Received: 1 July 2021 | Revised: 22 September 2021 | Accepted: 25 September 2021

DOI: 10.1111/jcpe.13560

ORIGINAL ARTICLE

Journal of Clinical Periodontology WILEY

A multi-centre randomized controlled trial comparing connective tissue graft with collagen matrix to increase soft tissue thickness at the buccal aspect of single implants: 3-month results

Jan Cosyn[1] | Célien Eeckhout[1] | Véronique Christiaens[1] | Aryan Eghbali[1,2] | Stijn Vervaeke[1] | Faris Younes[1] | Thomas De Bruyckere[1]

[1]Faculty of Medicine and Health Sciences, Oral Health Sciences, Department of Periodontology and Oral Implantology, Ghent University, Ghent, Belgium

[2]Faculty of Medicine and Pharmacy, Oral Health Research Group (ORHE), Vrije Universiteit Brussel (VUB), Brussels, Belgium

Correspondence
Jan Cosyn, Faculty of Medicine and Health Sciences, Oral Health Sciences, Department of Periodontology and Oral Implantology, Ghent University, Corneel Heymanslaan 10, B-9000 Ghent, Belgium.
Email: jan.cosyn@ugent.be

Funding information
The project was supported by a grant (18-178) from the Osteology Foundation, Switzerland, and by a grant (BOF.STG.2019.0004.01) from Ghent University, Belgium. Biomaterials were delivered free of charge by Geistlich Pharma AG (Wolhusen, Switzerland).

Abstract

Aim: To compare connective tissue graft (CTG) with collagen matrix (CMX) in terms of changes over time in buccal soft tissue profile (BSP) when applied at single implant sites.

Materials and methods: Patients with a single tooth gap in the anterior maxilla and horizontal mucosa defect were enrolled in a multi-centre randomized controlled trial. All sites had a bucco-palatal bone dimension of at least 6 mm and received a single implant and immediate implant restoration using a full digital workflow. Sites were randomly allocated to the control (CTG) or test group (CMX: Geistlich Fibro-Gide®, Geistlich Pharma AG, Wolhusen, Switzerland) to increase buccal soft tissue thickness. Primary outcome was increase in BSP at T1 (immediately after operation) and T2 (3 months) based on superimposed digital surface models. Secondary parameters included patient-reported clinical and aesthetic outcomes.

Results: Thirty patients were included per group (control: 50% females, mean age 50; test: 53% females, mean age 48). Even though surgeons applied thicker grafts when using CMX, sites treated with CMX demonstrated 0.78 mm (95% CI 0.41–1.14) more shrinkage between T1 and T2 than sites treated with CTG. The final increase in BSP was 1.15 mm (95% CI 0.88–1.43) for CTG and 0.85 mm (95% CI 0.58–1.13) for CMX. The mean difference of 0.30 mm (95% CI −0.01 to 0.61) at T2 in favour of CTG was of borderline significance ($p = .054$). There were no significant differences between the groups in terms of post-operative bleeding ($p = .344$), pain ($p = .331$), number of analgesics taken ($p = .504$), oedema ($p = .227$), and pink aesthetic score ($p = .655$). VAS for post-operative haematoma was 6.56 (95% CI 0.54–12.59) lower for CMX, and surgery time could be reduced by 9.03 min (95% CI 7.04–11.03) when applying CMX. However, CMX resulted in significantly more marginal bone loss (0.38 mm; 95% CI 0.15–0.60), deeper pockets (0.30 mm; 95% CI 0.06–0.54), and more mid-facial recession (0.75 mm; 95% CI 0.39–1.12) than CTG.

Clinical trial registration: This study was registered in ClinicalTrials.gov (NCT04210596).

Conclusions: CTG remains the gold standard for increasing soft tissue thickness at the buccal aspect of implants.

KEYWORDS
collagen matrix, connective tissue graft, dental implant, single tooth

Clinical Relevance

Scientific rationale for study: Connective tissue graft (CTG) has been well documented to increase buccal soft tissue thickness. However, a second surgical site is needed. Recently, a collagen matrix (CMX) has been developed.

Principal findings: CTG and CMX are both effective in augmenting soft tissues in the short term. However, sites treated with CMX demonstrated more shrinkage, more marginal bone loss, deeper pockets, and more mid-facial recession than CTG. On the other hand, peri-implant aesthetics were similar, and CMX reduced surgery time.

Practical implications: Longer follow-up is needed to make clinical recommendations with respect to the use of CMX.

1 | INTRODUCTION

Systematic reviews based on human re-entry studies and study casts demonstrate substantial dimensional changes of the alveolar ridge following tooth extraction (Tan et al., 2012; Couso-Queiruga et al., 2021). At 6 months post extraction, horizontal and vertical shrinkage of the alveolar ridge amounts to 29%–63% and 11%–22%, respectively (Tan et al., 2012). In non-molar sites, this results in horizontal, vertical mid-facial, and mid-lingual ridge reduction of 2.73, 1.71, and 1.44 mm, respectively (Couso-Queiruga et al., 2021). The magnitude of these changes is clinically relevant, as these create a clear buccal concavity in the alveolar ridge. Especially in the premaxilla, a buccal concavity may hamper aesthetic rehabilitation.

When sufficient bone is present for implant installation, a connective tissue graft (CTG) is considered the gold standard approach to reconstruct the buccal soft tissue profile of the alveolar ridge (Thoma et al., 2014). Ultrasonic evaluation has demonstrated over 90% horizontal stability of CTG at 1-year (De Bruyckere et al., 2015) and 85% at 5-year follow-up (Eghbali et al., 2018). Profilometric evaluation showed most resorption of the graft during the early healing phase and resulted in a linear increase in buccal soft tissue profile of 1.19 mm after 1 year of follow-up (De Bruyckere et al., 2020). The latter is mainly the result of CTG thickening buccal soft tissues, yet also crown installation has a relevant impact since prosthetic components enable the displacement of soft tissues to the buccal aspect (De Bruyckere et al., 2020). Clinical studies have demonstrated stable buccal soft tissue volume between permanent crown installation and 1- or 3-year follow-up (Huber et al., 2018; De Bruyckere et al., 2020; Thoma et al., 2020). Interestingly, the lateral palate or tuberosity area seem equally effective as CTG donor sites in terms of soft tissue volume gain (Rojo et al., 2018, 2020).

In spite of the clinical effectiveness of CTG, the greatest drawback is the need for a second surgical site for tissue harvesting. This may lead to complications such as palatal bleeding, pain, swelling, infection, or necrosis (Griffin et al., 2006). The harvesting procedure and the dimensions of the graft have been shown to have an impact on patient discomfort (Del Pizzo et al., 2002; Zucchelli et al., 2014; Burkhardt et al., 2015). Even though thick CTGs may cause more post-operative pain, they are inevitable when large buccal concavities need to be eliminated. An important limitation is that thick CTGs are not always available. As a result, the outcome of soft tissue augmentation is affected by the amount of soft tissue that can be harvested from the donor site.

In order to overcome the aforementioned limitations of autogenous CTGs, a cross-linked porcine-derived collagen matrix (Geistlich Fibro-Gide®, Geistlich Pharma) has been developed. This collagen matrix (CMX) was compared with CTG in a pre-clinical study. Histomorphometric measurements on decalcified sections revealed well-integrated grafts with similar soft tissue augmentation up to 2 months (Thoma et al., 2017). Thereafter, degradation and remodelling have been observed, leading to a minimal increase in soft tissue thickness at 6 months for either strategy (Thoma et al., 2017, 2020; Naenni et al., 2018). CMX and CTG have also been clinically compared in an exploratory randomized controlled trial (RCT) using 3D-printed stents and digital surface models (Thoma et al., 2016; Zeltner et al., 2017; Huber et al., 2018). Based on 10 cases in each treatment arm, no inferiority could be shown for CMX in terms of increase in tissue thickness and stability up to 3 years (Thoma et al., 2020). Patients expressed slightly more pain following CTG during the early stages of healing (Thoma et al., 2016). De Angelis et al. (2021) compared CMX with CTG in a clinical study based on 17 cases in each treatment arm. Similar increase in buccal soft tissue thickness was found after 1 year. Patients expressed less pain, and surgery time could be reduced following CMX application. However, these findings should be interpreted with caution, since it concerns a non-RCT, sample size calculation was lacking, and an endodontic needle was used to assess soft tissue thickness without proper standardization. In a recent consensus meeting, profilometric evaluations based on digital surface models have been advocated over other methods to study soft tissue alterations since these have shown to be most accurate (Cosyn et al., 2021; Thoma et al., 2021).

Finally, other clinical studies have been published on collagen matrixes, demonstrating minor increase in buccal soft tissue profile (Sanz-Martín et al., 2019; Eeckhout et al., 2020; Schmitt et al., 2021), making their clinical effectiveness in relation to CTG still poorly understood. Since soft tissue augmentation is considered a technique-sensitive procedure, also the surgeon could have a relevant impact on its effectiveness. Only multi-centre RCTs can elucidate this. To the best of our knowledge, such studies have not been conducted so far.

