Journal of Clinical Periodontology

WILEY

Journal of Clinical Periodontology

ORIGINAL ARTICLE OPEN ACCESS

Impact of Collagen Membrane in Vertical Ridge Augmentation Using Ti-Reinforced PTFE Mesh: A Randomised Controlled Trial

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Received: 29 June 2024 | **Revised:** 8 December 2024 | **Accepted:** 6 January 2025

Funding: The authors received no specific funding for this work.

Keywords: alveolar bone loss | alveolar ridge augmentation | bone regeneration | cone-beam computed tomography | dental implants

ABSTRACT

Aims: This non-inferiority randomised clinical trial aimed to compare vertical bone gain (VBG), volumetric bone changes and incidence of complications after vertical ridge augmentation (VRA) using perforated titanium-reinforced dense-polytetrafluoroethylene (PTFE) mesh covered by a collagen membrane (CM) or used alone.

Materials and Methods: Thirty patients with vertical bone defects were randomly assigned to receive VRA with either PTFE + CM or PTFE alone. Meshes were removed after 9 months. Clinical assessments included complication rates, pseudo-periosteum type and bone density. VBG, effective regeneration rate and the need for additional augmentation were evaluated using CBCT reconstructions.

Results: Non-inferiority of PTFE alone compared with PTFE + CM was not demonstrated for absolute and relative VBG (4.5 ± 2.1 mm vs. 4.1 ± 2.7 mm, 79.2% ± 16.6% vs. 85.8% ± 10.6%, respectively), effective regeneration rates (69.3% ± 17.9% vs. 72.3% ± 16.4%, respectively) or complication rates (6.7% in both groups). A higher incidence of type 1 pseudo-periosteum was observed in the PTFE + CM group.

Conclusion: The non-inferiority of PTFE alone compared with PTFE + CM for absolute VBG was not established. However, both techniques led to comparable outcomes for VBG, complication rates and bone density. The higher incidence of type 1 pseudo-periosteum and lacking bone volume in the PTFE + CM group suggests that adding a collagen membrane may help prevent soft tissue ingrowth.

Trial Registration: Clinicaltrials.gov identification number: NCT04843488

1 | Introduction

Vertical ridge augmentation (VRA) techniques, including guided bone regeneration (GBR), protected bone regeneration with titanium (Ti) meshes, distraction osteogenesis, and the use of block grafts (such as inlays, onlays and cortical plates) offer effective alternatives for the reconstruction of deficient alveolar ridges (Urban et al. 2019). Despite its potential, VRA procedures are

technique-sensitive and demand a substantial biological effort to regenerate defects without bone wall support to stabilise the clot and graft (Tay et al. 2022; Urban et al. 2019). GBR procedures are frequently associated with complications, with an incidence rate of approximately 16% (Alotaibi et al. 2023). The most prevalent complication is membrane and/or mesh exposure, which immediately becomes contaminated with bacteria from the oral environment and may impair the outcome of the regenerative procedure (Sanz-Sánchez et al. 2022; Urban et al. 2023).

Systematic reviews comparing evidence for VRA procedures demonstrated a significant advantage with GBR using non-resorbable meshes, particularly when considering the ratio of vertical bone gain (VBG) to the incidence of complications (Alotaibi et al. 2023; Urban et al. 2019). A meta-analysis further indicated that Ti-reinforced dense polytetrafluoroethylene (PTFE) meshes yield superior results in VRA compared with other techniques (Zhang et al. 2022). In general, GBR procedures aim to utilise membranes that can create and maintain a stable subperiosteal space above the bony defect. This allows osteoprogenitor cells to colonise the area while mechanically excluding the faster-migrating epithelial and connective tissue cells (Retzepi and Donos 2010). Although occlusive membranes effectively fulfil this primary principle, they may simultaneously hinder vascularization from the periosteal vessels of the flap covering the defect. As a result, the regenerating area confined by the membrane might rely solely on nourishment from the basal bone vasculature.

A Ti-reinforced perforated d-PTFE mesh has recently been introduced. Its perforations may enhance the revascularization of the bone graft from the surgical flap and facilitate interaction with the periosteum, supporting the influx of progenitor cells (Urban, Mirsky, et al. 2024). However, these same perforations may reduce the membrane's ability to act as a cell barrier, compromising one of the GBR principles, the cell-occlusion property (Dahlin et al. 1989; Schenk et al. 1994). As a result, it is often recommended to combine this type of mesh with a collagen membrane (CM) to compensate for this limitation. A case series by Urban et al. reported on 65 vertical defects treated with Ti-reinforced perforated PTFE meshes covered by CMs (Urban et al. 2021). The study reported very few complications (3%; 1 infection and 1 exposure), a VBG of 5.2 mm (96.5% of the defect), and complete defect fill in 89.2% of cases (Urban et al. 2021). Despite these positive outcomes, the use of CMs may increase the overall treatment cost. To date, the effect of using perforated PTFE meshes alone on bone regeneration outcomes following VRA are yet to be established.

Therefore, the aim of the present study was to evaluate the non-inferiority of PTFE mesh alone compared with PTFE mesh covered with CM in VRA procedures, in terms of absolute VBG as primary outcome. Secondary outcomes were the (i) relative VBG, (ii) volumetric bone gain, (iii) horizontal bone gain (HBG), (iv) incidence of complications, (v) type of pseudo-periosteum, (vi) bone density and (vii) the ability to place the implants in a prosthetically driven position after 9 months of healing. The research hypothesis (H1) was that PTFE alone (test group) would not be inferior to PTFE + CM (control group) in terms of absolute VBG (primary outcome).

2 | Materials and Methods

2.1 | Trial Design and Participants

The present parallel non-inferiority randomised controlled clinical trial included partially edentulous patients presenting to a private practice (Urban Regeneration Institute, Budapest, Hungary) requiring VRA procedures in the maxilla or mandible. Individuals were treated with bone graft and a perforated PTFE mesh alone, or PTFE mesh covered with a CM. All procedures were performed by a single experienced practitioner (I.U.) from April 2021 to May 2023.

The study was conducted in accordance with the Declaration of Helsinki and ethics approval was obtained from the Institutional Review Board for Human Studies of the University of Szeged (Protocol 269/2019-SZTE). Manuscript preparation was performed in accordance with the CONSORT guidelines (Schulz, Moher, and Altman 2014), and the criteria established by the Implant Dentistry Core Outcome Set and Measurement (ID-COSM) initiative (Tonetti et al. 2023).

Individuals were selected according to the following eligibility criteria.

2.1.1 | Inclusion Criteria

- Adults (≥ 18 years old) presenting good oral hygiene (plaque index of < 10%) (Silness and Loe 1964) and willing to be present at all study visits.
- Partially edentulous individuals (maxilla or mandible) who required vertical (> 1 mm) and horizontal ridge augmentation for late implant placement in at least one tooth site.

2.1.2 | Exclusion Criteria

- Heavy smokers (> 10 cigarettes/day).
- Alcohol or chronic drug abuse.
- Acute local or systemic infections.
- Uncontrolled diabetes mellitus or other metabolic disorders.
- Severe hepatic or renal dysfunction.
- Autoimmune diseases.
- Uncontrolled periodontitis.
- History of radiotherapy in the previous 5 years.
- Patients receiving immunosuppressive therapy.
- Patients under bisphosphonate therapy.

Prior to any intervention, the potential risks and benefits of the procedure were reviewed with the participants and written consent was obtained. The following information was collected: gender, age at time of surgical treatment and cigarette consumption (self-reported).

