sup>22</sup>

The present study has several limitations. First, the application of the CMX requires careful release of the periosteum, which in turn may cause slightly increased morbidity. Second, since this study was designed as a feasibility study evaluating safety and usability, the number of patients enrolled is low. Third, greater tissue increase would be desirable in a more coronal aspect 1 to 3 mm from the gingival margin to potentially avoid dark coloration from abutments in thin tissue biotypes. Finally, a direct comparison of CMX to a CTG in a larger study population would provide more insight into the effectiveness of tissue increase and morbidity for patients. Therefore, the results have to be interpreted with caution. Future research is needed to assess the long-term stability of soft tissue grafting using CMX.

## Conclusions

Combining a novel CMX and GBR revealed a significant soft tissue thickness increase of 1.56 mm at implant sites after 8 weeks, with no significant decrease between 4 and 8 weeks. The overall tissue contour increase was most significant at a distance of 5 mm from the mucosal margin, corresponding to a tissue increase at the implant shoulder area. Periodontal parameters and patient-related outcomes revealed no significant changes over time.

## Acknowledgments

The authors acknowledge the support of Sibylle Huber, Geistlich Pharma AG, Wolhusen, Switzerland. The authors thank Mrs Denise Winkelmann and Olivia Bucher of the Department of Oral Surgery and Stomatology, School of Dental Medicine, University of Bern, for patient care. The authors appreciate the expertise and support of Dr M. Meyer (Consult AG, Bern, Switzerland) for the statistical analysis. The authors reported no conflicts of interest related to this study.

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