Hence, the primary objective of this study was to compare CTG with CMX in a multi-centre superiority trial in terms of changes over time in buccal soft tissue profile when applied at single implant sites demonstrating a minor horizontal mucosa defect. The following research hypotheses were adopted:

H0. *There is no difference in the changes over time in buccal soft tissue profile between CTG and CMX.*

H1. *There is a difference in the changes over time in buccal soft tissue profile between CTG and CMX.*

2 | MATERIALS AND METHODS

2.1 | Patient selection

Patients in need of a single implant restoration in the premaxilla were enrolled between September 2019 and September 2020 to participate in a multi-centre RCT comparing two soft tissue augmentation procedures. Patients were selected on the basis of inclusion and exclusion criteria.

Inclusion criteria were as follows:

- At least 21 years old;
- Good oral hygiene, defined as full-mouth plaque score ≤25% (O'Leary et al., 1972);
- Presence of a single tooth gap in the premaxilla (15–25) with both neighbouring teeth present;
- Failing tooth removed at least 3 months prior to enrolment;
- At least 5 mm of keratinized mucosa available at the single tooth gap;
- Class I defect at the single tooth gap as clinically assessed (bucco-palatal loss of tissue with a normal apico-coronal ridge height) (Seibert, 1983);
- Bucco-palatal bone dimension of at least 6 mm at the central and crestal aspect of the single tooth gap as assessed on cone beam computed tomography (CBCT) to ensure complete embedding of an implant by bone;
- Signed informed consent.

Exclusion criteria were as follows:

- Systemic diseases;
- Smoking;
- Periodontal disease;
- Untreated caries lesions;
- Need for horizontal bone augmentation at the time of implant placement.

2.2 | Randomization, allocation concealment, and blinding

Six experienced implant surgeons working in different periodontal practices in Belgium were selected to participate in this multi-centre RCT. The digital workflow, the implant placement protocol, the application of CTG and CMX, the restorative protocol, and the clinical parameters to be registered were thoroughly discussed among the six surgeons in a training and calibration session before the start of the trial. Fully documented cases where CTG or CMX had been applied were used for this purpose.

Patients were randomly assigned to either the control group (CTG) or test group (CMX). Block randomization was performed per centre, meaning that each centre received an equal number of sealed envelopes for every treatment group. Group allocation was revealed just before surgery and remained concealed for the evaluating examiner and statistician to allow for unbiased registrations and analyses, respectively.

2.3 | Pre-operative digital planning

A fully digital workflow was adopted for every patient. A low-dose small-field CBCT and intra-oral scan were taken and imported into designated software (DTX Studio®, Nobel Biocare AB, Göteborg, Sweden). A stereolythographic surgical guide was fabricated on the basis of a 3D digital implant planning. The same software was used to design a screw-retained CAD/CAM provisional restoration (TempShell®, Nobel Biocare).

2.4 | Treatment procedures and post-operative care

Patients were instructed to take systemic antibiotics (amoxicilline 2 g) and anti-inflammatory medication (ibuprofen 600 mg) 1 h before operation. Just prior to the treatment, patients rinsed with a 0.12% chlorhexidine solution (Perio-aid® Intensive Care, Dent-Aid Benelux, Houten, The Netherlands), and local anaesthesia (Septanest special®, noradrenaline 1/100,000; Septodont, Saint Maur des Fossés, France) was administered.

Following a crestal incision at the single tooth gap and sulcular incisions at the neighbouring teeth, a full-thickness muco-periosteal flap was raised. Then, the surgical guide was positioned. The passive fit of the guide was assessed, and if necessary adapted. A dental implant (NobelReplace CC PMC® TiUnite, Nobel Biocare) was installed as digitally planned in an optimal 3D position (Buser et al., 2004).

Thereupon, a sealed envelope containing the assignment for either one of two treatment modalities was opened:

- Control group: autogenous connective tissue graft (CTG);
- Test group: collagen matrix (CMX).

In the control group, a CTG was harvested from the palatal mucosa in the premolar area by means of the single incision technique as described by De Bruyckere et al. (2015). In brief, a palatal incision was made at a distance of 3 mm from the free gingival margin and perpendicular to the bone. Through this incision, a second superficial incision was made at full depth of the surgical blade. A third incision, again through the same incision line, was made parallel to the second one, yet close to the bone. Finally, a CTG could be harvested following dissection at the mesial, distal, and apical aspect. The optimal size of the CTG was tailored to the dimensions of the site. The palatal wound was closed with double-cross sutures (Vicryl® Plus 4/0, Ethicon, OH). In the test group, a CMX with an initial dimension of 15 × 20 × 6 mm was used. The thickness of the graft was adapted to the defect with a scalpel as deemed appropriate by the surgeon. Thereupon, sterile saline was applied onto the graft and slight compression was made. The graft was further trimmed with scissors to arrive at the ideal dimensions. Following a superficial incision to release muscle tension, the graft was brought into the buccal envelope and fixed with two single sutures (Seralon 6/0, Serag Wiessner, Naila, Germany) onto the buccal mucosa.

Thereafter, a hollow CAD/CAM provisional acrylic restoration (TempShell®, Nobel Biocare), which had been designed using 3D planning software (DTX Studio®, Nobel Biocare), was connected onto a temporary titanium abutment (Temporary Snap Abutment Engaging®, Nobel Biocare) using flowable composite (G-aenial Flo X®, GC America, Alsip, IL). Attention was paid to a concave buccal emergence profile and perfect polishing of the transmucosal part. Following installation of the screw-retained provisional restoration, tension-free primary wound closure was achieved using inter-proximal vertical mattress sutures and single sutures (Seralon® 6/0, Serag Weissner, Naila, Germany). Figure 1 illustrates the surgical procedure in both groups.

Anti-inflammatory medication (ibuprofen 600 mg) was continued as deemed necessary by the patient. Patients rinsed with a 0.12% chlorhexidine solution twice daily for 1 week. Then, the sutures were removed. The provisional crown was replaced by a permanent crown by the general dentist after 3 months.

2.5 | Changes in buccal soft tissue profile

An intra-oral scan (Trios, 3shape, Copenhagen, Denmark) was taken at the following time points in each patient: T0 (pre-op), T1 (immediately post-op), and T2 (at 3 months). The obtained digital surface models in STL (Surface Tessellation Language) format were imported into designated software (SMOP, Swissmeda AG, Zurich, Switzerland) to analyse volumetric and profilometric changes by a blinded examiner.

A study-relevant area of interest (AOI) at the buccal aspect was selected for each augmented site at T2. The AOI reached from 0.5 mm below the soft tissue margin to 4 mm more apical. In the mesio-distal dimension, the AOI reached from the mesial to the distal line angle of the implant crown. The AOI varied between patients because of the individual anatomic differences but was kept constant in each patient across time points.

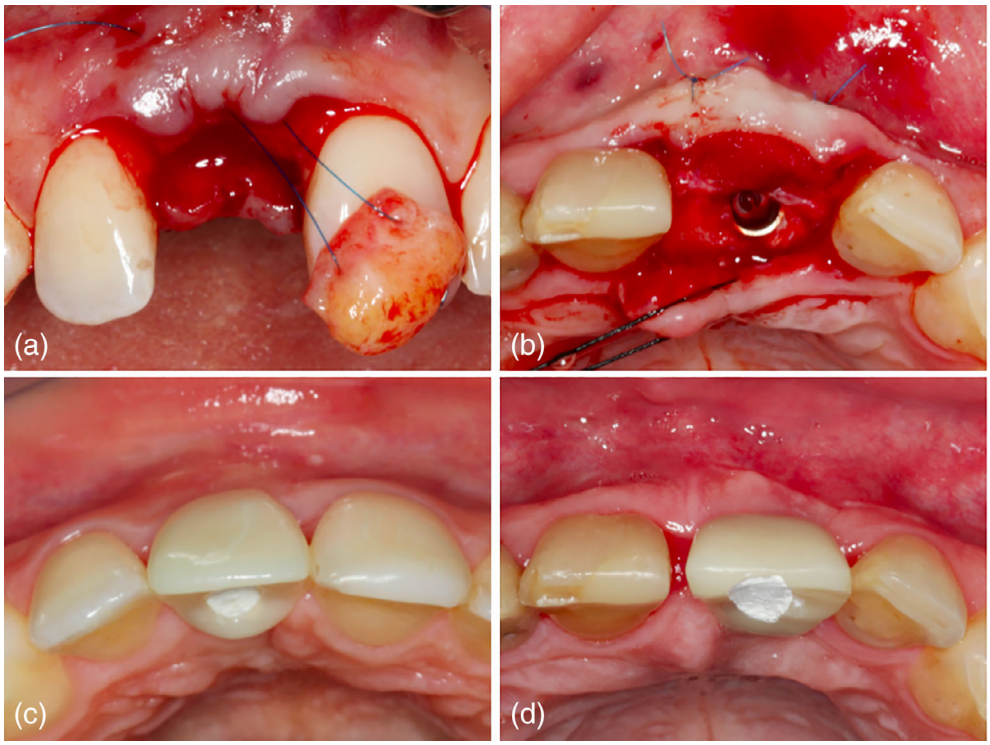

FIGURE 1 (a,b) Case illustrating a patient of the control group (CTG). (a) Frontal view of CTG, which is about to be pulled into the buccal envelope. (b) Occlusal view at 3 months follow-up. (c,d) Case illustrating a patient of the test group (CMX). (c) Occlusal view of CMX brought into the buccal envelope and fixed with two single sutures. (d) Occlusal view at 3 months follow-up. CMX, collagen matrix; CTG, connective tissue graft

After determining the AOI, the horizontal extent of the initial buccal defect was measured using the same software (Figure S1). Therefore, the centre of the implant crown was determined at T2. On the cross-sectional slide, a line was constructed perpendicular to the centre of the implant crown crossing the most coronal extent of the AOI at T0. On the corresponding axial slide, another reference line was drawn connecting the most buccal extent of the soft tissues at both neighbouring teeth. Perpendicular to this reference line, the horizontal extent of the buccal defect (HD) was measured.