2.2 | Interventions

The present study was divided into two surgical phases: ridge augmentation surgery (T0) and PTFE mesh removal with implant placement after 9 months (T1). At baseline, all individuals underwent a cone beam computed tomography (CBCT) scan (Accuitomo, MORITA, Japan) to confirm eligibility in the study (vertical and horizontal defects as well as absence of acute local infections). Prior to the first surgical intervention, the presence of keratinized mucosa (KM) 2 mm below the crest was determined using a UNC15 probe (UNC15; Hu-Friedy). KM was classified into present (≥1 mm) or absent (<1 mm) at all sites.

All surgical procedures were performed following a previously reported methodology (Urban et al. 2021) and are illustrated in Figures 1a–l and 2a–l. A prophylactic systemic antibiotic coverage with 500 mg amoxicillin TID or, in the case of penicillin allergy, 150 mg clindamycin QID was prescribed to all individuals 24 h prior to surgery. On the day of surgery, following local anaesthesia, para-marginal incisions were performed for maxillary sites exhibiting a good vestibule depth and keratinized tissue, whereas in advanced maxillary defects with loss of vestibule depth and limited amount of KM, a mid-crestal incision was made. In mandibular sites, a mid-crestal incision was performed in the KM of the edentulous ridge, with sulcular incisions around adjacent teeth. Full-thickness mucoperiosteal flaps were raised with the aid of periosteal elevators. The flaps were extended at least 5 mm apical to the alveolar crest. Two vertical releasing incisions were performed in the mesio-buccal and disto-buccal aspects, ≥1 tooth away. The depth and location of the vertical releasing incisions depended on the depth of the vestibule and the extent of the existing defect (Urban et al. 2016). Subsequently, mobilisation of the buccal and lingual flaps was performed by means of periosteal releasing incisions. For mandibular sites, the lingual flap was elevated to the mylohyoid muscle attachment and bluntly separated according to three zones of interest previously described (Urban et al. 2017; Urban, Saleh, et al. 2024). The area to be covered by the mesh and the bone defect dimensions were estimated using an UNC15 probe (Figures 1b and 2b).

Later, perforations of the cortical bone were performed with the aid of a small-diameter round bur, to increase blood supply to the recipient bed. Autogenous bone graft was harvested from adjacent sites using a bone scraper (SafeScraper TWIST, Osteogenics Biomedical) and/or trephines (Modified Trephine Bur, Hu-Friedy) to obtain a 1:1 ratio of autogenous bone to deproteinized bovine bone mineral (DBBM; Bio-Oss, Geistlich Pharma AG). The combined bone graft was positioned on the residual ridge to estimate the desired bone augmentation. An appropriately sized Ti-reinforced perforated dense PTFE mesh (RPM, Osteogenics Biomedical) was chosen and adjusted to completely cover the graft and at least 2 mm of adjacent native bone. The PTFE mesh was stabilised with the aid of titanium pins (Master Pin, Meisinger) or screws (Pro-fix, Osteogenics Biomedical) (Urban et al. 2016, 2021), first on the palatal/lingual aspect of the site (Figures 1c and 2c), and then on the buccal.

Subsequently, patients were assigned to the following groups:

- PTFE group: Ti-reinforced PTFE mesh alone (Figure 1d).

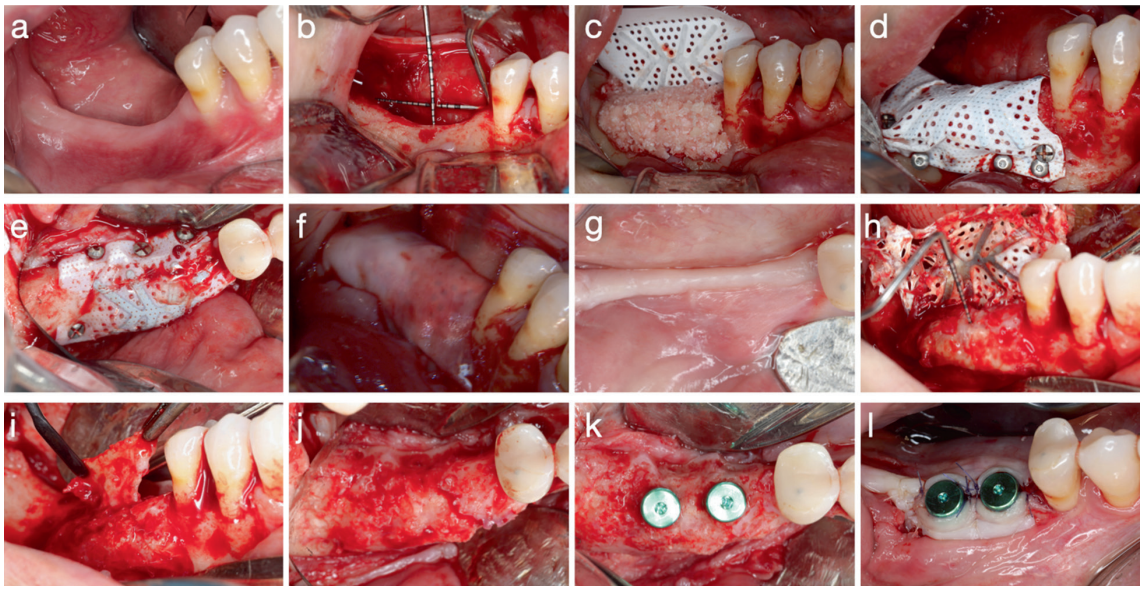

FIGURE 1 | Representative case from the PTFE + CM group with a step-by-step demonstration of the surgical procedure. (a) Pre-operative buccal view of a posterior mandibular area requiring vertical GBR. (b) Measurements of the vertical dimensions of the defect. (c) A titanium-reinforced PTFE membrane was fixed in place after decortication of the recipient site and placement of particulate deproteinized bovine bone mineral combined with autogenous graft (1:1 ratio). (d, e) Buccal and occlusal views of the titanium-reinforced PTFE membrane fixed in place with titanium pins and screws. (f) Native collagen membrane covering the defect without stabilisation. Coronal flap advancement was obtained before closure. Tension-free flap closure was performed using the double-layer suturing technique. (g) Clinical view of the regenerated area 9 months after surgery. (h) Re-entry surgery after flap and membrane elevation; intra-operative evaluation of pseudo-periosteum formation and bone density. (i) Pseudo-periosteum removal. (j) Occlusal view of the defect after GBR, showing the excellent dimensions and vital-looking ridge. (k) Two implants in place in biologically and prosthetically ideal positions. (l) Buccal view after suture, demonstrating adequate implant position following successful VBA.

