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Efficacy of a collagen matrix for soft tissue augmentation after implant placement compared to connective tissue grafts: A multicenter, noninferiority, randomized controlled trial

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Abstract

Objectives: To test whether soft tissue volume augmentation using a collagen matrix (VCMX) leads to noninferior results in terms of gain of mucosal thickness at single implant sites, compared to connective tissue grafts (SCTG).

Methods: The study was designed as a multi-center randomized controlled clinical trial. Subjects in need of soft tissue volume augmentation at single tooth implant sites were consecutively recruited at nine centers. The deficient mucosal thickness at the implant sites (one per patient) was augmented by applying either a VCMX or a SCTG. Patients were examined at 120 days (abutment connection = primary endpoint), 180 days (final restoration), and 360 days (1-year after insertion of the final restoration). Outcome measures included: transmucosal probing of the mucosal thickness (crestal = primary outcome), profilometric measurements of the tissue volume, and patient-reported outcome measures (PROMs).

Results: Out of the 88 patients, 79 attended the one-year follow-up. The median increase of the crestal mucosal thickness between pre-augmentation and 120 days was

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0.3 ± 2.1 mm in the VCMX group and 0.8 ± 1.6 mm in the SCTG group ($p = .455$). Non-inferiority of the VCMX compared to the SCTG was not observed. The respective numbers at the buccal aspect amounted to 0.9 ± 2.0 mm (VCMX) and 1.1 ± 1.4 mm (SCTG; $p = .431$). PROMs including pain perception favored the VCMX group.

Conclusion: It remains inconclusive whether soft tissue augmentation using a VCMX is noninferior to SCTG in terms of crestal mucosal thickening at single implant sites. However, the use of collagen matrices favors PROMs especially pain perception, while achieving similar buccal volume gains along with comparable clinical and aesthetic parameters to SCTG.

KEYWORDS
collagen matrix, dental implants, esthetics, patient-reported outcomes, soft tissue augmentation, subepithelial connective tissue graft, tissue transplantation

1 | INTRODUCTION

Placing and restoring dental implants to replace missing teeth and thereby restore function has proven to be a highly effective and predictable therapeutic option in partially and fully edentulous patients (Howe et al., 2019; Jung et al., 2008, 2012; Morton et al., 2018). Along with functional and health-related considerations, aesthetic patient desires come into play in visible areas of the dentition esthetic and must be met (Arunyanak et al., 2017; Vilhjalmsson et al., 2011). In contrast to earlier efforts that concentrated on anchorage, bone integration, and longevity of the implant-borne restorations, more recent efforts have concentrated on patient-reported outcome measures (PROMs), including satisfaction with the aesthetic appearance.

The esthetic appearance and its stability over time are heavily influenced by the volume and stability of the soft tissues around the implant, the abutment, and the margins of the restoration (Bienz et al., 2017). Additionally, thicker tissues can mask the color of the underlying restorative materials, which could otherwise be the source of unappealing discolorations (Benic et al., 2017; Jung et al., 2007). In addition to producing a more aesthetically pleasing appearance, the gain in soft tissue volume that result from increasing the soft tissue quantity and quality, i.e., keratinized instead of lining mucosa, has the potential to promote peri-implant health over time (Tavelli et al., 2021; Thoma et al., 2018). As a result, the augmentation and maintenance of peri-implant soft tissues have gained increased attention within the clinical and scientific community (Giannobile et al., 2018; Schwarz et al., 2018).

Historically, transplantation of a connective tissue graft has been the treatment of choice to increase the mucosal thickness at implant sites in cases of volume deficiencies (Cairo et al., 2017; Esposito et al., 2012; Seibert, 1983). Recent systematic reviews have demonstrated that the subepithelial connective tissue graft harvested from the palate leads to pleasing and predictable results (Thoma et al., 2009, 2014). However, transplantation of autogenous tissue is invariably accompanied by patient morbidity attributable to the donor site, and this increased morbidity has been a focus of recent clinical investigations (Burkhardt & Lang, 2015; Tavelli et al., 2020; Thoma et al., 2023). The source of this increased morbidity may arise from undisturbed wound healing, extensive bleeding, tissue necrosis, infection, and sensory disturbances (Griffin et al., 2006; Tavelli et al., 2020), which often cause pain or discomfort in patients undergoing mucosal grafting (Del Pizzo et al., 2002; Griffin et al., 2006; Wessel & Tatakis, 2008). To reduce this patient morbidity resulting from autogenous tissue graft harvesting, efforts have been made to develop products that can replace the autogenous graft (Sanz et al., 2009; Schmitt et al., 2016; Thoma et al., 2010, 2023; Zucchelli et al., 2020).

These soft tissue substitutes (matrices) made of porcine-derived collagen have been clinically tested reporting highly promising results (Chappuis et al., 2018; Cosyn et al., 2021; Thoma et al., 2011, 2016, 2022). According to histological evidence, these collagenous matrices are incorporated by the host tissues, remodeled, and replaced by connective tissue (Thoma et al., 2011, 2016). This enables the increase of soft tissue volume in areas where it is lacking (Naenni et al., 2018) and the maintenance of that over time (Thoma et al., 2020, 2023).

However, the published studies evaluating the outcomes of collagenous matrices as soft tissue substitutes have mostly been single centered with only one multicenter study having recently been published (Cosyn et al., 2021), thus limiting the generalizability of the clinical findings. Therefore, the present study aims to test whether the use of a collagen matrix leads to noninferior results when compared to the subepithelial connective tissue graft in a multicenter study.

2 | MATERIALS AND METHODS

2.1 | Study design

The present study was designed as a multicenter, noninferiority, randomized controlled trial investigating the efficacy of a volume collagen matrix (VCMX) compared to the autogenous subepithelial connective tissue graft (SCTG) for soft tissue volume augmentation in partially

edentulous patients. The study was performed according to the ISO Standard 14155:2011 in clinical investigations using medical devices in human patients (appendices VIII and X of the Medical Device Directive 93/42/EEC and with the Declaration of Helsinki 2013) and followed the extension of the CONSORT 2010 statement for non-inferiority trials (Piaggio et al., 2012). Ethical approval was obtained by each center individually. The two treatment modalities were randomly assigned to the patients in a ratio of 1:1 according to a randomization protocol prepared by a statistician. Each investigation center received a total of 24 numbered and concealed envelopes containing the randomized assignment of the treatment to a subject number. The numbered randomization envelopes were consecutively opened by the investigator/surgeon immediately prior to the soft tissue augmentation surgery and the recruitment continued until the a priori sample size was reached. Patients in need of soft tissue volume augmentation at single implant sites in areas of esthetic concerns were consecutively recruited, informed, and screened for inclusion. This decision was based on assumptions of patient recruitment capabilities (Perperoglou et al., 2022). The randomization list was kept concealed until database closure. Thereafter, it was forwarded to the statistician.