Each time point was compared to the pre-op model (T0–T1, T0–T2) by superimposing the two models using the best-fit algorithm at the unchanged adjacent tooth surfaces. A mean volumetric change (mm^3) within the AOI for each patient at T1 and T2 was calculated by the software. As the size of the AOI (mm^2) differed among patients, the mean volumetric change was divided by the AOI, resulting in the mean change in buccal soft tissue profile. Figure 2 illustrates volumetric and profilometric changes in the AOI in a patient from the control group and test group.

2.6 | Patient-reported outcome measures

Prior to surgery, patients were informed that self-assessment of post-operative bleeding, pain, oedema, and haematoma would be requested 1 week following surgery. Post-operative bleeding was dichotomously scored (yes/no). Post-operative pain, oedema, and haematoma were registered by means of the visual analogue scale (VAS). Patients responded on a 100-mm line the amount of post-operative pain, oedema, and haematoma, with "no postoperative pain/edema/hematoma" and "severe postoperative pain/edema/hematoma" as extremes.

The number of analgesics (ibuprofen 600 mg) taken and the willingness of patients to undergo the same treatment again were also registered 1 week following surgery. The latter was evaluated with a 0–2 score (0 being no, 1 being maybe, and 2 being yes).

Patients' aesthetic satisfaction was registered 3 months following surgery by means of VAS. They were offered the following question: "How satisfied are you with the aesthetic outcome of the soft tissues surrounding the implant?" Patients responded on a 100-mm line, with "most unsatisfied" and "most satisfied" as extremes.

2.7 | Clinical outcomes

2.7.1 | Graft dimensions, wound closure, and surgery time

In both groups, the final dimensions of the graft (width × length × thickness) were measured with a periodontal probe by the treating surgeon.

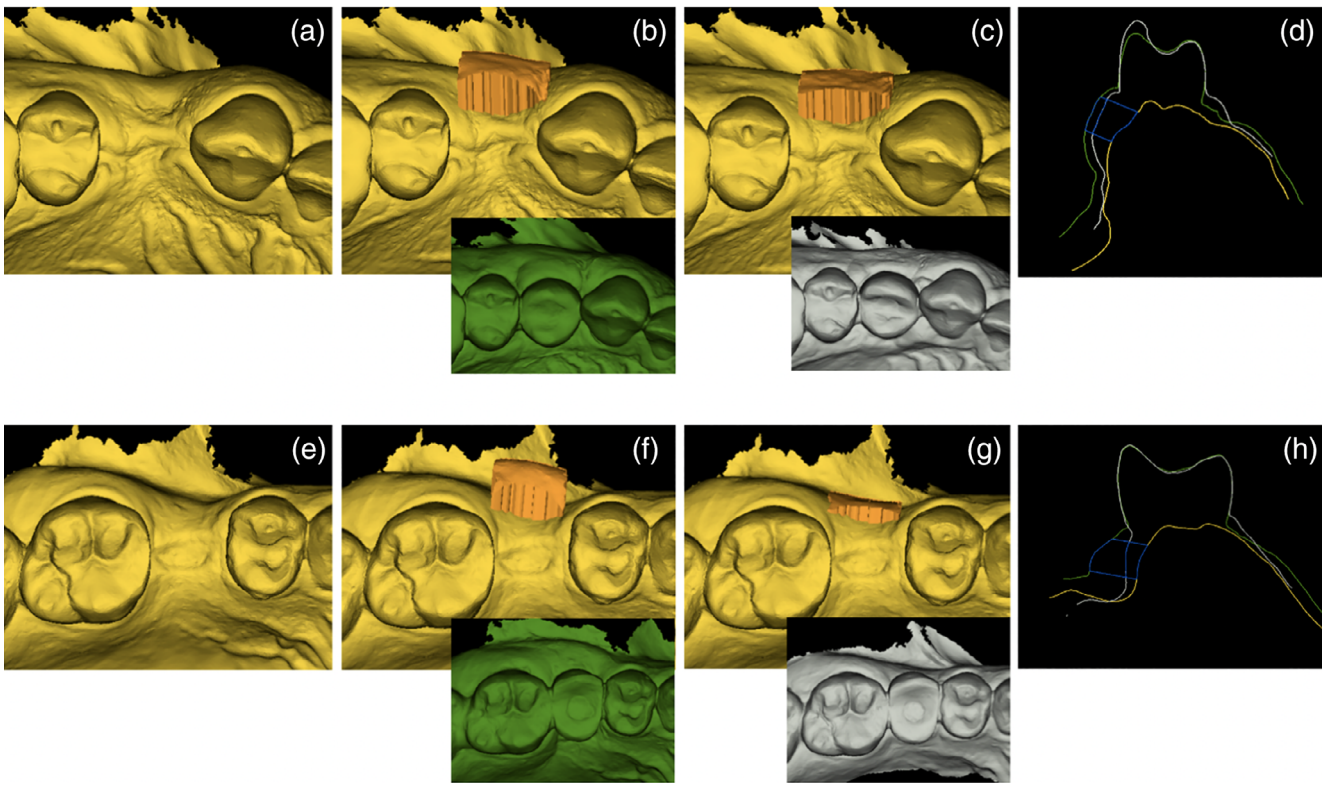

FIGURE 2 (a–d) Case illustrating a patient of the control group (CTG). (a) Occlusal view of the digital surface model at T0 (yellow) showing a Seibert class I defect. (b) Volumetric and profilometric changes in the area of interest (orange) between T0 (yellow) and T1 (green). (c) Volumetric and profilometric changes in the area of interest (orange) between T0 (yellow) and T2 (grey). (d) Cross-section through the superimposed digital surface models in the centre of the area of interest (blue) at the different time points. (e–h) Case illustrating the above-mentioned for a patient of the test group (CMX). CMX, collagen matrix; CTG, connective tissue graft

Although primary wound closure was aimed for, it was registered when this was not achieved.

In both groups, the time needed for the grafting procedure (time from opening the randomization envelope to the final suture at the augmentation site) was recorded.

2.7.2 | Complications

Any biological or technical complication that occurred within the 3-month period was recorded by the treating surgeon.

2.7.3 | Marginal bone loss

Peri-apical radiographs were taken with the long-cone paralleling technique at implant placement and at 3 months. Measurements were performed by a blinded examiner in designated software (DBSWIN Imaging Software, Dürr Dental SE, Bietigheim-Bissingen, Germany). The distance from the implant–abutment interface to the first bone-to-implant contact (so-called bone level) was assessed at the mesial and distal aspect of each implant. To control for enlargement, the implant length served as the reference distance. Marginal bone loss was calculated at 3 months by subtracting bone levels at 3 months from bone levels at implant placement. Mesial and distal values were averaged to receive one value per implant.

2.7.4 | Probing depth, plaque, and bleeding on probing

Probing depth was registered by the treating surgeon at four locations (mesio-buccal, buccal, disto-buccal, and oral) around the implant at 3 months. Measurements were rounded up to the nearest 0.5 mm. A mean value was calculated per implant.

Plaque and bleeding on probing were assessed by the treating surgeon at four locations (mesio-buccal, buccal, disto-buccal, and oral) around the implant at 3 months. Each location was scored 0 or 1 (absence or presence of plaque or bleeding on probing, respectively). Both parameters were expressed as percentage.

2.8 | Aesthetic outcomes

2.8.1 | Mid-facial recession

Mid-facial recession at 3 months was calculated. This was performed in the same software (SMOP, Swissmeda AG, Zurich, Switzerland) on digital surface models of T1 and T2. The distance from the incisal edge of the crown to the buccal mucosal margin (so-called mid-facial soft tissue level) was determined at the centre of each implant to the nearest 0.01 mm. Mid-facial recession was calculated by subtracting mid-facial soft tissue levels at 3 months from post-operative mid-facial soft tissue levels. Positive values indicated recession; negative values indicated vertical regrowth. Mid-facial recession was assessed by a blinded examiner.

2.8.2 | Pink aesthetic score and mucosal scarring index

The pink aesthetic score (PES) (Furhauser et al., 2005) and mucosal scarring index (MSI) (Wessels et al., 2019) were registered by a trained and blinded examiner using frontal and occlusal clinical pictures taken at 3 months. The PES results in a score from 0 (worst aesthetic outcome) to 14 (perfect aesthetic outcome). The MSI results in a score from 0 (no scar) to 10 (most extreme scar).