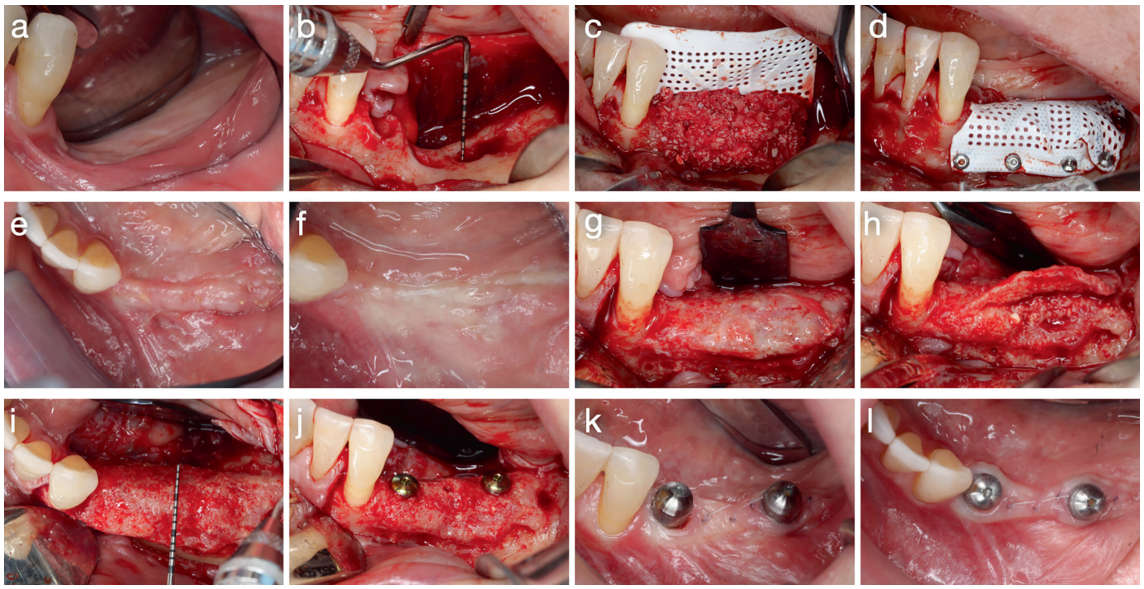

FIGURE 2 | Representative case from the PTFE group with a step-by-step demonstration of the surgical procedure. (a) Pre-operative buccal view of a posterior mandibular area that required vertical GBR. (b) Measurements of the vertical dimensions of the defect. (c) A titanium-reinforced PTFE membrane was fixed in place after decortication of the recipient site and placement of particulate deproteinized bovine bone mineral combined with autogenous graft (1:1 ratio). (d) Buccal view of the titanium-reinforced PTFE membrane fixed in place with titanium pins and screws. Coronal flap advancement was obtained before closure. Tension-free flap closure was performed using the double-layer suturing technique. (e, f) Clinical view of the regenerated area 9 months after surgery. (g) Re-entry surgery after flap and membrane elevation; intra-operative evaluation of pseudo-periosteum formation and bone density. (h) Pseudo-periosteum removal. (i) Occlusal view of the defect after GBR, noting the excellent dimensions and vital-looking ridge. (j) Two implants in place in biologically and prosthetically ideal positions. (k, l) Buccal and occlusal views after 3 weeks, demonstrating adequate implant position following successful VBA.

– PTFE + CM group: Ti-reinforced PTFE mesh covered with a native CM (Bio-Gide, Geistlich Pharma AG) without stabilization (Figure 1d–f).

Double-layered suturing was employed by means of horizontal mattress sutures (GORE-TEX CV-5 Suture, W.L. Gore & Associates) positioned 4–5 mm from the incision line to promote intimate adaptation of the borders and prevent mesh exposure, followed by single interrupted sutures to secure the flap edges.

The sutures were removed between 2 and 3 weeks. Patients were prescribed amoxicillin 500 mg TID for 7 days or, in the case of allergy, clindamycin 150 mg QID for 6 days. A non-steroidal anti-inflammatory drug (50 mg diclofenac potassium TID or ibuprofen 200 mg TID) was prescribed for 1 week after the surgery. Individuals received post-operative instructions including a 2-week soft diet as well as rinses with 0.2% chlorhexidine-based mouthwash two times a day. No removable partial dentures were used during the entire healing period. All patients underwent weekly evaluation during the initial 3 weeks after surgery, followed by assessments at 6 weeks. Subsequently, monthly evaluations were conducted until the conclusion of the follow-up period.

After 9 months of healing (T1), individuals underwent another CBCT scan and the ability to place the implants in a prosthetically-driven position was assessed using DTX Studio software (Nobel BioCare, Zurich, Switzerland). Then, re-entry procedures were performed in the augmented sites (Figures 1g,h and 2f,g). Limited mucoperiosteal flaps were elevated to remove the PTFE mesh and titanium pins and/or screws as well as to place the implants. The type of pseudo-periosteum (Figures 1h and 2h,i) and the ridge dimensions (Figures 1i and 2j) were assessed. Dental implants (Nobel Biocare, Zurich, Switzerland; Thommen Medical, Cleveland, OH, USA) were placed according to the manufacturer's instructions, left for non-submerged healing, and the surgical sites closed with sutures (Figures 1j,k and 2k,l).

2.3 | Outcomes

2.3.1 | Outcome Measures

The primary endpoint of the present study was the absolute VBG. Secondary endpoints included the relative VBG, HBG, regenerated bone volume (RBV), effective regeneration rate (ERR), incidence of healing complications, pseudo-periosteum type, bone density and ability to place the implants in a prosthetically-driven position.

2.3.2 | Vertical Bone Gain

Pre- and post-procedure CBCT scans (T0 and T1) were superimposed using a dedicated software (3D Slicer). With an opacity of 100% for T0 and 0% for T1, the baseline vertical bone defect was assessed by a single calibrated examiner (TGA). First, on the axial reconstruction, a line was drawn connecting the mesial and distal bone peaks of the defect (Figure 3a). The cross-sectional reconstruction was then positioned at the deepest point of the defect, and a vertical line was drawn from the defect crest to the line connecting the bone peaks, determining the baseline vertical bone defect (Figure 3b,c).