2.2 | Inclusion criteria

- Implant placement at least 6 weeks and a maximum of 6 months prior to enrolment
- Necessity of soft tissue augmentation in a single tooth gap
- One tooth adjacent to each side of the defect with a mean bleeding on probing (BoP) of <20%
- Basic periodontal examination (BPE) < 2
- 18 years or older
- Ability to comply with the study-related procedures such as exercising good oral hygiene and attending the follow-up procedures
- Ability to fully understand the nature of the proposed surgery and ability to understand and sign the informed consent form

2.3 | Exclusion criteria

- Presence of a vertical bony dehiscence >3 mm at the implant site assessed at the time of soft tissue augmentation surgery
- Heavy smoker with >10 cigarettes per day
- Presence of periodontal disease
- Insulin-dependent diabetes
- General contraindications for dental and/or surgical treatment including coagulants
- History of malignancy, radiotherapy, or chemotherapy for malignancy within the past 5 years
- Women of childbearing age not using a highly effective method for contraception
- Pregnancy or breastfeeding
- Previous or current medication affecting mucosal healing in general, e.g., steroids, large doses of anti-inflammatory drugs
- Disease or condition affecting connective tissue metabolism, e.g., disease of arteries in the operating zone, bone metabolic diseases, alcohol abuse
- Any systemic diseases that contraindicate implant placement, e.g., thyroid dysfunction autoimmune disease
- Allergy to collagen
- Participation in an investigational device or drug clinical trial within the last 6 months

A calibration meeting was performed prior to the start of the investigation. No restrictions were made in terms of the minimal number of patients to be included by each center (Perperoglou et al., 2022; Ruvuna, 2004).

2.4 | Primary endpoint

The primary endpoint was the gain in mucosal soft tissue thickness at the crest of the ridge.

2.5 | Clinical procedures

2.5.1 | Screening

Before entering the study patients provided informed consent. Thereafter, a screening visit was performed including periodontal measurements and an impression or a digital scan of the study site. Patients received a general oral examination at all study visits and were provided with oral hygiene instruction when deemed necessary by the therapist or the examiner.

2.5.2 | Soft tissue augmentation surgery

Prior to surgery, the patients rinsed with a 0.2% solution of chlorhexidine digluconate for 60 seconds. In addition, the patients took anti-inflammatory drugs and antibiotics before surgery. Following local anesthesia, the surgical procedures were as follows:

Mandible

Sulcular incisions around the neighboring teeth and a mesiodistal crestal incision were made. A full-thickness flap was elevated on the lingual side and a split flap was prepared on the buccal side without elevating the periosteum thus generating a soft tissue pouch. This pouch was extended in size to a degree larger than the expected size of the graft to mobilize the buccal tissue and allow for tension-free wound closure.

Maxilla

Sulcular incisions around the neighboring teeth and a mesiodistal crestal incision were made. On the buccal side, a split flap was prepared according to the procedures described for the mandible. On

the palatal side, the flap design consisted of two parallel vertical incisions extending to the bone with a length of about 9 mm. A split thickness flap was prepared by horizontal incision penetrating in a coronal-apical direction 3 mm coronal to the most apical extent of the vertical incisions. Thereafter, a blade was used to connect apically the two vertical incisions extending deeper with the external bevel for approximately 3–4 mm in apico-coronal direction to split the palatal tissue in another plane. The intermediate layer created by these two incisions allowed the flap to slide crestally (Tinti & Parma-Benfenati, 1995).

At this time point, the sealed envelopes were opened containing the treatment modality assigned by randomization:

- Test group: Cross-linked volume collagen matrix (VCMX) (Geistlich Fibro-Gide®, Geistlich Pharma AG, Wolhusen, Switzerland);
- Control group: Autogenous subepithelial connective tissue graft (SCTG)

A representative case of each treatment group is presented in Figure 1. Briefly, in the VCMX group, the matrix (initial dimension: 25 mm × 25 mm × 6 mm) was trimmed to the size desired for the recipient bed and the final volume of the VCMX was measured prior to implantation. Conversely, in the SCTG group, an autogenous graft was harvested from the palate using a single incision technique. The area of harvesting was located between the palatal root of the first molar and the mesial aspect of the canine. The surgeon made a clinically based decision regarding the side of the palate from which to harvest the graft. Similarly, the volume of this graft was measured before its placement at the recipient site. Thereafter, the grafts were placed into the prepared buccal pouches, immobilized, and stabilized in the desired position by the application of one horizontal mattress suture non-resorbable 5-0 suture (Gore Tex 5-0; W.L. Gore & Associates, Inc). One horizontal mattress suture was applied through the buccal flap to position the graft without tension. Single interrupted sutures were used to adapt the wound margins and to achieve primary closure of the augmented site. Due to the coronal advancement of the palatal island flap in the maxilla, a small area on the palate was left for secondary healing.

In the SCGT group, the incision at the palate was closed placing one or more crossover sutures. Since the size of the single tooth gaps was not standardized, the size of the graft/matrix had to be customized to match the dimensions of the defect site, as determined by the treating clinician.

Anti-inflammatory drugs and antibiotics were prescribed for the postoperative phase until suture removal. The type of anti-inflammatory drugs and antibiotics prescribed in the different centers was not standardized. Patients were instructed to rinse twice daily with a 0.2% solution of chlorhexidine for 10 days. Existing provisionals were adapted as necessary to avoid interference with the healing process.