2.9 | Sample size calculation

A sample size calculation was performed in SAS Power and Sample Size using the Satterthwaite *t*-test. The calculation was based on finding a mean difference of at least 0.5 mm in the changes in buccal soft tissue profile between the groups with a standard deviation of 0.5 mm for CTG and 0.7 mm for CMX (as adopted from Zeltner et al., 2017). With alpha set at 0.05 and a power of 0.80, the sample size calculation indicated 25 patients to be included per group. To compensate for dropouts, this number was increased to 30 patients per group.

2.10 | Statistical analysis

SPSS Statistics 27 (SPSS Inc., Chicago, IL) was used for data analysis. A linear mixed model was used to analyse the primary outcome (changes in buccal soft tissue profile) taking into account the clustering of patients within centres. Treatment group, time, and their interaction were modelled as fixed factors. Patient and centre were random factors. Estimated marginal means and 95% confidence intervals (CIs) were calculated per treatment group and per time point. The variability in the model explained by the patient and the centre was calculated.

The same model was applied to analyse the AOI and continuous secondary outcomes. Poisson regression was used to compare the groups in terms of the number of analgesics taken. Binary logistic regression was adopted to compare the groups in terms of primary wound closure and post-operative bleeding. Odds ratios (ORs) and 95% CIs were calculated.

Inter-assessor reliability on marginal bone loss, PES, and MSI was assessed on the basis of 20 randomly selected cases using the intra-class correlation coefficient (ICC). The level of significance was set at .05.

3 | RESULTS

3.1 | Patient groups

The CONSORT flow diagram is shown in Figure 3. Table 1 gives an overview of the baseline characteristics. The control group consisted

of 15 males and 15 females with a mean age of 50.1 (SD = 17.0) years. The test group consisted of 14 males and 16 females with a mean age of 48.2 (SD = 16.3) years.

The mean horizontal extent of the buccal defect (HD) measured 1.71 and 1.62 mm in the control and test group, respectively.

Implant sites included 8 central incisors, 8 lateral incisors, 3 canines, and 11 premolars in the control group, and 9 central incisors, 7 lateral incisors, 2 canines, and 12 premolars in the test group.

The implant diameter was 3.5 or 4.3 mm, and the implant length varied from 8.5 to 13 mm.

None of the patients was lost to follow-up. One implant in the control group was lost at 1-week follow-up because of mobility. All other implants survived.

Eight protocol deviations with respect to the restorative procedure were registered in the control group and seven in the test group. In these patients, a healing abutment was installed instead of a screw-retained provisional restoration because of low primary implant stability (control group: $n = 4$; test group: $n = 6$), a deep bite (control group: $n = 3$; test group: $n = 0$), or implant placement in a canine position where high occlusal forces were expected (control group: $n = 1$; test group: $n = 1$). Because of reduced chair time, three patients in the control group and two in the test group received a conventional provisional crown fabricated in the dental lab after 24 h instead of receiving immediately a CAD/CAM provisional acrylic restoration designed beforehand. Hence, 40 patients received a CAD/CAM provisional restoration on the day of surgery.

3.2 | Changes in buccal soft tissue profile

The mean AOI amounted to 28.63 and 28.07 mm^2 in the control and test group, respectively. There was no significant difference between the groups ($p = .553$).

In the control group, the volumetric increase was 39.85 mm^3 at T1 and 30.86 mm^3 at T2. In the test group, the volume gain was 50.93 mm^3 at T1 and 22.55 mm^3 at T2.

Dividing the volumetric soft tissue changes by the AOI resulted in the increase in buccal soft tissue profile. Figures 4 and 5 illustrate the increase in buccal soft tissue profile. The raw data are shown in Figure 4 per patient, treatment group, time point, and centre.

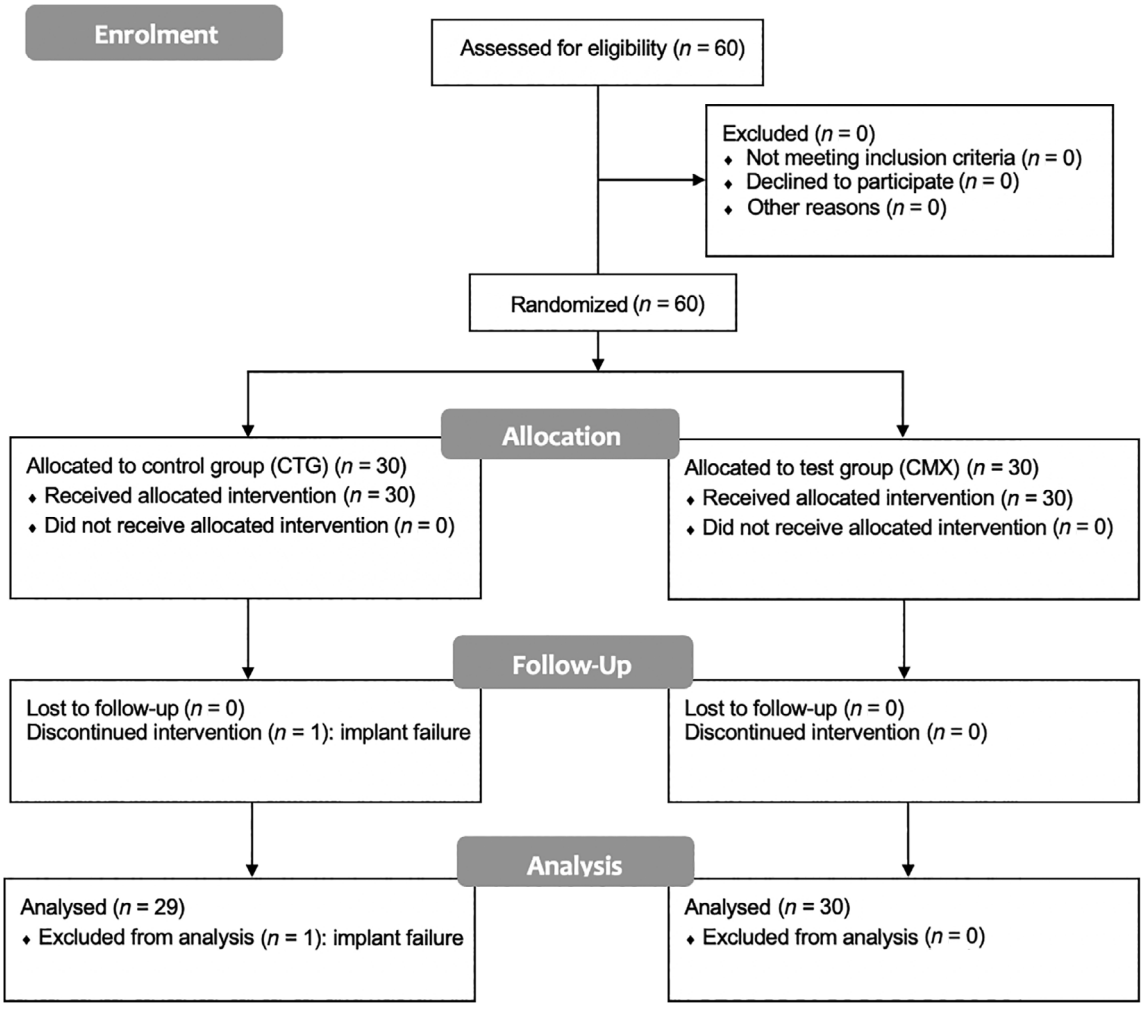

FIGURE 3 CONSORT flow diagram. CMX, collagen matrix; CTG, connective tissue graft

TABLE 1 Baseline characteristics

	CTG	CMX
Gender		
Male	15 (50%)	14 (46.67%)
Female	15 (50%)	16 (53.33%)
Age (years)		
Mean	50.1	48.2
SD	17.0	16.3
Range	19–77	20–77
Initial horizontal buccal defect (HD)		
Mean	1.71	1.62
SD	0.76	0.62
Range	0.44–3.21	0.68–2.61
Implant position		
Central incisor	8 (26.67%)	9 (30%)
Lateral incisor	8 (26.67%)	7 (23.33%)
Canine	3 (10%)	2 (6.67%)
Premolar	11 (36.67%)	12 (40%)
Implant length		
8 mm	2 (6.67%)	2 (6.67%)
10 mm	5 (16.67%)	7 (23.33%)
11.5 mm	15 (50%)	17 (56.67%)
13 mm	8 (26.67)	4 (13.33%)
Implant diameter		
3.5 mm	20 (66.67)	24 (80%)
4.3 mm	10 (33.33%)	6 (20%)

Abbreviations: CMX, collagen matrix; CTG, connective tissue graft.

The estimated marginal means are illustrated per treatment group and time point in Figure 5.

A significant time effect (within group difference) was observed in both groups. In the control group, the increase in buccal soft tissue profile immediately post surgery (T1) was 1.43 mm (95% CI 1.15–1.70). Between T1 and T2, a significant shrinkage of 0.27 mm (95% CI 0.01–0.53; $p = .039$) was observed, pointing to final increase in buccal soft tissue profile of 1.15 mm (95% CI 0.88–1.43). In the test group, the increase in buccal soft tissue profile immediately post surgery (T1) was 1.90 mm (95% CI 1.63–2.18). Between T1 and T2, a significant shrinkage of 1.05 mm (95% CI 0.79–1.31; $p < .001$) was observed, pointing to a final increase in buccal soft tissue profile of 0.85 mm (95% CI 0.58–1.13).