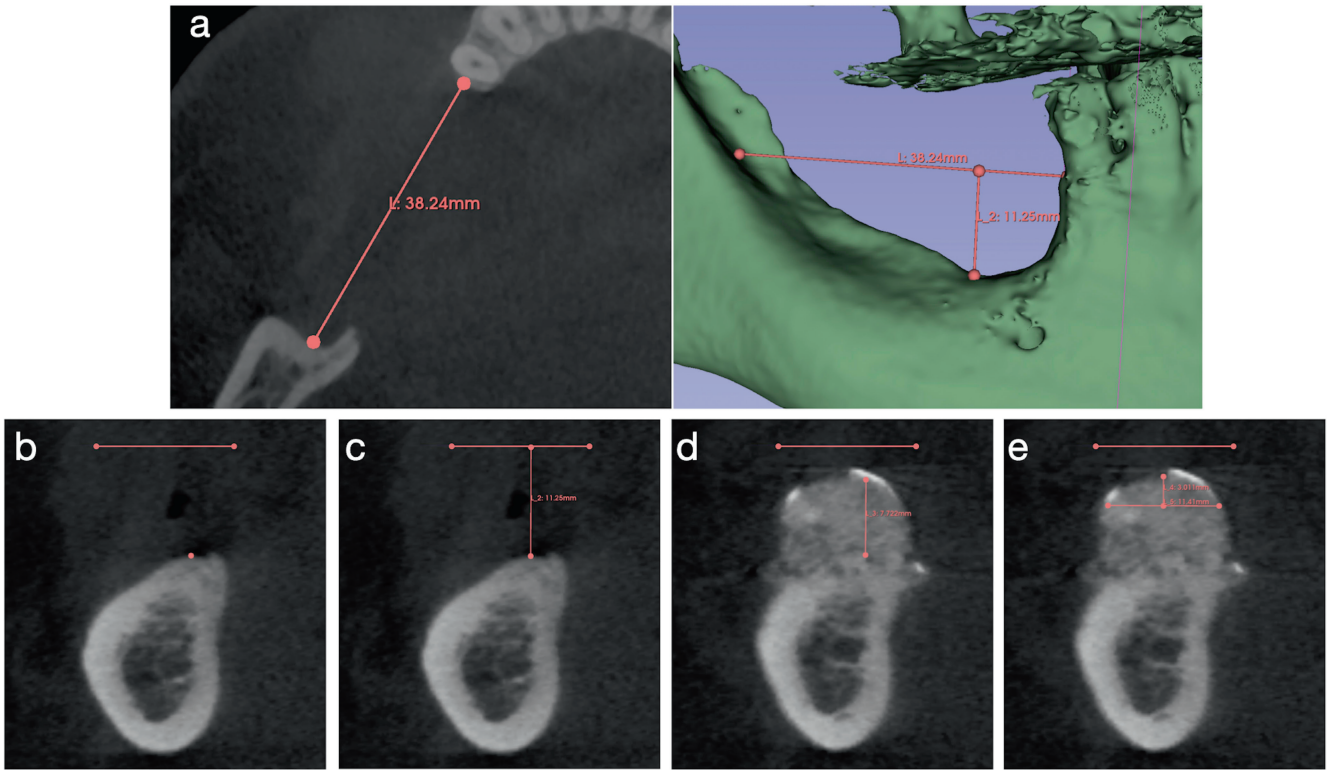

FIGURE 3 | Linear measurements on CBCT scans. (a) On the axial reconstruction, a line was drawn connecting the mesial and distal bone peaks of the defect and the deepest point of the defect was determined. (b) The cross-sectional reconstruction was positioned in the same location and the distance from the point to the line represents the baseline vertical bone defect (c). (d) At the same cross-sectional reconstruction, after changing the opacity, the distance from the defect crest to the most coronal point of augmented bone determined the vertical bone gain. (e) The horizontal dimension of the bone crest at T1 was measured on the superimposed cross-sectional scans by drawing a line parallel to and 3 mm away from the tangent to the residual bone crest.

To calculate the vertical bone height at T1, the corresponding cross-sectional reconstruction was used, adjusting the opacity to 0% for T0 and 100% for T1. The distance from the defect crest to the most coronal point of the augmented bone was determined (Figure 3d).

Subsequently, the following variables were obtained:

- Absolute vertical bone gain (aVBG—mm): The amount of bone gained in millimetres, regardless of baseline vertical bone defect.
- Relative vertical bone gain (rVBG—%): The percentage of VBG in relation to the baseline bone defect.

To ensure examiner calibration, all linear measurements were performed twice on 10 CBCT reconstructions, with a minimum interval of two weeks between assessments. An intra-class correlation coefficient (ICC) of 0.991 (95% CI: 0.982–0.996) was achieved.

2.3.3 | Horizontal Bone Gain

The HBG at T1 was measured on the same cross-sectional CBCT reconstruction previously described. The measurement was performed using a line intersecting the buccal and lingual/palatal edges of the regenerated bone area, drawn parallel to the tangent of the residual bone crest at a distance of 3 mm from the crest (Figure 3e).

2.3.4 | Regenerated Bone Volume and Effective Regeneration Rate

The superimposed CBCTs reconstructions were transformed into 3D models employing a threshold segmentation range between 400 and 1500 (Figure 4a,b). Then, the region of interest (ROI) was determined based on the following landmarks:

a. Coronal border: The most coronal portion of the PTFE mesh.
b. Apical border: In the anterior maxilla, this referred to the floor of the nasal cavity; in the posterior maxilla, to the floor of the maxillary sinus; and in the mandible, to the inferior border of the body of the mandible.
c. Lateral borders: The models were segmented 2 mm mesially and distally from the borders of the PTFE mesh.

The ROI volumes (mm^3) were obtained using the quantification and segment statistics tools. Bone volume was established as the difference in volume before and after regeneration. First, the augmented bone volume (ABV) was determined, including all the regenerated area to the PTFE mesh. Then, the RBV was

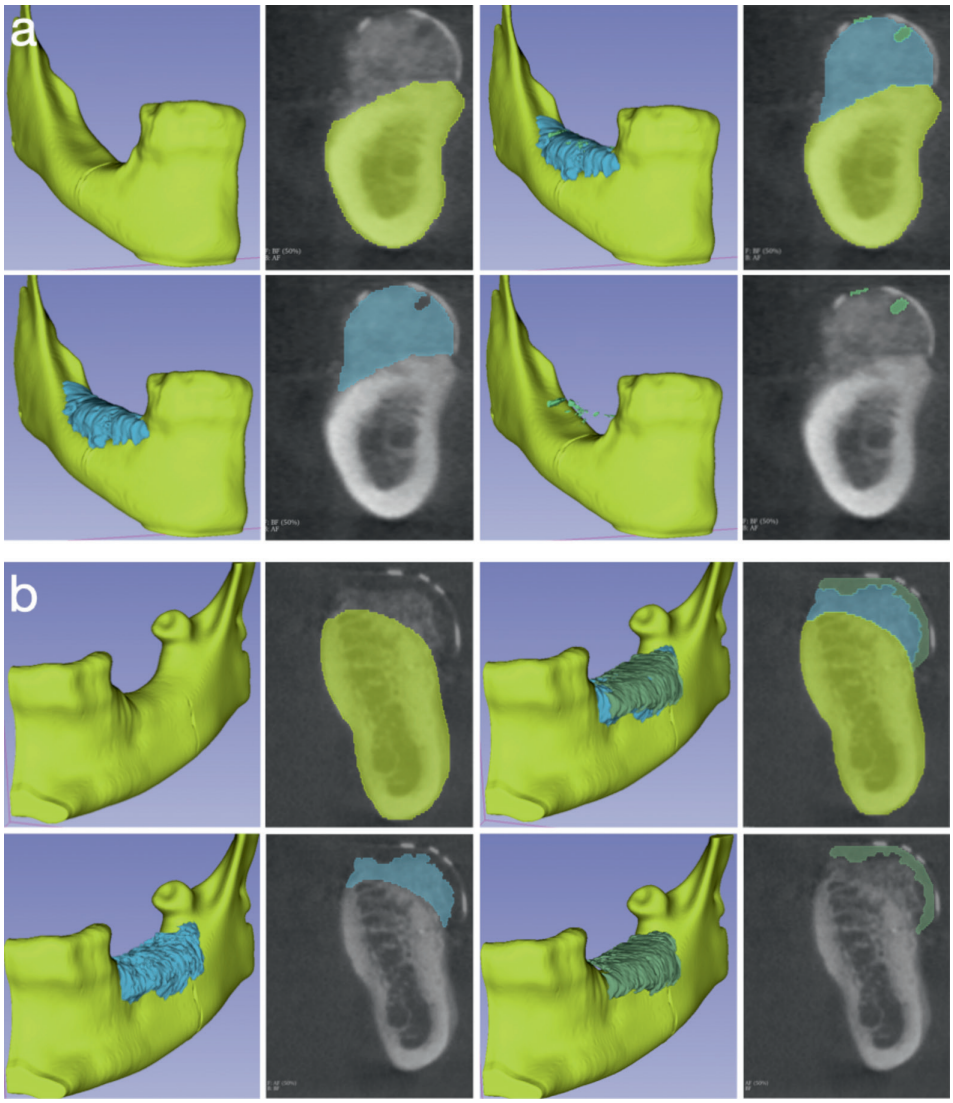

FIGURE 4 | Enhanced STL models and superimposed images of cone beam computed tomography (CBCT) from two surgical sites: One (a) belonging to the PTFE + CM group and the other (b) to the PTFE group. The yellow volumes and areas represent the mandibular segment before regeneration. The blue volumes and areas depict the regenerated bone volume at 9 months, derived from the difference resulting from the superimposition of the pre- and post-regeneration segments. The green volumes and areas indicate the lacking bone volume, primarily represented by the pseudo-periosteum.

obtained by measuring only the mineralized bone tissue, excluding the PTFE mesh and pseudo-periosteum (non-mineralized tissue) through manual selection on cross-sectional reconstructions using an eraser tool. The difference between ABV and RBV was defined as lacking bone volume (LBV). Finally, the ERR was calculated, that is, the percentage of RBV relative to ABV (RBV/ABV*100). All measurements were performed by an independent and blind examiner (TGA).