2.5.3 | Follow-up examinations

Seven to ten days following grafting, sutures were removed, and the area of surgery was cleaned with a mild prophylaxis paste. At this time point, the healing of the soft tissues at the recipient and

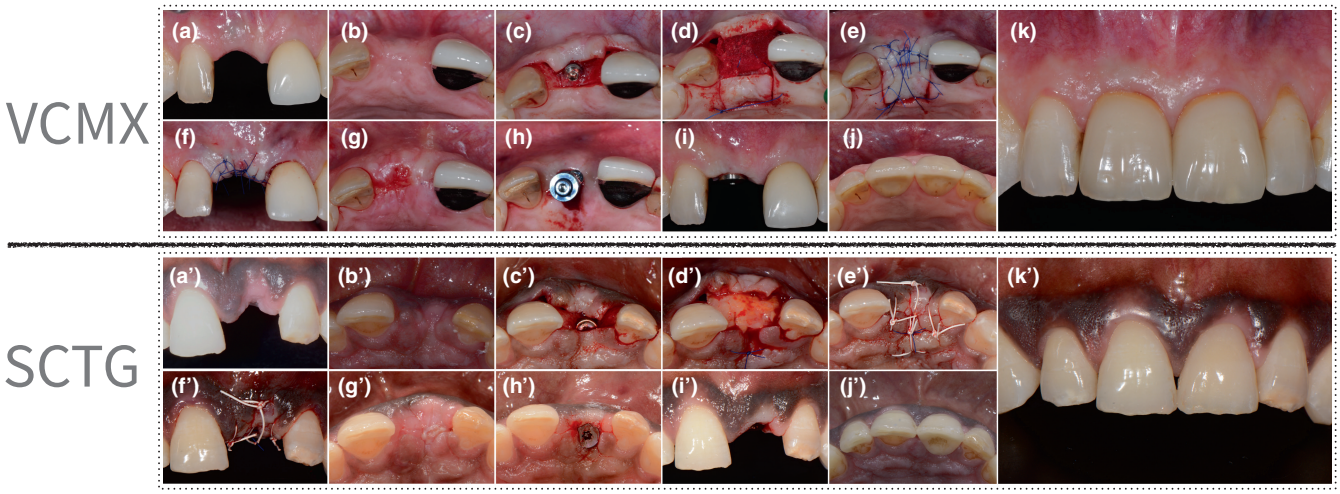

FIGURE 1 Representative cases of each treatment group. VCMX: (a) Pre-operative view revealing a tissue discoloration due to insufficient tissue volume. (b) Occlusal view showing the volume deficiency. (c) Implant uncovering and preparation of the buccal pouch. (d) Preparation of palatal island flap. VCMX was placed crestally and buccally and stabilized with a horizontal mattress suture. (e) Flap advancement and suturing. (f) Buccal view after suturing. (g) One-week post-op. (h) Abutment connection. (i) Buccal view after abutment connection. (j) Occlusal view after final crown delivery. (k) Buccal view after final crown delivery. SCTG: (a') Pre-operative view (b′) Occlusal view showing the volume deficiency. (c′) Implant uncovering and preparation of the buccal pouch (d′) Insertion of SCTG harvested from the palate and placed in the desired position (crestally and buccally). (e') Flap advancement and stabilization with a horizontal mattress suture. (f′) Buccal view after suturing. (g') One-week post-op. (h′) Abutment connection. (i′) Buccal view after abutment connection. (j') Occlusal view after final crown delivery. (k′) Buccal view after final crown delivery.

at the donor site (if applicable) were evaluated. This evaluation encompassed swelling and incomplete wound closure. Furthermore, patient-reported outcome measures (PROMs) were collected. Then 30 days after surgery (FU-30), the patients were recalled and the area of grafting and the graft donor site in the control were clinically examined. In addition, soft tissue healing was evaluated again, the PROMs collected, periodontal parameters recorded, and an impression was taken for 3D volume analysis. At 120 days post-surgically (FU-120), abutment connection was performed. A small crestal incision was placed to provide access to the head of the implant. Then, the cover screw was removed and replaced with a healing cap. In agreement with the situation at FU-30, PROMs were collected again. The final restoration was fabricated and seated on the implant according to standard clinical procedures 180 days after soft tissue grafting. The final examination took place 1 year after the delivery of the final restoration.

2.6 | Evaluation of soft tissue volume

For the evaluation of the dimensional changes at the defect sites resulting from the grafting procedures, impressions were taken at the following time points: preoperatively on day 0 (BL-1) and at the follow-up examinations at days 30 and 120. A new baseline (BL-2) was set after placement of the final restoration on day 180, which was used for the follow-up visit on day 540 after BL-2. These impressions were used to fabricate master casts made from dental stone. These casts were optically scanned with a 3D camera (Fickl et al., 2009; Schneider et al., 2009). The resulting images representing the different treatment time points of examination (day 0, i.e., BL-1, days 30, 120, 180, i.e., BL-2, day 540 after BL-2) were superimposed and matched in one common coordinate system. The buccal surfaces of the neighboring teeth were used as reference points for the superposition of the different images. Subsequently, a defined area of interest at each defect site was measured, and the volume difference between the time points was calculated. Due to an individually variable anatomic situation, the measured area varied between the sites but was kept constant at one site over time. The area of interest exhibited a trapezoid shape (Figure S1). In a bucco-oral dimension, it extended from the most coronal aspect of the lingual defect side to roughly 1 cm into the buccal mucosa, and in mesiodistal dimension from one adjacent tooth (mesial) to the other adjacent tooth (distal) at 1 mm from the adjacent tooth (Figure S1).

To allow a direct comparison of the different sites and the different treatment modalities, the calculated variable Δd represented the volume difference per measured area (Δd [mm] = Δ vol [mm^3]/area [mm^2]; Swissmeda, SMOP, Switzerland). Volume difference was assessed between day 0, i.e., BL-1 (soft tissue augmentation surgery), FU-30, and FU-120 (before abutment connection) as well as between FU-180, i.e., BL-2 (after delivery of the final restoration) and FU-540 after BL-2 (follow-up examination). All the 3D analyses were performed by a very experienced and calibrated examiner with volumetric analyses (Dr. Leonardo Mancini), who was not involved in any surgical or prosthetic procedure. The volume changes in both treatment groups were then calculated. The volumetric analyses were performed on two separate occasions at least 1 month apart. For the 2nd occasion, 7 random patients were selected, and the intra-examiner reliability was calculated with the intra-class correlation coefficient (ICC). The ICC for volumetric changes was 0.91 (95% CI: 0.55–0.98).

2.7 | Clinical measurements

For the assessment of the periodontal tissue health status, the following parameters were recorded at six sites around the teeth adjacent to the augmentation site during the BL-1, FU-10, FU-30, FU-120, FU-180, and FU-540 examinations: Plaque Index (PI) (Loe, 1967), keratinized tissue width (KTW), probing pocket depth (PD), bleeding on probing (BOP). All these assessments were also recorded at the implant site after delivery of the restoration during the FU-180 and FU-360 examinations and for keratinized tissue width (KTW) for the target site at all time points. To quantify the change in soft tissue thickness during the study, transmucosal probing of the soft tissue was performed with an endodontic instrument. Standardization of these measurements was assured by applying a personalized stent (Swissmeda, SMOP, Switzerland) with three standardized openings for the endodontic instrument. All measurements taken with the endodontic file were performed in duplicate and the mean values were calculated thereafter. A standard deviation was not calculated and only means were recorded in the CRF. These stents were fabricated as previously described (Thoma et al., 2016). The measurements of mucosal thickness were done at BL-1, FU-30, FU-120, FU-180, and FU-540. Esthetic outcomes were assessed by means of the Pink Esthetic Score (PES) (Furhauser et al., 2005).