A significant treatment × time interaction ($p < .001$) was found, implying that the changes in buccal soft tissue profile over time were significantly different between CTG and CMX. Sites treated with CMX demonstrated 0.78 mm (95% CI 0.41–1.14; $p < .001$) more shrinkage between T1 and T2 than sites treated with CTG.

No significant treatment effect could be seen at T2, even though a trend towards 0.30 mm (95% CI −0.01 to 0.61; $p = .054$) additional increase in buccal soft tissue profile was observed in favour of the control group.

28.95% and 7.89% of the variability in the model could be explained by the patient and surgeon, respectively.

3.3 | Patient-reported outcome measures

The results on secondary outcomes can be found in Table 2. There were no significant differences between the groups in terms of post-operative bleeding ($p = .344$), pain ($p = .331$), and oedema ($p = .227$) but there was for post-operative haematoma ($p = .033$). The mean VAS for post-operative haematoma was 10.23 in the control group and 3.67 in the test group, pointing to a mean difference of 6.56 (95% CI 0.54–12.59) in favour of the test group. The mean number of analgesics taken was 5.24 and 4.47 in the control and test group, respectively. There was no significant difference between the groups ($p = .504$).

In the control group, no patient was unwilling to undergo the treatment again. Two patients were uncertain. In the test group, there were two patients who were not willing to undergo the treatment again and two were uncertain.

There was no significant difference between the groups in patient's aesthetic satisfaction of the soft tissues at 3 months following surgery ($p = .686$). The mean VAS was 80.72 in the control group and 82.05 in the test group.

3.4 | Clinical outcomes

3.4.1 | Graft dimensions, wound closure, and surgery time

The mean graft dimensions were 9.6 × 6.6 × 2.4 mm (width × length × thickness) in the control group and 9.7 × 6.7 × 3.3 mm in the test group. There was no significant difference between the groups in graft width ($p = .928$) or length ($p = .782$), but there was a significant difference in thickness ($p < .001$). Mean graft thickness per treatment group and centre is shown in Figure S2. More variation in graft thickness was observed in the test group.

In eight and two patients in the control and test group, respectively, no primary wound closure was achieved (OR = 0.20; 95% CI 0.04–0.96; $p = .087$).

The mean time needed for the grafting procedure amounted to 22.03 and 13.00 min in the control and test group, respectively. The mean difference of 9.03 min (95% CI 7.04–11.03; $p < .001$) in favour of the test group was significant.

3.4.2 | Complications

In the control group, one patient experienced intolerable pain and oedema. Systemic antibiotics and opioid analgesics (tramadol 50 mg, maximum 400 mg/day) were prescribed, whereafter the symptoms disappeared. In another patient from the control group, one implant showed mobility after 1 week and was removed. Two patients showed

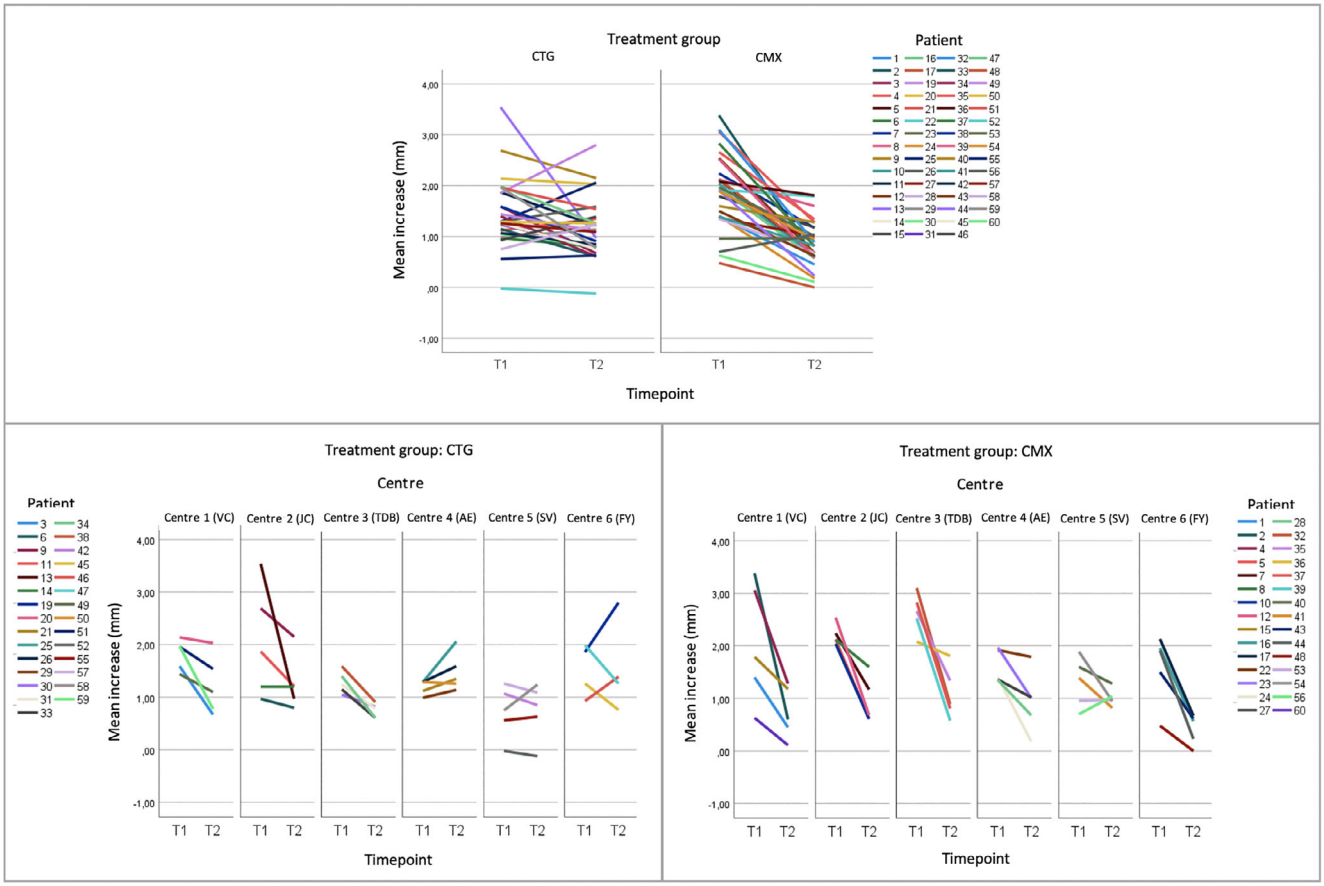

FIGURE 4 Increase in buccal soft tissue profile per patient, treatment group, time point, and centre (raw data). CMX, collagen matrix; CTG, connective tissue graft

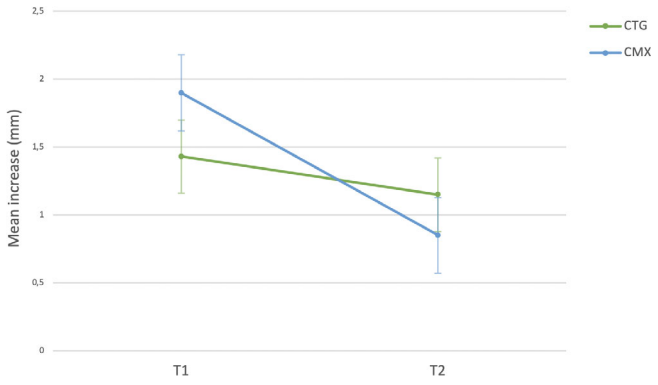

FIGURE 5 Increase in buccal soft tissue profile per treatment group and time point (estimated marginal means; 95% CI). CMX, collagen matrix; CTG, connective tissue graft

a wound dehiscence after 1 week. All but one implant survived in the control group.

In the test group, all patients experienced uneventful healing, except for one patient experiencing heavy post-operative bleeding. Wound compression was performed, which resolved the problem. One patient showed a wound dehiscence after 1 week. All implants survived in the test group.

Five crown fractures occurred in the control group and one in the test group (crown detached from temporary titanium abutment: $n = 4$; shell detached from flowable composite: $n = 2$). This amounted to an overall crown fracture rate of 6/40 (15%). In each group, one crown-loosening was registered.

3.4.3 | Marginal bone loss

The ICC for assessing inter-assessor reliability on marginal bone loss was 0.992 ($p < .001$), suggesting excellent agreement between duplicate measurements.

Mean marginal bone loss was 0.34 mm in the control group and 0.72 mm in the test group at 3 months. The mean difference of 0.38 mm (95% CI 0.15–0.60; $p = .001$) in favour of the control group was significant.