2.3.5 | Incidence of Complications

The incidence of complications was assessed during surgery and during the 9-month post-operative follow-up and classified according to Fontana et al. (2011). Specifically, surgical complications were divided into:

a. damage to the flap;
b. neurological complications;
c. vascular complications.

Healing complications were assessed during postoperative follow-up and classified as follows:

- Class I: Small mesh exposure (≤ 3 mm) without purulent exudate.
- Class II: Wide mesh exposure (> 3 mm) without purulent exudate.
- Class III: Exposure of the mesh with purulent exudate.
- Class IV: Abscess formation without exposure of the mesh.

The incidence of complications during implant placement into the augmented bone, such as fracture or displacement of the newly formed ridge, was also evaluated.

2.3.6 | Pseudo-Periosteum Type

The pseudo-periosteum thickness was clinically assessed at T1. Pseudo-periosteum was defined as the connective tissue between the regenerated bone and the PTFE mesh (Cucchi et al. 2019). The thickness of the pseudo-periosteum was measured in the mesial, middle and distal part of the grafted area with the aid of a periodontal probe (Figure 2h). The thickest measurement obtained was later used to classify the site according to Cucchi et al. (2019) into:

- Type 1: No pseudo-periosteum or a layer of soft tissue thinner than 1 mm.
- Type 2: A regular soft tissue layer between 1 and 2 mm.
- Type 3: An irregular layer of soft tissue and/or a layer thicker than 2 mm.

2.3.7 | Bone Density

Clinical bone density was determined at T1 by assessing the resistance of the newly formed bone to probe penetration, as described by Cucchi et al. (2017). The evaluation was conducted by a single examiner (IU) who tested the upper part of the ridge vertically and the buccal side horizontally applying a calibrated probing force of 30 g (Cucchi et al. 2017). Clinical bone density was categorised into three classes:

1. High density: Absence of probe penetration into the newly formed bone.
2. Medium density: Partial penetration of the probe into the newly formed bone.
3. Low density: Total penetration of the probe into the newly formed bone.

2.3.8 | Implant Placement and Need for Additional Bone Augmentation

The CBCT images were transferred into an imaging software (DTX Studio, Nobel BioCare, Zurich, Switzerland). Implants were digitally placed following the proper three-dimensional position with a 1.5 mm shadow used as safety margin (Figure S1). After that, the presence/absence of available bone around the implant was determined at both buccal and lingual aspects, 1, 3 and 5 mm apically from the implant shoulder, by a blinded examiner (AF), as described previously (Fok, Pelekos, and Tonetti 2020). Additional bone augmentation was deemed necessary if less than 1.5 mm-thick buccal or palatal/lingual walls were observed on CBCT reconstructions. The need for additional bone augmentation was subsequently verified clinically after implant placement.

2.4 | Sample Size

To date, no other clinical study has compared the same surgical techniques. Therefore, the publication of Cucchi et al. (2017) was used as reference. The authors reported a VBG of 4.2 ± 1 mm in the d-PTFE mesh group and 4.1 ± 1 mm in the Ti-mesh covered by a cross-linked collagen membrane (Cucchi et al. 2017). The null hypothesis (H0) proposed that PTFE alone was inferior to the PTFE + CM technique in terms of absolute VBG (primary outcome), whereas the research hypothesis (H1) stated that PTFE alone (test group) was not inferior to PTFE + CM (control group) in terms of absolute VBG (primary outcome), with the non-inferiority margin set at 1.1 mm. If the absolute VBG of PTFE alone was equal or higher than the absolute VBG of PTFE + CM minus 1.1 mm, the research hypothesis would be confirmed.

Using an online sample size calculator (Sealed Envelope 2012), it was determined that a minimum of 13 patients per group (total of 26 patients) would be required to detect a difference of 1.1 mm (non-inferiority margin) in absolute VBG between the groups, assuming a standard deviation of 1 mm, a significance level of $\alpha = 0.025$ (one-sided) and a power of 80%. To account for potential dropouts, the sample size was increased to 30 patients.

2.5 | Randomization and Blinding

The study director, responsible for the random assignment of patients to treatment groups post-enrolment, remained uninvolved in clinical interventions or study measurements. A computer-generated table, accessible solely to the study director, facilitated random assignment. An opaque envelope, concealing assignment to either group, was only opened and revealed to the surgeon after the PTFE mesh was stabilised. Patients and radiographical examiners were mutually masked. Similarly, the study analyst remained unaware of group allocation. Data from groups labelled PTFE and PTFE + CM were received by the analyst, who then provided two 90% CIs for the differences (PTFE minus PTFE + CM and vice versa). Masking persisted until the study was concluded, maintaining the integrity of the corrected difference.

2.6 | Statistical Analysis

Descriptive statistics including mean, standard deviation (SD), median and interquartile range (IQR) were reported for continuous variables. For categorical variables, absolute and relative frequencies were applied. The non-inferiority analysis was performed for absolute bone gain (primary endpoint) using a one-sided 95% confidence interval (CI) approach and a non-inferiority limit of 1.1 mm. While for other bone regeneration outcomes (relative bone gain, HBG, RBV, LBV and ERR) and complications, non-inferiority analysis was performed using a one-sided 95% CI approach and a non-inferiority limit of 10%.

Superiority analyses were carried out to evaluate significant differences in terms of intervention group and all other variables. A Shapiro–Wilk normality test was carried out. Relative VBG did not follow a normal distribution. Therefore, both parametric and non-parametric approaches were applied accordingly. Linear regression models were estimated to assess the relationship between linear or volumetric measurements of bone gain

differences, obtained via CBCT, and independent factors and covariates, including treatment group, demographic profile and baseline dimensions. Univariate models were applied followed by multiple models to obtain adjusted beta coefficients and 95% CIs.

Relative bone gain was analysed by Mann–Whitney test to compare distributions between groups. Then, differences were analysed under different strata of independent factors. Logistic regression models were estimated to analyse the outcomes 'bone density' and 'pseudo-periosteum classification', providing raw and adjusted odds ratios (ORs) to assess the association with the independent variables. All statistical analyses were carried out considering the patient as a statistical unit, using SPSS 15.0 Modeller software (IBM). The level of significance adopted in the tests was set at 5%.

3 | Results

3.1 | Study Population

A total of 30 patients (21 females; mean age 51.2 ± 10.6 years) exhibiting 30 defects completed the study and were available for the analysis. No dropouts were reported. In total, nine sites in the posterior mandible, four in the posterior maxilla, one in the anterior mandible and one in the anterior maxilla were treated and evaluated in the PTFE group. Six sites in the posterior mandible, two in the posterior maxilla, one in the anterior mandible and six in the anterior maxilla were assessed in the PTFE + CM group. The baseline vertical defect was 5.59 ± 2.11 mm in the PTFE-alone group and 4.75 ± 2.95 mm in the PTFE + CM group. The corresponding baseline anteroposterior defect extension was 20.07 ± 7.63 mm and 20.07 ± 6.67 mm, respectively.

Statistical tests performed to evaluate the homogeneity between the relevant demographic characteristics between the groups at baseline are shown in Table 1. Statistical significance was observed solely in relation to the mean age parameter, with the PTFE-alone group exhibiting a higher average age than the PTFE + CM group (55.1 ± 9.2 years vs. 47.3 ± 10.8 years, respectively; $p = 0.041$).

TABLE 1 | Demographic and intervention characteristics across the two study groups.