2.8 | Patient-reported outcome measures (PROMs)

Patients were asked to document their consumption of analgesics/anti-inflammatory medication daily and to assess their experience of pain using a visual analog scale (VAS). These parameters were recorded from the day of surgery until suture removal and at day 30 post-op. In addition, an Oral Health Impact Profile (OHIP-14) questionnaire was handed to the patients and filled out at the beginning of the following visits: day 0 (soft tissue augmentation surgery), FU-10, FU-120, FU-180, and FU-540.

2.9 | Safety evaluation

Alongside the recording of swelling, pain, wound dehiscence, bleeding, and the intake of medications, any adverse events occurring during the study were documented.

2.10 | Statistical analysis

2.10.1 | Sample size calculation

Sample size considerations were based on the primary endpoint "gingival thickness at 3 months measured by transmucosal probing" from a previously published randomized clinical pilot study (Thoma et al., 2016).

Accordingly, the parameters were set as follows:

Mean gain in VCMX: 1.35 mm.

Mean gain in SCTG: 0.8 mm.

Errors: $\alpha = 0.025$ (one-sided) and $\beta = 0.2$ (power = 80%).

Common standard deviation: 1.6 mm.

Non-inferiority margin: 0.5 mm.

The non-inferiority margin of 0.5 mm was chosen based on clinical judgment (Schulz et al., 2010) as a difference <0.5 mm was considered clinically negligible (Kaji & Lewis, 2015). The sample size calculation was performed with a statistical software (Query - Power and Sample Size Version 9.2.1.0, Statistical Solutions Ltd), for the detailed calculation see Figure S2. The software calculated a sample size of 78 (38 patients per group) and considering a drop-out rate of ≈ 10% a total of 88 patients were enrolled in the study.

The primary outcome was to assess the non-inferiority of VCMX compared to SCTG (gold standard) in terms of crestal mucosal thickness gains at single implant sites at day 120 compared to day 0 (baseline) measured by trans-mucosal probing at the crest (occlusal) of the soft tissue ridge.

2.10.2 | Statistical hypotheses

The statistical hypotheses of the non-inferiority test were formulated as follows:

H0: mSCTG − mVCMX ≥ δ ('inferiority')

H1: mSCTG − mVCMX < δ ('non-inferiority').

Analyses were performed according to the intention-to-treat principle. The last-observation-carried-forward (LOCF) method was applied in case of missing data at day 120, i.e., the value measured at day 30 was taken to impute the missing value at day 120 (applied to five patients in total). To evaluate the primary effectiveness endpoint, the following univariate analysis of covariance (ANCOVA) model was applied: The primary endpoint variable (change in mucosal soft tissue thickness from day 0 to day 120) was the dependent variable, the treatment group was the fixed effect, and mucosal soft tissue thickness at baseline (day 0) included as a covariate. The treatment difference (SCTG minus VCMX) in the least-squares means and its two-sided 95% confidence interval (CI) were estimated based on the ANCOVA model. Non-inferiority of VCMX to SCTG would be claimed if the upper bound of the 95% CI was below the non-inferiority margin of 0.5 mm. The overall experiment-wise type I error rate for the study was set to $\alpha = 0.025$ (one-sided).

2.10.3 | Descriptive statistics

Categorical data were presented in frequency tables using counts and percentages. Percentages were based on the total number of patients in the respective analysis set (i.e., missing values were included in the percentage calculation).

Standard descriptive including mean, standard deviation, lower quartile (Q1), median, and upper quartile (Q3) were calculated for continuous variables.

2.10.4 | Exploratory statistics

Secondary endpoints were analyzed using ANOVA for repeated measures (using the MIXED procedure in SAS®) to estimate the main effects involving group, time, and their interaction (group*time). The Wilcoxon rank-sum test was used for variables not normally distributed (cumulative ibuprofen consumption, PES scores, surgery time). Exploratory two-sided 95% CIs were calculated for the total incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs), for each treatment arm as well as for the differences between the two treatment arms. All resulting *p*-values and CIs were two-sided and were interpreted in the exploratory sense only. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc).

3 | RESULTS

The present multicenter study enrolled 88 patients at 9 centers (Clinic of Reconstructive Dentistry, University of Zurich; Facultad de Odontologia, Universidad Complutense de Madrid; Private practice Hürzeler/Zuhr, Munich; Department of Oral Surgery, Heinrich Heine University of Düsseldorf; Private Practice Drs. Bonnet et Motagné; Department of Periodontology and Implant Dentistry, Eastman Dental Hospital Rome; Division of Fixed Prosthodontics and Biomaterials, University of Geneva; Private Practice Grimm Zahnaerzte; Department of Periodontology, Operative, and Preventive Dentistry, University Hospital Bonn) between April 2014 and December 2017. An overview of baseline demographics is given in Table 1. All enrolled patients were randomized (group VCMX (45 patients); group SCTG (43 patients)). The number of patients treated by the 9 centers was 88 (total), 33 (17 VCMX/16 SCTG), 15 (8/7); 3 (2/1); 3 (1/2); 2 (1/1.); 7 (4/3); 8 (4/4); 6 (3/3); and 11 (5/6), respectively. The location of the augmented sites is displayed in Table S1.

Seventy-nine (VCMX 41 and SCTG 38) patients (89.8%) completed the study according to the protocol (Figure 2). Nine patients discontinued the study prematurely for the following reasons: AE/SAE (two patients) noncompliance (one patient), withdrawal of informed consent (one patient), loss to follow-up (four patients), and unknown reason (one patient).

TABLE 1 Patient demographics at baseline.

	Total, *n* = 88		Collagen matrix (VCMX)		Connective tissue graft (SCTG)	
	n	%	*n*	%	*n*	%
Gender						
Male	49	55.7	26	57.8	23	53.5
Female	39	44.3	19	42.2	20	46.5
Smoking						
Non-smokers (0/day)	68	77.3	35	77.8	33	76.7
Smokers (1–10/day)	20	22.7	10	22.2	10	23.3
Age (mean ± SD)	48.0 ± 15.6		48.6 ± 15.7		47.4 ± 15.7	

Abbreviations: SCTG, subepithelial connective tissue graft; SD, standard deviation; VCMX, volume collagen matrix.