3.4.4 | Probing depth, plaque, and bleeding on probing

Mean probing depth was 3.36 mm in the control group and 3.66 mm in the test group at 3 months. The mean difference of 0.30 mm

TABLE 2 Secondary outcomes

	CTG	CMX	Difference	*p*-Value
Patient-reported outcome measures				
Post-op bleeding (yes/no)	0.44 (0.28–0.62)	0.33 (0.16–0.57)	1.61[a] (0.62–4.15)	.344
Post-op pain (VAS)	25.94 (15.61–36.26)	20.50 (10.19–30.81)	5.44 (−2.16 to 13.03)	.159
Post-op oedema (VAS)	18.74 (10.26–27.22)	14.63 (6.18–23.09)	4.11 (−2.59 to 10.80)	.227
Post-op haematoma (VAS)	10.23 (4.22–16.24)	3.67 (−2.31 to 9.64)	6.56 (0.54–12.59)	**.033**
Total number of analgesics	5.24 (3.04–9.03)	4.47 (3.98–5.02)	1.17 (0.73–1.88)	.504
Patients' aesthetic appreciation at T2 (VAS)	80.72 (71.86–89.58)	82.05 (73.32–90.77)	1.33 (−5.18 to 7.84)	.686
Clinical outcomes				
Graft width (mm)	9.62 (8.24–11.00)	9.67 (8.29–11.04)	0.05 (−0.59 to 0.69)	.877
Graft length (mm)	6.62 (5.84–7.39)	6.73 (5.96–7.51)	0.12 (−0.42 to 0.66)	.669
Graft thickness (mm)	2.40 (1.98–2.82)	3.25 (2.83–3.67)	0.85 (0.53–1.17)	**<.001**
Primary wound closure (yes/no)	0.73 (0.60–0.84)	0.93 (0.79–0.98)	0.20[a] (0.04–0.96)	.087
Surgery time (min)	22.03 (17.54–26.52)	13.00 (8.51–17.49)	9.03 (7.04–11.03)	**<.001**
Marginal bone loss (mm)	0.34 (0.01–0.67)	0.72 (0.39–1.04)	0.38 (0.15–0.60)	**<.001**
Probing depth (mm)	3.36 (2.99–3.73)	3.66 (3.29–4.03)	0.30 (0.06–0.54)	**.017**
Plaque (%)	22.86 (9.10–36.62)	22.50 (8.75–36.25)	0.36 (−7.87 to 8.59)	.931
Bleeding on probing (%)	27.76 (9.34–46.18)	26.67 (8.25–45.09)	1.10 (−6.58 to 8.77)	.778
Aesthetic outcomes				
Midfacial recession (mm)	0.16 (−0.46 to 0.77)	0.91 (0.30–1.52)	0.75 (0.39–1.12)	**<.001**
Pink aesthetic score (/14)	10.47 (9.74–11.21)	10.59 (9.86–11.32)	0.12 (−0.40 to 0.63)	.655
Mucosal scarring index (/10)	2.03 (1.66–2.41)	1.73 (1.37–2.10)	0.30 (−0.22 to 0.82)	.256

Note: Continuous variables: estimated marginal mean (95% confidence interval), mean difference (95% confidence interval), *p*-value between groups.
Abbreviations: CMX, collagen matrix; CTG, connective tissue graft; VAS, visual analogue scale.
[a]Categorical variables: proportion (95% confidence interval), odds ratio (95% confidence interval), *p*-value between groups.

(95% CI 0.06–0.54; $p = .017$) in favour of the control group was significant. Plaque and bleeding on probing varied between 20% and 30% on average at 3 months and did not differ between the groups ($p \geq .778$).

3.5 | Aesthetic outcomes

Mean mid-facial recession was 0.16 mm in the control group and 0.91 mm in the test group at 3 months. The mean difference of 0.75 mm (95% CI 0.39–1.12; $p < .001$) in favour of the control group was significant.

The ICC for assessing inter-assessor reliability on PES and MSI was 0.721 ($p = .004$) and 0.672 ($p = .010$), respectively, suggesting moderate agreement between duplicate measurements.

Mean PES was above 10 and did not differ between the groups ($p = .655$). Mean MSI was limited to about 2 and did not differ between the groups ($p = .256$). Hence, the peri-implant aesthetic outcome was pleasing in both groups.

4 | DISCUSSION

The primary objective of this multi-centre RCT was to compare CTG with CMX in terms of changes over time in buccal soft tissue profile when applied at single implant sites demonstrating a minor horizontal mucosa defect. The present study only provides interim results after 3 months. In spite of the short interval, these findings are worthy of reporting since both grafting materials are different and therefore distinct patterns in remodelling and degradation during the early phases of healing may be expected. In a pre-clinical study, CMX-treated sites demonstrated moderate degradation of the matrix network and slight to moderate infiltration with inflammatory cells during the first 2 months (Thoma et al., 2017). CTG-treated sites showed full degradation of the graft with no inflammation at 2 months. Interestingly, however, no adverse tissue reactions were observed at any site, and similar soft tissue dynamics were found between the groups, pointing to maximum soft tissue thickness at the most coronal level at 1 month and continuous reduction thereafter (Thoma et al., 2017; Naenni et al., 2018). Human histological analyses are in line with these findings (Thoma et al., 2016). CMX-treated sites showed a dense and sometimes looser network of collagen fibres around a vascularized CMX body, which could still be identified at 3 months. At CTG-treated sites, no distinction could be made between transplanted and newly formed connective tissue, and vascularization was observed throughout the specimens at 3 months (Thoma et al., 2016). Clinically, CMX- and CTG-treated sites showed minimal changes over time, with similar outcomes in terms of augmentation at 3 months (Thoma et al., 2016). Another reason why interim results are worthy of reporting relates to

permanent crown installation, which has a considerable influence on buccal soft tissue profile due to buccal soft tissue displacement (Eeckhout et al., 2020). In this study, permanent crowns were installed after 3 months. Therefore, the true impact of soft tissue grafting on buccal soft tissue profile could be assessed only at 3 months. In the present study, the alternative research hypothesis was accepted since soft tissue dynamics were significantly different between the control group and test group. Even though surgeons applied thicker grafts when using CMX, sites treated with CMX demonstrated 0.78 mm (95% CI 0.41–1.14) more shrinkage between T1 and T2 than sites treated with CTG. The final increase in buccal soft tissue profile was 1.15 mm (95% CI 0.88–1.43) for CTG and 0.85 mm (95% CI 0.58–1.13) for CMX. The mean difference of 0.30 mm (95% CI −0.01 to 0.61) in favour of CTG was of borderline significance ($p = .054$).

Clinical studies with profilometric evaluations after CTG application at single implants demonstrated increase in buccal soft tissue profile between 0.69 and 1.53 mm after 3 months of follow-up (Zeltner et al., 2017; Rojo et al., 2018; De Bruyckere et al., 2020; Schmitt et al., 2021). The increase in buccal soft tissue profile of 1.15 mm in the present study is in agreement with these observations. Profilometric data on the CMX used in the present study are scarce in the literature. Zeltner et al. (2017) applied this CMX at single implants and showed an increase in buccal soft tissue profile of 0.77 mm after 3 months of follow-up. The increase in buccal soft tissue profile of 0.85 mm in the present study is in line with this observation. Interestingly, Zeltner et al. (2017) compared CMX to CTG and found similar increase in buccal soft tissue profile after 3 months of follow-up (CTG: 0.79 mm; CMX: 0.77 mm), which contrasts our findings. However, the present RCT was a superior trial based on 60 patients instead of 20 and was performed at six centres. Hence, it provides information on the clinical effectiveness of both procedures when applied by different surgeons and may therefore show higher external validity.

Surprisingly, there were no significant differences between the groups in terms of patient-reported outcomes, except for postoperative haematoma with a mean difference in VAS of 6.56 (95% CI 0.54–12.59) in favour of CMX. Although CTG required a second surgical site, the number of analgesics taken by patients did not differ significantly between the groups. These findings are in accordance with those of Thoma et al. (2016). The acceptance of a donor site by patients was confirmed by the fact that no patient was unwilling to undergo the treatment again.

Graft thickness differed significantly between the groups. CMX grafts were 0.85 mm (95% CI 0.53–1.17; $p < .001$) thicker than CTGs. In addition, the variation in graft thickness was higher when using CMX. For three surgeons (VC, SV, FY) this thickness was 2–3 mm, for two surgeons (JC, AE) it was 3–4 mm, and for one surgeon (TDB) it was more than 4 mm. Interestingly, using a thicker matrix failed to result in higher increase in buccal soft tissue profile at 3 months, as illustrated in Figure 3. A thicker matrix may hamper primary wound closure and will be more compressed, which does not seem beneficial in terms of clinical effectiveness. Possibly, CMX grafts may have been oversized in general, since randomization ensured comparable defects in both groups and CMX grafts were significantly thicker than CTGs. To what extent CMX thickness may explain the mediocre effectiveness in the test group is unclear. Future studies should assess the effectiveness of CMX for different, yet standardized graft dimensions.

An advantage of using CMX instead of CTG was that surgery time could be reduced by 9.03 min (95% CI 7.04–11.03). This is in accordance with a clinical study of De Angelis et al. (2021). However, Thoma et al. (2016) found no significant difference in surgery time between the application of CTG or CMX.