Characteristics	PTFE + CM ($n = 15$)	PTFE alone ($n = 15$)	p
Patient level			
Gender; *n* (%)			
Female	11 (73.3%)	10 (66.7%)	1.000 (Fis)
Male	4 (26.7%)	5 (33.3%)	
Age; (years ± SD)	47.3 ± 10.8	55.1 ± 9.2	0.041 (MW)*
Site level			
Arch; *n* (%)			
Maxilla	8 (53.3%)	5 (33.3%)	0.269 (Chi^2)
Mandible	7 (46.7%)	10 (66.7%)	
Area; *n* (%)			
Anterior	7 (46.7%)	3 (20.0%)	0.121 (Chi^2)
Posterior	8 (53.3%)	12 (80.0%)	
KG in the crest; *n* (%)			
Absent	5 (33.3%)	9 (60.0%)	0.143 (Chi^2)
Present	10 (66.7%)	6 (40.0%)	
Defect dimensions; (mm ± SD)			
Vertical defect size	4.75 ± 2.95	5.59 ± 2.11	0.137 (MW)
Anteroposterior size	20.07 ± 6.67	20.07 ± 7.63	0.902 (MW)

Abbreviations: Chi^2, chi-square test; Fis, Fischer's exact test; KG, keratinized gingiva; MW, Mann–Whitney test; ns, not significant.
*$p < 0.05$.

3.2 | Absolute and Relative Vertical Bone Gain

Linear and volumetric measurements of regenerated bone are shown in Table 2. The absolute VBG was 4.47 ± 2.05 mm in the PTFE group and 4.11 ± 2.69 mm in the PTFE + CM group. Non-inferiority was not shown (Figure 5a); however, superiority analysis revealed that these differences were not statistically significant ($p = 0.680$). A simple linear regression identified that baseline vertical defect size significantly influenced absolute VBG ($p < 0.001$; Table S1), but no effect from the treatment group was detected. Specifically, each 1 mm increase in baseline defect size correlated with an additional 0.93 mm gain. The anteroposterior defect size showed a strong positive correlation with absolute VBG ($p = 0.05$). Adjusting for age and baseline vertical defect size, the multiple regression model estimated no significant difference between the groups ($p = 0.136$; Table S1).

The relative VBG between the PTFE group and the PTFE + CM group was 79.2% ± 16.6% vs. 85.8% ± 10.6%, respectively (Table 2). Non-inferiority was not shown (Figure S2), but superiority analysis demonstrated that these differences were not statistically significant ($p = 0.436$). The defect size, absolute and relative bone gain according to baseline defect size (< or ≥ 5 mm) are illustrated in Figure S3.

3.3 | Horizontal Bone Gain

Both treatments resulted in comparable HBG values at 9 months, with 10.34 ± 2.16 mm in the PTFE group and 9.67 ± 1.50 mm in the PTFE + CM group ($p = 0.338$; Table 2). Non-inferiority was shown between the two treatments (Figure S2). The simple and multiple linear regression models have established that the area where the defect was located was associated with HBG in both ($p = 0.020$ and $p = 0.057$, Table S3), demonstrating a larger bone gain in the posterior teeth. Defects in younger patients gained a larger amount than in older ones ($p = 0.067$).

TABLE 2 | Linear/volumetric bone measurements and clinical outcomes in the two study groups after 9 months of healing.

Outcome	PTFE + CM ($n = 15$)	PTFE alone ($n = 15$)	p
Linear bone measurements			
Absolute vertical bone gain; mm ± SD	4.11 ± 2.69	4.47 ± 2.05	0.680 (simple LR) 0.136 (multiple LR)
Relative vertical bone gain; % ± SD	85.8 ± 10.6	79.2 ± 16.6	0.436 (MW)
Horizontal bone gain; mm ± SD	9.67 ± 1.50	10.34 ± 2.16	0.338 (simple LR) 0.473 (multiple LR)
Volumetric bone measurements			
Augmented bone volume; (mm^3 ± SD)	1595.3 ± 752.8	2229.8 ± 980	0.057 (simple LR) 0.083 (multiple LR)
Regenerated bone volume; (mm^3 ± SD)	1201.3 ± 719	1649.1 ± 1066.6	0.188 (simple LR) 0.266 (multiple LR)
Lacking bone volume; (mm^3 ± SD)	394 ± 229.4	580.7 ± 264.8	0.048 (simple LR)* 0.035 (multiple LR)*
Effective regeneration rate; (% ± SD)	72.3 ± 16.4	69.3 ± 17.9	0.630 (simple LR) 0.531(multiple LR)
Complications; *n* (%)			
Yes	1 (6.7%)	1 (6.7%)	1.000 (Fis)
No	14 (93.3%)	14 (93.3%)	
Pseudo-periosteum			
Type 1	11 (73.3%)	4 (26.7%)	0.014 (simple LR)* 0.057 (multiple LR)
Type 2	4 (26.7%)	10 (66.7%)	
Type 3	0 (0%)	1 (6.7%)	
Bone density			
High	6 (40.0%)	5 (33.3%)	0.705 (simple LR) 0.294 (multiple LR)
Medium	9 (60.0%)	9 (60.0%)	
Low	0 (0%)	1 (6.7%)	
Need for additional augmentation			
Yes	0 (0%)	0 (0%)	1.000 (Fis)
No	15 (100%)	15 (100%)	

Abbreviations: Chi^2, chi-square test; Fis, Fischer's exact test; KG, keratinized gingiva; LR, linear regression models; MW, Mann–Whitney test; ns, not significant.
*$p < 0.05$.

3.4 | Regenerated Bone Volume

3.4.1 | Augmented Bone Volume

The mean ABV was 2229.8 ± 980 mm^3 in the PTFE group and 1595.3 ± 752.8 mm^3 in the PTFE + CM group ($p = 0.057$; Table 2; Figure S4). Both the simple and multiple linear regression models identified no significant association between any of the variables analysed and ABV (Table S4).

3.4.2 | Regenerated Bone Volume

Mean RBV was 1649.1 ± 1066.6 mm^3 in the PTFE group and 1201.3 ± 719.0 mm^3 in the PTFE + CM group. Non-inferiority was not shown (Figure S2), but superiority analysis demonstrated no statistically significant differences between the two groups ($p = 0.188$; Table 2; Figure S4). None of the factors analysed in either the simple or multiple linear regression models showed a significant association with RBV (Table S5).

3.4.3 | Lacking Bone Volume

Mean LBV was 580.7 ± 264.8 mm^3 in the PTFE group and 394.0 ± 229.4 mm^3 in the PTFE + CM group. Non-inferiority was not demonstrated (Figure S2), and superiority analysis revealed that these differences were statistically significant ($p = 0.048$; Table 2; Figure S4). These results were confirmed in the multiple linear regression analysis ($p = 0.035$; Table S6).