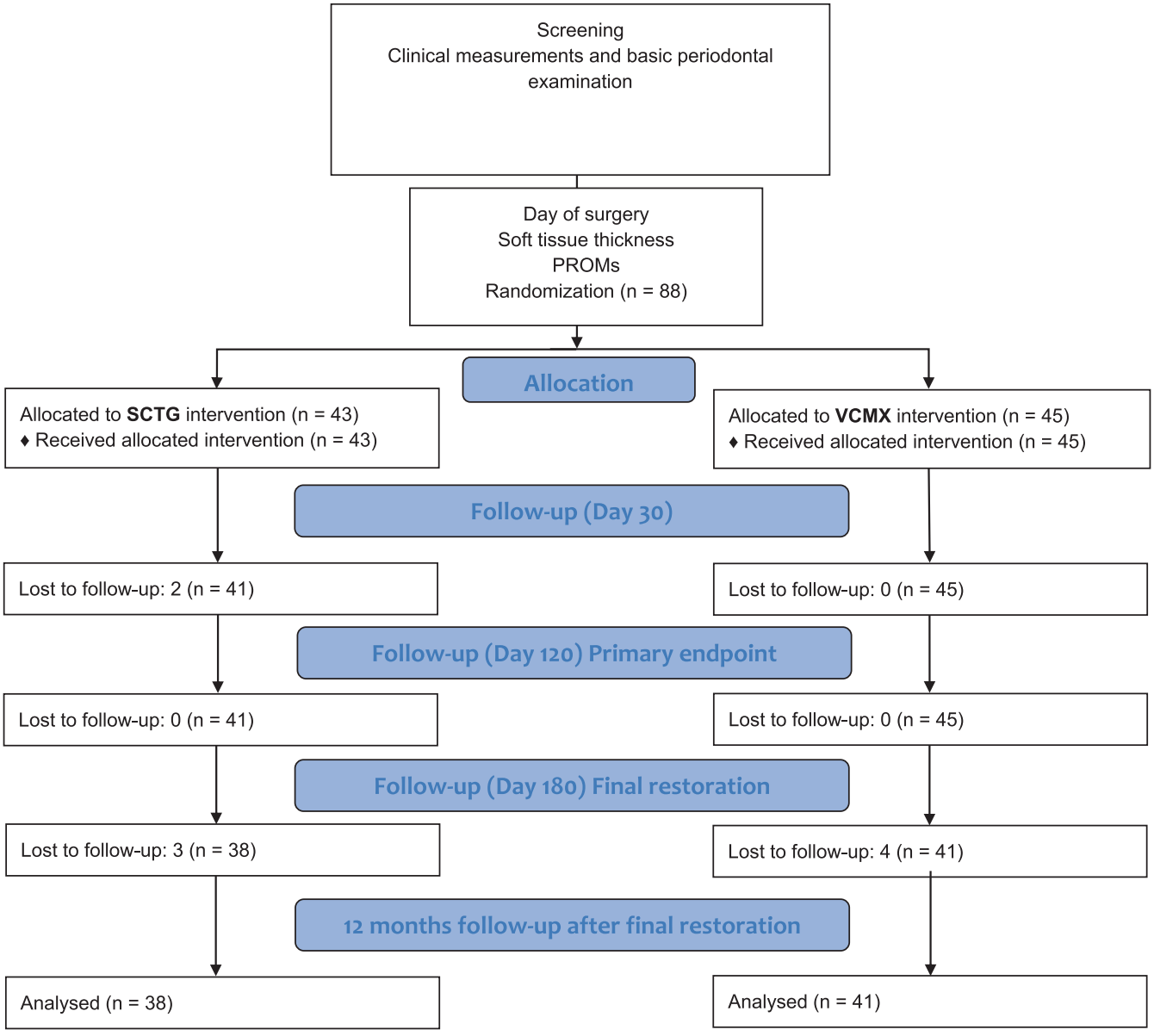

FIGURE 2 Consort flowchart.

3.1 | Graft dimensions

The mean dimension of the graft was 538.8 $mm^3 \pm 325.1$ in group VCMX and 240.0 $mm^3 \pm 143.4$ in group SCTG ($p < .0001$).

3.2 | Duration of surgery

The mean duration for the surgical procedure (start of surgery to end of suturing) revealed no major differences between the two groups (VCMX: 42.3 min ±18.0; SCTG: 48.7 min ±15.9; intergroup $p = .059$).

3.3 | Effects of soft tissue augmentation

3.3.1 | Gain in mucosal thickness (measured by transmucosal probing)

Between pre-augmentation and 120 days, the mean increase of the crestal mucosal thickness (primary endpoint) amounted to 0.3 mm ± 2.1 mm in the VCMX group and 0.8 mm ± 1.6 mm in the SCTG group (Table 2). The adjusted mean treatment difference of 0.46 mm (95% CI: −0.25 to 1.17) from the ANCOVA model failed to show non-inferiority of VCMX to SCTG treatment as the upper limit of the 95% CI was above the non-inferiority margin of 0.5 mm ($p = .455$; Figure 3; Table 3). To further confirm these results and to rule out a possible "center effect," an exploratory analysis was performed using the center as a random effect and examining the treatment*center interaction in the ANCOVA mixed model. Despite the considerable heterogeneity between the centers, the center analysis further confirmed that VCMX was unable to demonstrate non-inferiority compared to SCTG ($p = .178$; Figure S3). In addition, to assess the potential impact of an outlier found in one of the centers we performed a sensitivity analysis. The sensitivity analysis showed that the presence or absence of the outlier had no significant impact on the results ($p = .800$; Figure S4).

When analyzing the linear measurement of soft tissue thickness using the endodontic instrument, no significant differences between the groups were found. The mean gain in mucosal thickness between pre-augmentation and 120 days at the buccal site amounted to 0.91 mm ± 2.0 mm in the VCMX group and 1.19 mm ± 1.43 mm in the SCTG group (intergroup comparison: $p = .43$). The respective numbers at the more apical site were 1.15 mm ± 2.42 mm in the VCMX group and 1.04 mm ± 2.23 mm in the SCTG group (intergroup comparison: $p = .95$). All other data including the mucosal thickness at baseline and at 30 days as well as the respective changes are reported in Tables 2 and 3.