Few biological complications occurred in the present study, indicating that soft tissue augmentation with either CTG or CMX is a safe procedure. Although attention was paid to tension-free primary wound closure, three patients demonstrated wound-healing complications after 1 week (two in the control group and one in the test group). Technical complications were more common and included 6 fractures out of 40 (15%) CAD/CAM provisional acrylic restorations (TempShell®, Nobel Biocare). These restorations were chairside connected onto a temporary titanium abutment using a flowable composite. The relatively high fracture rate of these restorations may be explained by polymerization shrinkage stress of the flowable composite and the lack of chemical bonding between the acrylic shell and the flowable composite. CAD/CAM acrylic restorations were used as part of a fully digital workflow in this study, based on pre-operative digital implant planning, designing a provisional restoration, fabrication of a stereolithographic surgical guide, and CAD/CAM provisional restoration. Guided implant surgery was performed in all patients since this approach has shown to result in the most accurate implant positioning (Younes et al., 2018; Smitkarn et al., 2019). This was considered important since the effectiveness of soft tissue augmentation can be studied only at the buccal aspect of perfectly installed implants.

In the test group, a cross-linked porcine-derived collagen matrix was used for soft tissue augmentation. Cross-linking may avoid fast biodegradation, which has been shown to result in more soft tissue augmentation at 3 months follow-up than non-cross-linked porcine-derived collagen matrixes. Indeed, the increase in buccal soft tissue profile using the latter was 0.51 mm in the study of Eeckhout et al. (2020) and only 0.35 mm in the study of Schmitt et al. (2021). On the other hand, cross-linking can increase inflammation, possibly resulting in wound-healing complications (Thoma et al., 2012; Rothamel et al., 2014). In a pre-clinical study, moderate inflammation was observed up to 2 months when using a cross-linked CMX (Thoma et al., 2017). This had no clear effect on clinical parameters in an exploratory study of Thoma et al. (2016). However, in the present RCT based on 60 patients, CMX resulted in significantly more marginal bone loss (0.38 mm; 95% CI 0.15–0.60) and deeper pockets (0.30 mm; 95% CI 0.06–0.54) than CTG at 3 months follow-up. This suggests a relevant impact of CMX on the early stages of healing when leaving part against a provisional acrylic restoration (Sanz-Martín et al., 2019). In any case, the observed differences could not be explained by disparities in primary wound closure, and their clinical relevance is currently difficult to assess. However, marginal bone loss in the test group (0.72 mm) exceeds what has been described for the implant system after 3 months of follow-up (Lambrechts et al., 2021).

It is therefore important to evaluate clinical parameters over time to observe whether they stabilize, improve, or deteriorate. Only then can clinical recommendations be made.

Mid-facial recession was also significantly higher for CMX than for CTG (0.75 mm; 95% CI 0.39–1.12). Possibly, soft tissues were more released for CMX application, given its thicker dimension, resulting in a more coronal advancement of the flap in the test group. On the other hand, this does not seem to correspond with a lower VAS on post-operative haematoma in that group. The clinical relevance of higher mid-facial recession in the test group is probably clinically negligible given a PES of 10.59, which did not differ significantly from the PES of 10.47 in the control group. MSI was low in both groups, which may confirm a pleasing peri-implant aesthetic outcome in both groups.

For a correct interpretation of the present study, the following limitations need to be taken into account. First, the present article reports on short-term outcomes. Patients need to be observed over a longer period to determine the clinical effectiveness of both augmentation procedures, the impact of CMX on clinical parameters, and the clinical relevance of the observed differences. Second, the sample size calculation was based on the primary study outcome. Hence, the present study may have been underpowered for some secondary outcome variables. Third, some secondary outcomes were assessed by the treating surgeon and not by a blinded examiner for practical reasons, which could have introduced information bias. Finally, although all participating surgeons had experience with the CMX used in this study, they all had much more training in soft tissue grafting using CTG. On the other hand, two surgeons (JC, TDB) had a lot of experience with CMX, and their results in terms of increase in buccal soft tissue profile were not superior to those obtained by the other surgeons, as illustrated in Figure 3. This is in line with the fact that only 7.89% of the variability in the model could be explained by surgeon.

5 | CONCLUSION

CTG and CMX are both effective in increasing soft tissue thickness at the buccal aspect of single implants in the short term. However, soft tissue dynamics differed significantly. Even though surgeons applied thicker grafts when using CMX, sites treated with CMX demonstrated more shrinkage during the early healing phase. In addition, CMX resulted in more marginal bone loss, deeper pockets, and more mid-facial recession than CTG. Longer follow-up is needed to determine the clinical effectiveness of both augmentation procedures, the impact of CMX on clinical parameters, and the clinical relevance of observed differences. Only then can clinical recommendations be made.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. Ellen Deschepper for the statistical analysis.

CONFLICT OF INTEREST

Prof. Cosyn has collaboration agreements with Nobel Biocare AB (Göteborg, Sweden) and Straumann (Basel, Switzerland). Prof. Christiaens has a collaboration agreement with Southern Implants (Irene, South-Africa), and Dr. Stijn Vervaeke has a collaboration agreement with Denstply Sirona (Mölndal, Sweden).

AUTHOR CONTRIBUTIONS

Principal investigator, funding, coordination, research protocol development, surgeon, data interpretation, second and final draft: Jan Cosyn. *Literature review, data collection, data interpretation, first and second draft*: Célien Eeckhout. *Research protocol, surgeon, data interpretation, second and final draft*: Véronique Christiaens, Aryan Eghbali, Stijn Vervaeke, Faris Younes, and Thomas De Bruyckere.

ETHICS STATEMENT

The study was approved by the Ethical Committee of Ghent University Hospital (B670201940413) and registered in ClinicalTrials.gov (NCT04210596). It was conducted in accordance with the ethical standards of the Declaration of Helsinki in 1975, as revised in 2013. The study was reported following the guidelines of the CONSORT statement (Schulz et al., 2010).

DATA AVAILABILITY STATEMENT

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

ORCID

Jan Cosyn https://orcid.org/0000-0001-5042-2875
Aryan Eghbali https://orcid.org/0000-0002-1515-8965
Stijn Vervaeke https://orcid.org/0000-0002-1416-6787
Faris Younes https://orcid.org/0000-0003-3716-5119

REFERENCES

Burkhardt, R., Hämmerle, C. H., & Lang, N. P. (2015). Self-reported pain perception of patients after mucosal graft harvesting in the palatal area. *Journal of Clinical Periodontology*, *42*(3), 281–287. https://doi.org/10.1111/jcpe.12357

Buser, D., Martin, W., & Belser, U. C. (2004). Optimizing esthetics for implant restorations in the anterior maxilla: Anatomic and surgical considerations. *The International Journal of Oral & Maxillofacial Implants*, *19*(Suppl), 43–61.

Cosyn, J., Wessels, R., Cabeza, R. G., Ackerman, J., Eeckhout, C., & Christiaens, V. (2021). Soft tissue metric parameters, methods and esthetic indices in implant dentistry: A critical review. *Clinical Oral Implants Research* (In press).

Couso-Queiruga, E., Stuhr, S., Tattan, M., Chambrone, L., & Avila-Ortiz, G. (2021). Post-extraction dimensional changes: A systematic review and meta-analysis. *Journal of Clinical Periodontology*, *48*(1), 126–144. https://doi.org/10.1111/jcpe.13390

De Angelis, P., De Angelis, S., Passarelli, P. C., Liguori, M. G., Pompa, G., Papi, P., Manicone, P. F., & D'Addona, A. (2021). Clinical comparison of a xenogeneic collagen matrix versus subepithelial autogenous connective tissue graft for augmentation of soft tissue around implants. *International Journal of Oral and Maxillofacial Surgery*, *50*(7), 956–963. https://doi.org/10.1016/j.ijom.2020.11.014

De Bruyckere, T., Cabeza, R. G., Eghbali, A., Younes, F., Cleymaet, R., & Cosyn, J. (2020). A randomized controlled study comparing guided bone regeneration with connective tissue graft to reestablish buccal convexity at implant sites: A 1-year volumetric analysis. *Clinical Implant*

Dentistry and Related Research, *22*(4), 468–476. https://doi.org/10.1111/cid.12934

De Bruyckere, T., Eghbali, A., Younes, F., De Bruyn, H., & Cosyn, J. (2015). Horizontal stability of connective tissue grafts at the buccal aspect of single implants: A 1-year prospective case series. *Journal of Clinical Periodontology*, *42*(9), 876–882. https://doi.org/10.1111/jcpe.12448

Del Pizzo, M., Modica, F., Bethaz, N., Priotto, P., & Romagnoli, R. (2002). The connective tissue graft: A comparative clinical evaluation of wound healing at the palatal donor site. A preliminary study. *Journal of Clinical Periodontology*, *29*(9), 848–854. https://doi.org/10.1034/j.1600-051x.2002.290910.x

Eeckhout, C., Bouckaert, E., Verleyen, D., De Bruyckere, T., & Cosyn, J. (2020). A 3-year prospective study on a porcine-derived acellular collagen matrix to re-establish convexity at the buccal aspect of single implants in the molar area: A volumetric analysis. *Journal of Clinical Medicine*, *9*(5). https://doi.org/10.3390/jcm9051568

Eghbali, A., Seyssens, L., De Bruyckere, T., Younes, F., Cleymaet, R., & Cosyn, J. (2018). A 5-year prospective study on the clinical and aesthetic outcomes of alveolar ridge preservation and connective tissue graft at the buccal aspect of single implants. *Journal of Clinical Periodontology*, *45*(12), 1475–1484. https://doi.org/10.1111/jcpe.13018