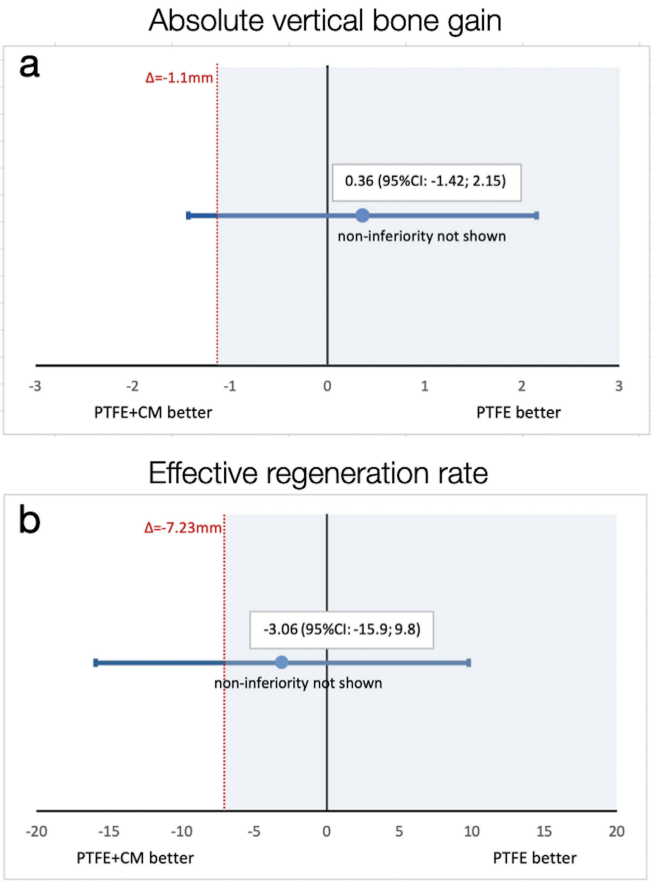

FIGURE 5 | Non-inferiority plots: Error bars indicated one-sided 95% confidence intervals of the mean values between the PTFE and PTFE+CM groups (PTFE minus PTFE + CM). The red broken line delineates the difference in the score shows the non-inferiority margin (delta), set at 10%; tinted area indicates the zone of non-inferiority. (a) Absolute vertical bone gain: The CI includes Δ; therefore, non-inferiority has not been shown ($-1.43 \leq -1.10$). (b) Effective regeneration ratio: The CI includes Δ; therefore, non-inferiority has not been shown ($-15.9 \leq -7.23$).

3.4.4 | Effective Regeneration Rate

ERR was 69.3% ± 17.9% in the PTFE group and 72.3% ± 16.4% in the PTFE + CM group (Table 2). Non-inferiority was not shown (Figure 5b); however, superiority analysis revealed that these differences were not statistically significant ($p = 0.630$). The effect estimates from both the simple and multiple linear regression models showed no significant association between any of the variables considered and ERR (Table S7).

3.5 | Complications

There was only one healing complication in each group, resulting in a similar overall incidence of complications (6.7%, 95% CI: 0.8, 22.1%; $p = 1$; Table 2). They were Class I (mesh exposure 6 months after surgery) and Class IV (infectious event 3 weeks post-intervention) in the PTFE and PTFE + CM groups, respectively. Regarding overall complications, the estimated mean difference was 0.00 (95% CI −0.19, 0.19) and non-inferiority was not shown ($0.19 \geq 0.10$). Considering the classification of complications, non-inferiority was shown for infections but not for exposures (Figure S2).

For the patient with site infection in the PTFE + CM group, a comprehensive surgical protocol was implemented. This included elevating a flap, cleaning the site with chlorhexidine-based irrigations, removal of the infected graft using a curette and applying a compress of 200 mg doxycycline putty for 1 min (Urban et al. 2023). Subsequently, the surgical site was covered with a new CM, and the wound was closed by primary intention. In the PTFE group patient, the PTFE mesh was excised, the granulation tissue and non-integrated graft particles were removed, and a new native CM was placed to cover the surgical site. No flap/vascular/neurological complications occurred during the first surgery or during implant placement.

3.6 | Pseudo-Periosteum

The dimensions of the pseudo-periosteum in the mesial, middle, and distal sites, as well as overall, are shown in Figure S5. Type-1 and type-2 pseudo-periosteum were observed in 11 and 4 sites in the PTFE + CM group, respectively. In the PTFE group, a type-1 pseudo-periosteum was observed in 4 sites; 10 sites and 1 site presented, however, a type-2 and type-3 pseudo-periosteum, respectively (Table 2). The results of a simple linear regression model revealed that the addition of the collagen membrane represented the only factor significantly associated with a higher probability of developing a type-1 pseudo-periosteum at 9 months after surgery (OR = 7.56; 95% CI: 1.50–38.2; $p = 0.014$). Multiple logistic regression model,

adjusted for age and location of defect, confirmed the result of the univariate analysis, demonstrating that defects treated with CM showed an increased probability of having a type-1 pseudo-periosteum (OR = 5.50; 95% CI: 0.95–31.9; $p = 0.057$; Table S8).

3.7 | Bone Density

High bone density was reported in 40% and 33.3% of sites in the PTFE and PTFE + CM groups, respectively, while 60% of sites in both groups exhibited medium bone density. Low bone density was observed only in one site within the PTFE group (6.7%; Table 2). A simple linear regression analysis identified a significant association between the probability of high bone density and mandible sites ($p = 0.014$). Subsequent multiple model estimates confirmed these findings, indicating a significantly higher probability of high bone density in the mandible (OR = 17.1, $p = 0.014$; Table S9). Neither of the two treatment groups demonstrated a significant influence on the density of the newly formed bone (OR = 3.18, $p = 0.29$; Table S9).

3.8 | Implant Placement and Need for Additional Bone Augmentation

The volume of regenerated bone enabled a proper three-dimensional and prosthetically guided placement of the implants in all surgical sites of both the test and control groups (Table 2). In fact, no bone augmentation procedure was required at any site, as all implant sites exhibited a bone wall thickness ≥ 1.5 mm in both the buccal and lingual/palatal aspects (Figures 1, 2 and S1).

4 | Discussion

The present study aimed to assess the non-inferiority of PTFE mesh alone compared with PTFE mesh covered with a CM in VRA procedures, with absolute VBG as the primary outcome. A non-inferiority design was selected due to the potential cost associated with the use of collagen membranes. However, perforated PTFE alone lacks the cell-selective properties of CM and, thus, the absence of CM could lead to worse outcomes. The non-inferiority margin was set at 1.1 mm, indicating that PTFE alone would be considered non-inferior to PTFE + CM if the results fell within this predefined margin. The results indicated that non-inferiority was demonstrated only for HBG. For absolute and relative VBG, RBV, LBV, ERR and healing complications, non-inferiority was not shown, as the CIs were too wide to support definitive conclusions. Additionally, superiority tests also revealed no significant differences between the two groups in terms of absolute and relative VBG, bone density, or ERRs. Nevertheless, a higher frequency of type-1 pseudo-periosteum and less LBV was associated with the PTFE + CM group.

It is crucial, though often overlooked, that articles addressing infrabony defects around teeth and vertical bony defects in edentulous sites should report both absolute bone gain and relative bone gain. In fact, the maximum regeneration potential of the procedure is dictated by the bone peak adjacent to the defect. For instance, a substantial defect (e.g., 10 mm) can result in an ABG of 8 mm and a consequent RBG of 80%, potentially leading to incomplete bone fill. Conversely, a 5 mm defect, when successfully filled with bone, would yield 100% RBG and complete filling, but with a maximum ABG of 5 mm. In the present study, due to randomization, the mean size of vertical defects at baseline tended to be slightly deeper in the PTFE alone group. This resulted in a lower aVBG in the PTFE + CM (4.47 ± 2.05 mm vs. 4.11 ± 2.69) but a higher rVBG (79.2% ± 16.6% vs. 85.8% ± 10.6%) possibly justified by the slightly shallower size of the defects before surgery. Indeed, a recent study from the present co-authors reported that defects < 5 mm exhibited greater rVBG and achieved 100% complete bone fill compared with defects sized 5–8 mm and > 8 mm when using a Ti-reinforced PTFE mesh in conjunction with a native CM in vertical ridge augmentation (Urban et al. 2021). Therefore, it may be recommended with a cluster randomization considering vertical defect depth or inclusion criteria that ensure the inclusion of defects with very similar vertical depth at baseline.