3.3.2 | Changes in ridge contour (measured by the superimposition of casts/scans)

The mean changes in ridge contour measured by the superimposition of the scans taken at the various time points at the buccal side between baseline and 120 days amounted to 0.44 mm ± 0.73 in the VCMX group and to 0.64 mm ± 0.81 in the SCTG group (intergroup comparison: $p = .26$).

The contour changes between the insertion of the final restoration and 12 months were minimal and amounted to −0.11 mm ± 0.33 for VCMX ($p = .03$) and −0.01 mm ± 0.34 for SCTG respectively (intergroup comparison: $p = .28$).

3.3.3 | Clinical and periodontal measurements

Clinical and periodontal parameters (KT, PD, BOP, and PI) assessed at the neighboring teeth revealed healthy conditions, minimal changes over time, and minimal differences between the groups. For details see Table S2.

3.4 | Adverse events (AEs) and experience of pain

3.4.1 | Overall adverse events

During the observation period between baseline and 1 year after insertion of the final restoration, a total of 75 AEs were documented, defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects regardless of whether they were related to the investigational medical device, the comparator (SCTG), or the procedure.

The percentage of patients affected by AEs in group VCMX was 40.0% (18 out of 45 patients), whereas in the SCTG group, it was

TABLE 2 Soft tissue thickness in the crestal site at the different time points in both treatment groups changes over time.

	Collagen matrix (VCMX)					Subepithelial connective tissue graft (SCTG)				
	n	Mean ± SD	Q1	Median	Q3	*n*	Mean ± SD	Q1	Median	Q3
Baseline	45	3.39 ± 1.86	2.00	3.00	4.00	41	3.27 ± 1.84	2.00	3.00	4.00
Day 30	43	4.06 ± 2.48	3.00	4.00	5.00	41	4.31 ± 1.45	3.50	4.00	5.00
Day 120	45	3.72 ± 2.40	3.00	3.50	4.50	41	4.12 ± 0.95	3.50	4.00	5.00
Change from baseline to 30 days	43	0.63 ± 2.03	−0.50	1.00	1.50	41	0.99 ± 1.72	0.50	1.25	2.00
Change from baseline to 120 days	45	0.33 ± 2.14	−1.00	0.50	1.50	41	0.85 ± 1.67	−0.50	1.00	2.00

Abbreviations: Q1, first quartile; Q3, third quartile; SCTG, subepithelial connective tissue graft; SD, standard deviation; VCMX, volume collagen matrix.

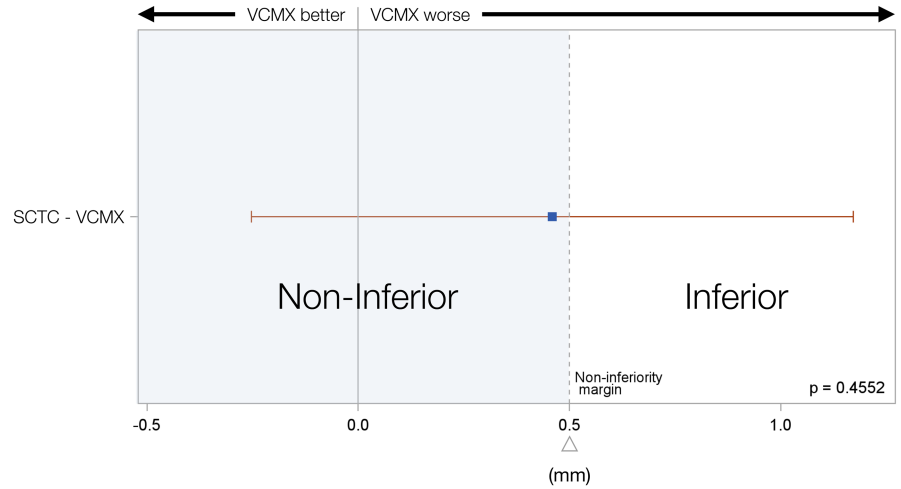

FIGURE 3 Treatment difference in crestal mucosal thickening at day 120. Difference of least squares means; error bars indicate two-sided 95% CIs ($n = 86$). The gray dashed line at Δ indicates the noninferiority margin (0.5 mm); the light blue tinted region to the left of Δ indicates the zone of noninferiority. As the CI includes Δ and zero, the result regarding noninferiority is inconclusive (noninferiority would be claimed if the CI lies wholly to the left of 0.5). The p-value of the "treatment" effect was assessed for noninferiority using ANCOVA. SCTG, subepithelial connective tissue graft; VCMX, volume collagen matrix.

46.5% (20 out of 43 patients). The incidence of AEs related to the investigational product or the SCTG was higher in group SCTG (23.3%) compared to the VCMX group (8.9%). The respective incidence rate for AEs related to the surgical procedure was similar (23.3% SCTG; 20.0% VCMX).

3.4.2 | Wound closure at the target site

Complete wound closure without visible dehiscence at the target site on the day of suture removal was observed in 62.2% of the patients in the VCMX group and 76.7% in the SCTG group. These numbers increased to 97.8% and 95.3% at 120 days in the VCMX and the SCTG groups, respectively.

3.4.3 | Swelling at the target site

Swelling at the target site was present on the day of suture removal in 26.7% of the patients in the VCMX group and 27.9% in the SCTG group. At later time points (30 days and 120 days), only a minority of the sites in both groups showed swelling.

3.5 | Patient-reported outcome measures (PROMs)

3.5.1 | Consumption of analgesics

The daily consumption of analgesics was recorded for the first 10 days after the surgery. The mean number of ibuprofen tablets taken by the patients was 5.6 ± 6.5 in the VCMX group and 6.9 ± 8.9 in the SCTG group (intergroup comparison: $p = .661$) as reported in Table S3.

3.5.2 | Pain scores based on VAS

Mean pain scores recorded on a visual analog scale from 0 to 100 were maximal on the day of surgery and then decreased significantly up to day 30 in both groups (Figure 4). VCMX significantly reduced pain perception compared to SCTG on days 2, 3, 5, 6, 7, 8, and 9 (Figure 4; Table S4). For the differences at each time point see Table S4.

3.5.3 | OHIP-14

Mean overall OHIP-14 scores were 7.3 ± 7.0 (VCMX) and 8.5 ± 10.5 (SCTG) at baseline (Table S5). At suture removal (day 10), the mean OHIP score in group VCMX amounted to 8.9 ± 8.3 and to 12.5 ± 12.0 in group SCTG (intergroup comparison: $p = .043$). During the follow-up assessments, the differences between the groups were minimal ($p > .05$). For differences at each time point see Table S5.