Furhauser, R., Florescu, D., Benesch, T., Haas, R., Mailath, G., & Watzek, G. (2005). Evaluation of soft tissue around single-tooth implant crowns: The pink esthetic score. *Clinical Oral Implants Research*, *16*(6), 639–644. https://doi.org/10.1111/j.1600-0501.2005.01193.x

Griffin, T. J., Cheung, W. S., Zavras, A. I., & Damoulis, P. D. (2006). Postoperative complications following gingival augmentation procedures. *Journal of Periodontology*, *77*(12), 2070–2079. https://doi.org/10.1902/jop.2006.050296

Huber, S., Zeltner, M., Hämmerle, C. H. F., Jung, R. E., & Thoma, D. S. (2018). Non-interventional 1-year follow-up study of peri-implant soft tissues following previous soft tissue augmentation and crown insertion in single-tooth gaps. *Journal of Clinical Periodontology*, *45*(4), 504–512. https://doi.org/10.1111/jcpe.12865

Lambrechts, T., Doornewaard, R., De Bruyckere, T., Matthijs, L., Deschepper, E., & Cosyn, J. (2021). A multicenter cohort study on the association of the one-abutment one-time concept with marginal bone loss around bone level implants. *Clinical Oral Implants Research*, *32*(2), 192–202. https://doi.org/10.1111/clr.13689

Naenni, N., Bienz, S. P., Benic, G. I., Jung, R. E., Hämmerle, C. H. F., & Thoma, D. S. (2018). Volumetric and linear changes at dental implants following grafting with volume-stable three-dimensional collagen matrices or autogenous connective tissue grafts: 6-month data. *Clinical Oral Investigations*, *22*(3), 1185–1195. https://doi.org/10.1007/s00784-017-2210-3

O'Leary, T. J., Drake, R. B., & Naylor, J. E. (1972). The plaque control record. *Journal of Periodontology*, *43*(1), 38. https://doi.org/10.1902/jop.1972.43.1.38

Rojo, E., Stroppa, G., Sanz-Martin, I., Gonzalez-Martín, O., Alemany, A. S., & Nart, J. (2018). Soft tissue volume gain around dental implants using autogenous subepithelial connective tissue grafts harvested from the lateral palate or tuberosity area. A randomized controlled clinical study. *Journal of Clinical Periodontology*, *45*(4), 495–503. https://doi.org/10.1111/jcpe.12869

Rojo, E., Stroppa, G., Sanz-Martin, I., Gonzalez-Martín, O., & Nart, J. (2020). Soft tissue stability around dental implants after soft tissue grafting from the lateral palate or the tuberosity area—A randomized controlled clinical study. *Journal of Clinical Periodontology*, *47*(7), 892–899. https://doi.org/10.1111/jcpe.13292

Rothamel, D., Benner, M., Fienitz, T., Happe, A., Kreppel, M., Nickenig, H. J., & Zöller, J. E. (2014). Biodegradation pattern and tissue integration of native and cross-linked porcine collagen soft tissue augmentation matrices—An experimental study in the rat. *Head & Face Medicine*, *10*, 10. https://doi.org/10.1186/1746-160x-10-10

Sanz-Martín, I., Encalada, C., Sanz-Sánchez, I., Aracil, J., & Sanz, M. (2019). Soft tissue augmentation at immediate implants using a novel xenogeneic collagen matrix in conjunction with immediate provisional restorations: A prospective case series. *Clinical Implant Dentistry and Related Research*, *21*(1), 145–153. https://doi.org/10.1111/cid.12696

Schmitt, C. M., Brückbauer, P., Schlegel, K. A., Buchbender, M., Adler, W., & Matta, R. E. (2021). Volumetric soft tissue alterations in the early healing phase after peri-implant soft tissue contour augmentation with a porcine collagen matrix versus the autologous connective tissue graft: A controlled clinical trial. *Journal of Clinical Periodontology*, *48*(1), 145–162. https://doi.org/10.1111/jcpe.13387

Schulz, K. F., Altman, D. G., & Moher, D. (2010). CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *BMJ (Clinical Research Edition)*, *340*, c332. https://doi.org/10.1136/bmj.c332

Seibert, J. S. (1983). Reconstruction of deformed, partially edentulous ridges, using full thickness onlay grafts. Part I. Technique and wound healing. *Compendium of Continuing Education in Dentistry*, *4*(5), 437–453.

Smitkarn, P., Subbalekha, K., Mattheos, N., & Pimkhaokham, A. (2019). The accuracy of single-tooth implants placed using fully digital-guided surgery and freehand implant surgery. *Journal of Clinical Periodontology*, *46*(9), 949–957. https://doi.org/10.1111/jcpe.13160

Tan, W. L., Wong, T. L., Wong, M. C., & Lang, N. P. (2012). A systematic review of post-extractional alveolar hard and soft tissue dimensional changes in humans. *Clinical Oral Implants Research*, *23*(Suppl. 5), 1–21. https://doi.org/10.1111/j.1600-0501.2011.02375.x

Thoma, D. S., Buranawat, B., Hammerle, C. H., Held, U., & Jung, R. E. (2014). Efficacy of soft tissue augmentation around dental implants and in partially edentulous areas: A systematic review. *Journal of Clinical Periodontology*, *41*(Suppl. 15), S77–S91. https://doi.org/10.1111/jcpe.12220

Thoma, D. S., Cosyn, J., Fickl, S., Jensen, S. S., Jung, R. E., Raghoebar, G. M., Rocchietta, I., Roccuzzo, M., Sanz, M., Sanz-Sánchez, I., Scarlat, P., Schou, S., Stefanini, M., Strasding, M., & Bertl, K. (2021). Consensus report of working group 2: Soft tissue management. *Clinical Oral Implants Research*. https://doi.org/10.1111/clr.13798

Thoma, D. S., Gasser, T. J. W., Jung, R. E., & Hämmerle, C. H. F. (2020). Randomized controlled clinical trial comparing implant sites augmented with a volume-stable collagen matrix or an autogenous connective tissue graft: 3-year data after insertion of reconstructions. *Journal of Clinical Periodontology*, *47*(5), 630–639. https://doi.org/10.1111/jcpe.13271

Thoma, D. S., Naenni, N., Benic, G. I., Hämmerle, C. H., & Jung, R. E. (2017). Soft tissue volume augmentation at dental implant sites using a volume stable three-dimensional collagen matrix—Histological outcomes of a preclinical study. *Journal of Clinical Periodontology*, *44*(2), 185–194. https://doi.org/10.1111/jcpe.12635

Thoma, D. S., Villar, C. C., Cochran, D. L., Hämmerle, C. H., & Jung, R. E. (2012). Tissue integration of collagen-based matrices: An experimental study in mice. *Clinical Oral Implants Research*, *23*(12), 1333–1339. https://doi.org/10.1111/j.1600-0501.2011.02356.x

Thoma, D. S., Zeltner, M., Hilbe, M., Hämmerle, C. H., Hüsler, J., & Jung, R. E. (2016). Randomized controlled clinical study evaluating effectiveness and safety of a volume-stable collagen matrix compared to autogenous connective tissue grafts for soft tissue augmentation at implant sites. *Journal of Clinical Periodontology*, *43*(10), 874–885. https://doi.org/10.1111/jcpe.12588

Wessels, R., De Roose, S., De Bruyckere, T., Eghbali, A., Jacquet, W., De Rouck, T., & Cosyn, J. (2019). The mucosal scarring index: Reliability of a new composite index for assessing scarring following oral surgery. *Clinical Oral Investigations*, *23*(3), 1209–1215. https://doi.org/10.1007/s00784-018-2535-6

Younes, F., Cosyn, J., De Bruyckere, T., Cleymaet, R., Bouckaert, E., & Eghbali, A. (2018). A randomized controlled study on the accuracy of free-handed, pilot-drill guided and fully guided implant surgery in partially edentulous patients. *Journal of Clinical Periodontology*, *45*(6), 721–732. https://doi.org/10.1111/jcpe.12897

Zeltner, M., Jung, R. E., Hämmerle, C. H., Hüsler, J., & Thoma, D. S. (2017). Randomized controlled clinical study comparing a volume-stable collagen matrix to autogenous connective tissue grafts for soft tissue augmentation at implant sites: Linear volumetric soft tissue changes up to 3 months. *Journal of Clinical Periodontology*, *44*(4), 446–453. https://doi.org/10.1111/jcpe.12697

Zucchelli, G., Mounssif, I., Mazzotti, C., Montebugnoli, L., Sangiorgi, M., Mele, M., & Stefanini, M. (2014). Does the dimension of the graft influence patient morbidity and root coverage outcomes? A randomized controlled clinical trial. *Journal of Clinical Periodontology*, *41*(7), 708–716. https://doi.org/10.1111/jcpe.12256

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Cosyn, J., Eeckhout, C., Christiaens, V., Eghbali, A., Vervaeke, S., Younes, F., & De Bruyckere, T. (2021). A multi-centre randomized controlled trial comparing connective tissue graft with collagen matrix to increase soft tissue thickness at the buccal aspect of single implants: 3-month results. *Journal of Clinical Periodontology*, *48*(12), 1502–1515. https://doi.org/10.1111/jcpe.13560