Analysing the individual complications, one complication was infectious (in the PTFE + CM group) and the other was mesh exposure (in the PTFE group). Furthermore, regarding the infectious complication, the comparability of performance between the two groups was further substantiated by the conclusive non-inferiority analysis. Concerning exposure, even though the number of events in the PTFE group was comparable to the number of infections in the PTFE + CM group (1/0 vs. 0/1), the same conclusion was not reached in the non-inferiority analysis. The difference in interpretation, despite similar counts, arises from the direction of the difference and how the CI relates to the non-inferiority margin. The difference in complication rates for both infection and exposure is calculated by subtracting the complication rate of the PTFE + CM group from that of the PTFE group. Because the PTFE + CM group had more infectious events, this results in a negative difference. Conversely, because the PTFE group had more exposures, this results in a positive difference. In addition to the direction of the differences (positive or negative), it is crucial to interpret the results based on the CI, which helps determine whether the observed difference is statistically significant and within the acceptable non-inferiority margin. Ultimately, the negative difference (−0.067) indicates fewer infections in the PTFE-alone group. Because the upper bound of the CI (0.076) is less than the non-inferiority margin (0.10), non-inferiority is demonstrated. However, the positive difference (0.067) indicates more exposures in the PTFE-alone group. Because the upper bound of the CI (0.209) exceeds the non-inferiority margin (0.10), non-inferiority is not confirmed. This underscores the importance of thoroughly considering the statistical context when interpreting such results, balancing the significance of the non-inferiority margin established based on statistical and clinical considerations, and subsequently translating these findings into clinical practice. In the two cases of infection and exposure, following the management protocols outlined earlier, there was no need for additional corrective surgery. In both instances, maintaining an adequate bone volume allowed for proper implant placement.

The present RCT showed a reduced incidence rate of post-operative complications when compared with findings reported in a study by Cucchi et al. and a recent systematic review (Alotaibi et al. 2023; Cucchi et al. 2017). In contrast, a meta-analysis by Urban et al., when analysing GBR procedures involving

non-absorbable meshes, reported 6.9% of complications, similar to the findings of the present study (Urban et al. 2019). Moreover, in a retrospective case series by the same author utilising the same type of PTFE mesh, the results (3%) proved to be even more favourable (Urban et al. 2021). The low incidence of complications in the current RCT can likely be attributed to the utilisation of a PTFE mesh distinguished by the presence of macropores, facilitating interaction between the periosteum of the flap and the regenerating tissue beneath the mesh. These technical features have enabled the amalgamation of titanium mesh characteristics (exhibiting macropores) with the antibacterial properties inherent in PTFE meshes (Barber et al. 2007; Gutta et al. 2009).

Regarding the type of pseudo-periosteum formation (Figure S6), the results presented a deviation from data reported by Cucchi et al. (2019), who compared conventional PTFE membranes and Ti-mesh plus CM (Cucchi et al. 2019). However, this discrepancy might arise from the different types of meshes utilised. In a more recent RCT, the results did not show any significant differences in pseudo-periosteal quality when customised Ti-mesh was covered or not by a cross-linked CM (Cucchi et al. 2021).

The present study revealed a higher prevalence of type 1 pseudo-periosteum in the PTFE + CM group, which could be attributed to the greater occlusivity provided by the addition of CM. The greater porosity of the PTFE mesh, in addition to promoting a better interaction of the periosteum with the regenerating tissue and facilitating better diffusion of bioactive substances for cell growth and regenerative processes, would also allow an easier passage of faster-growing epithelial and fibroblast cells from the flap. This could lead to overpopulation of the defect, limiting space for newly formed bone. The CM, by improving the occlusive properties of the PTFE mesh, appears to prevent the ingrowth of soft tissues while maintaining permeability to nutrients, ensuring the mineralization of the regenerated bone tissue. Additionally, the superior quality of the pseudo-periosteum observed in the PTFE + CM group could be attributed to the greater integration of the flap tissues with the collagen membrane, conferring greater microstability to the regenerating tissues beneath the meshes. Previous studies have suggested that the increase in thickness of the connective tissue beneath the meshes could derive from micromovements between the bone and the mesh (Shi et al. 2022; Wang and Boyapati 2006). These factors collectively contributed to a more complete understanding of the mechanisms that may have influenced pseudo-periosteal formation in the context of the present study.

The bone volume results are consistent with the previously discussed results of the linear clinical measurements and the type of pseudo-periosteum. Indeed, the ABV in the PTFE group showed a marginally significant advantage ($p = 0.057$), which, similar to the absolute VBG, could derive from the trend difference in the vertical dimension of the defect at baseline. However, the LBV was significantly greater in the PTFE group ($p = 0.048$), corresponding to the volume of pseudo-periosteum. It also exhibited greater type 2 and type 3 in the qualitative analysis and, consequently, a greater quantity of dense and non-mineralized connective tissue covering the RBV beneath the mesh.

Regarding bone density, the present RCT did not find a significant difference in bone density favoured by either of the two compared interventions. However, there was a greater likelihood of observing higher bone density in the mandibular sites, regardless of the surgical technique adopted. These results align with the findings of a recent study by Cucchi et al., which compared the clinical and histological outcomes of GBR procedures using Ti-mesh with and without CM (Cucchi et al. 2024). The study reported significantly higher rates of non-mineralized and dense connective tissue in maxillary sites, regardless of therapeutic modality. It can be deduced that bone density does not depend on the use of a CM but rather on the characteristics of the original basal bone, which influences those of the regenerated bone.

As the present RCT is the only study evaluating the efficacy of a perforated PTFE mesh together with a native CM, a direct comparison with previous studies was not possible. This unique feature highlights a limitation in drawing direct parallels with existing research on this topic. Another potential limitation of the present study arose from the different location of the analysed defects. Although a previous study suggested that the location of the defect might have minimal influence on the amount of bone gained (Urban et al. 2021), it is important to recognise that distinct anatomical features and limitations in different areas of the oral cavity might require various technical precautions, potentially influencing flap release manoeuvres. The short-term follow-up of this study cannot provide data on implant survival and peri-implant bone loss, crucial for evaluating the stability and long-term success of the intervention. Additionally, the measurement of the pseudo-periosteum with a periodontal probe may present some limitations. While recognising the potential measurement errors of 1 mm (Goodson et al. 1982) or 0.5 mm (Kingman et al. 1991) associated with the use of a periodontal probe to assess pocket depths, factors associated with tactile probing of these sites do not necessarily apply to directly assessing the periosteum thickness (Grossi et al. 1996). To minimise measurement variability, we implemented standardised protocols: all measurements were conducted by a single examiner using the same University of North Carolina (UNC) probe, with pre-study calibration for consistency, and performed under magnification (loupes). Finally, it must be emphasised that vertical ridge augmentation is a technique-sensitive procedure, and its success depends on the surgeon's experience; therefore, the external validity of the results of the present study may vary (Urban et al. 2023).

5 | Conclusions

The non-inferiority of PTFE mesh alone compared with PTFE mesh covered with a collagen membrane, in terms of absolute VBG, was not established. However, superiority analysis demonstrated that both techniques yielded comparable outcomes in terms of VBG, complication rates and bone density. Furthermore, the higher incidence of type 1 pseudo-periosteum and LBV in the PTFE + CM group suggests that the addition of a collagen membrane may help prevent soft tissue ingrowth.

Author Contributions

I.A.U. contributed to study conception and design, to data collection, analysis and interpretation, and to manuscript drafting and critical revising. A.R., M.S., D.R.D. and A.C. contributed to data interpretation, manuscript drafting and critical revising. D.R.D., Z.B., A.F. and T.G.A.

contributed to data collection. M.H.A.S. and Z.B. contributed to drafting and critically revising the manuscript. All the authors gave their final approval of the version to be published and agreed to be accountable for all aspects of the work.

Conflicts of Interest

Andrea Ravidà and Muhammad Saleh have consulting roles with Geistlich Pharma North America, while Istvan Urban has lectured for Geistlich Pharma and Osteogenics Biomedical, and Alessandro Cucchi has lectured for Geistlich Pharma, Osteogenics Biomedical, Biomax, Biotec, Zimvie, Sweden & Martina.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.