3.5.4 | Esthetic outcomes

The mean Pink Esthetic Score values at 180 days amounted to 9.8 ± 2.8 for the VCMX group and 10.1 ± 2.7 for the SCTG group. These values reached 9.8 ± 2.5 in the VCMX group and 10.5 ± 2.4 in the SCTG group at one-year follow-up after final restoration (intergroup comparison: $p = .206$).

4 | DISCUSSION

The present multicenter study predominantly revealed: (i) inconclusive evidence of whether VMCX is noninferior to SCTC in crestal

Gain in soft tissue thickness (occlusal) [mm]	*N*	LS mean	SE	95%CI lower	95% CI upper	*p*-value
Day 30						
Collagen matrix (VCMX)	43	0.65	0.26	0.13	1.18	NA
Connective tissue graft	41	0.97	0.27	0.42	1.51	NA
SCTG-VCMX	NA	0.31	0.38	−0.45	1.07	.4160
Day 120						
Collagen matrix (VCMX)	45	0.36	0.25	−0.13	0.85	NA
Connective tissue graft	41	0.82	0.26	0.30	1.33	NA
SCTG-VCMX	NA	0.46	0.36	−0.25	1.17	.4552

Abbreviations: CI, confidence interval; LS mean, least square mean; NA, not applicable; SCTG, subepithelial connective tissue graft; SE, standard error; VCMX, volume collagen matrix.

TABLE 3 Statistical comparison of soft tissue thickness gains at the crestal site from baseline to 30 days as well as from baseline to 120 days.

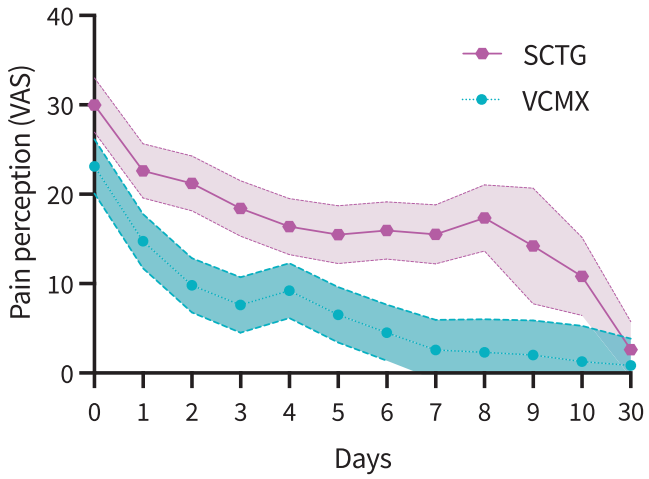

FIGURE 4 Line plot showing the reported pain perception (VAS 0–100) in both treatment groups. Shading indicates standard error. Patients randomized to VCMX reported significantly less pain ($p < .05$) compared to the SCTG group on days 2, 3, 5, 6, 7, 8, and 9.

mucosal thickness gains, (ii) similar ridge contour gains and changes between both treatments followed by ridge stability over time, (iii) lower pain perception and better PROMs with VCMX in the short term, (iv) comparable stable and healthy periodontal tissues, and (v) a similar rate of adverse events.

The volume gain at the crestal location amounted to 0.3 mm in the VMCX group and to 0.8 mm in the SCTG group, hence resulting in a difference of ≈ 0.5 mm in gain of soft tissue thickness. This difference in favor of SCTG is largely in line with a recent systematic review, showing an additional gain of approximately 0.5 mm over soft tissue substitutes (Valles et al., 2022). Conversely, when assessing the buccal contour changes, there were no significant differences between VMCX and SCTG. In this area, the increase in mucosal thickness amounted to 0.9 in VCMX and 1.2 mm for the SCTG group. This is of clinical importance, as the buccal side from an esthetic standpoint represents the center of attention. These differences in outcomes observed in the present study between the two sites (crestal and buccal) might be explained by the number of sites demonstrating incomplete wound closure on the day of suture removal. Incomplete wound closure was observed in 38% (VCMX) and 23% (SCTG) of the sites. The occurrence of wound dehiscence may have adversely affected the result of the augmentation procedure and possibly more so for the VCMX. This is because the collagen matrix is designed to heal in a submerged environment; once exposed, the resulting increased remodeling processes can lead to resorption of the matrix, which may clinically result in an invagination at the target site. Conversely, it is known that SCTGs can heal appropriately when left in an open healing environment or when unintentional exposures occur.

The superimposition of digital images taken at different time points for the assessment of volume changes represents a well-established method for evaluating the efficacy of soft and hard tissue augmentation interventions, both in terms of quantifying gain or loss of tissue, as well as for monitoring tissue stability over time (Tavelli et al., 2021). Its accuracy, reproducibility, and reliability have been demonstrated in various pre-clinical and clinical studies (Galarraga-Vinueza et al., 2020; Rebele et al., 2014; Sanz-Martin et al., 2019; Schneider et al., 2011; Windisch et al., 2007) and using the present method other research groups have successfully determined an appropriate sample size for their RCTs (Cosyn et al., 2021, 2022). The profilometric contour changes captured by superimposing the two digital scans – one taken at baseline and the other one 120 days later – demonstrated gains of 0.4 mm for VCMX and 0.6 mm for SCTG, with no significant differences between the groups. These values are slightly lower compared to those obtained in an RCT comparing the same matrix to SCTG, which found gains of 0.57 mm for the matrix and 0.98 mm for SCTG, with significant differences (Cosyn et al., 2022). The slight discrepancy with the present findings might be ascribed to methodological differences. In the present study, soft tissue augmentation was performed 3 months after implant placement and primary wound closure was aimed for, submerging both the implant and graft. In the study by Cosyn and colleagues soft tissue augmentation was performed concurrently with implant placement and immediate provisionalization (Cosyn et al., 2022). The fact that the flap in this situation only needs to be adapted to the circumference of the immediate temporary may explain the different results.

The present study revealed ridge stability over time. A previous single-center study using a similar experimental design (Huber et al., 2018) showed that the volume gained in the surgical augmentation procedure remained relatively stable in both treatment groups between crown insertion and the 12-month follow-up examination, consistent with present findings. It is well known that after an initial remodeling process prior to the insertion of the final restoration, the contour gains tend to remain stable over time and with minimal changes.

Interestingly, the study by Cosyn (Cosyn et al., 2022) reported 0.45 mm of shrinkage at one-year follow-up when applying SCTG (from a gain of 1.43 mm post-surgery to a residual gain of 0.98 mm at one-year follow-up). When applying VCMX the same authors reported a more pronounced shrinkage (1.33 mm) than STCG at one-year follow-up (VCMX; from a gain of 1.9 mm post-surgery to a residual gain of 0.57 mm at one-year follow-up). It should be noted, however, that Cosyn's RCT applied a different implant protocol and different timing for soft tissue augmentation and restoration.

In addition to standard clinical parameters, patient-reported outcomes and incidence of adverse effects were assessed in the present study. Patients in the experimental group reported significantly lower pain scores on the visual analog scale compared with the SCTG group, along with significantly lower OHIP-14 scores in the short term. These findings are largely consistent with a recent systematic review with meta-analysis, which demonstrated that soft tissue substitutes can significantly reduce pain perception in comparison to autogenous grafts following soft tissue augmentation (Thoma et al., 2023). Regarding the aesthetic outcomes, the Pink Esthetic Scores revealed very favorable values in both groups, without major differences between the treatment modalities.

This multicenter study revealed some heterogeneity among the participating centers in terms of the number of patients treated and the mean outcomes by the center. As for the unequal number of subjects per center, an equal number for multicenter studies would have delayed the enrolment (Senn, 1998). In fact, statisticians have pointed out that it is impractical to control the number of subjects per center, despite the inherent limitations (Ruvuna, 2004). As for the heterogeneity in the outcomes, these finding reflects the importance of the surgical handling of medical devices within surgical interventions, which is typically identified in multicenter studies, when assessing the center effect and is difficult to capture in single-center studies (Esposito et al., 2015). It should be noted that the investigated device was used for the first time in the majority of centers. In this sense, once the learning curve is over, one can anticipate better handling and performance of the surgical procedure, increasing the predictability of its application. This speculation is supported by the high number of sites demonstrating an incomplete wound closure at suture removal, albeit with a low amount of investigational device-related adverse events. The volume of the VCMX was on average more than twice that of SCTG, which may also partially account for the higher incidence of wound dehiscence during early healing.

Notably, in the current study, there were no substantial differences between the groups in the length of the surgical intervention despite the trend toward less surgery time ($p = .059$). Apart from the inherent learning curve, this might be attributed to the trimming, placement, and stabilization of the experimental device, which apparently consumed a similar amount as the harvesting and transplantation of the SCTG. This finding tends to differ from those of a recent study comparing VCMX with SCTG at single immediate implants, with an observed reduced surgery time for the VCMX group (Cosyn et al., 2021) or with those of a recent systematic review with meta-analysis including soft tissue substitutes (Thoma et al., 2023).

A special focus of the present clinical investigation was the reporting of adverse events (AEs). The overall number of adverse events was similar in both groups. The incidence of AEs related to the soft tissue graft/substitute, either VCMX or SCTG, was markedly higher in the SCTG group (23.3%), compared to the VCMX group (8.9%). Regarding the AEs related to the surgical procedure at the recipient site, the incidence rate was similar for both treatment modalities (23.3% SCTG; 20.0% VCMX). Two of the frequently assessed complications in these types of surgical interventions are the occurrence of flap dehiscence and swelling at the target site (Hammerle et al., 2014; Vignoletti et al., 2014). These events occurred at similarly low rates in both groups, which may indicate the safety and the clinical benefit of using this investigational device. In a recently published single-center study using this investigational device, the rate of dehiscences at the recipient site at the time of suture removal was higher, when compared with the use of autogenous grafts (Zeltner et al., 2017). These contradictory results may possibly be due to a different surgical design used in the present study, mainly related to the flap closure. Specifically, an island palatal flap was mobilized coronally to improve the tension-free adaptation of the buccal and the palatal wound margins (Tinti & Parma-Benfenati, 1995), which may have compensated for this expected different postsurgical behavior between the treatment groups.

Whereas the gain in crestal soft tissue thickness was larger in the SCTG group, the buccal volume gain was similar in both groups. This implies a possible positive clinical application of the VMCX for gaining soft tissue volume at esthetic implant sites and thus the future potential for replacing the autogenous soft tissue graft. For decision-making, it appears prudent that clinicians ask themselves how much they are willing to give up in terms of clinical efficacy relative to the standard of care (SCTG), in return for the benefits in terms of morbidity with soft tissue substitutes (Thoma et al., 2023). Conceivable, the best treatment is not necessarily the one that has the highest efficacy in RCTs but the one that is consistent with the patient's values and preferences (Chow et al., 2012; Thoma & Strauss, 2022). While from a clinical standpoint, a millimeter of difference might be relevant, this difference might be unimportant for the patient (Thoma & Strauss, 2022). Statistically significant differences do not necessarily equate to clinically important differences (Jaeschke et al., 1989;

Thoma et al., 2023; Thoma & Strauss, 2022). However, the minimal clinically important differences (Chow et al., 2012; Jaeschke et al., 1989; McGlothlin & Lewis, 2014; Thoma & Strauss, 2022) in implant-related outcomes remain to be established (McGlothlin & Lewis, 2014; Thoma et al., 2022; Thoma et al., 2023; Thoma & Strauss, 2022).

The present study has some limitations: (i) Heterogeneity of the results between centers. However, it is important to note that multi-center studies provide a more accurate representation of the performance of a technique or material compared to single-center studies, thereby enhancing external validity. In addition, we further assessed this limitation by performing sensitivity analyses. (ii) The rather high frequency of healing complications at the crestal site, which may have underestimated the maximum effectiveness of VMCX for soft tissue augmentation. (iii) The thickness of SCTG was not standardized between patients and clinicians due to the inherent defect variations and the anatomy of the donor site. This lack of standardization may have introduced some bias, influencing the clinical outcomes. iv. The initially thick tissue at the crestal site, which could have restricted the overall increase in soft tissue volume, potentially approaching a maximum thickness threshold.

5 | CONCLUSION

It remains inconclusive whether soft tissue augmentation using a collagen matrix is noninferior to SCTG in terms of crestal mucosal thickening at single implant sites. However, the use of collagen matrices favors PROMs, especially pain perception. Furthermore, collagen matrices achieve similar buccal volume gains and exhibit comparable clinical and aesthetic parameters to SCTG in the short term.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to conception and design of the study. CHF, KJ, IS, MS, MZ, LC, VC, FS, FJS, OZ, DA, FB, DTH, FB, ISM, and MS have been involved in data collection and data analysis. CHF, FJS, and DTH interpreted the data and drafted the manuscript. All authors critically revised the draft and approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors report conflict of interest related to the study or products involved.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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