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Vertical ridge augmentation with Ti-reinforced dense polytetrafluoroethylene (d-PTFE) membranes or Ti-meshes and collagen membranes: 3-year results of a randomized clinical trial

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Abstract

Background: The present study aimed to evaluate hard and soft tissue parameters around implants placed in augmented posterior mandible, comparing Ti-reinforced d-PTFE membranes with Ti-meshes covered with collagen membranes, after 3 years of follow-up.

Materials and Methods: Forty eligible patients were randomly assigned to group A (Ti-reinforced d-PTFE membrane) or group B (mesh covered with collagen membrane) for vertical ridge augmentation (VRA) and simultaneous implants. Implants were evaluated using specific peri-implant parameters for bone and soft tissues: probing pocket depth (PPD), modified plaque index (mPI), bleeding on probing (BoP), modified gingival index (mGI), thickness of keratinized tissue (tKT), width of keratinized tissue (wKT), fornix depth (FD), peri-implant bone level (PBL), interproximal bone peaks (IBP), marginal bone loss (MBL), interproximal bone loss (IBL).

Results: A total of 28 patients with 79 implants were evaluated after 3 years of follow-up. The mean value of MBL was 0.70 mm (group A = 0.73 mm; group B = 0.71 mm), while mean IBL was 0.54 mm (group A = 0.64 mm; group B = 0.40 mm). The treatment with meshes resulted not inferior to PTFE and their clinical results appeared similar. A strong correlation between PBL and IBP was confirmed. Both study groups showed an increase of tKT and wKT values.

Conclusion: In the posterior mandible, VRA using both techniques provides stable PBLs up to 3 years. A correct soft tissue management and a strict professional oral hygiene protocol play a crucial role on peri-implant health over time.

KEYWORDS

alveolar bone atrophy, alveolar bone loss, alveolar ridge augmentation, bone regeneration, dental implant

Summary box

What Is Known

- Guided bone regeneration is a reliable technique for the reconstruction of vertical defect
- Only few randomized clinical trials have evaluated peri-implant bone levels after bone augmentation procedures; no studies reported peri-implant soft tissue parameters.

What this Study Adds

- The efficacy of both techniques evaluated for vertical ridge augmentation (VRA) and the stability of hard and soft tissues around implants were confirmed.
- An increase of keratinized tissue, both in thickness and in width, was observed during the 3 years of follow-up. The achievement of a good stability of bone levels after VRA in posterior mandible was also assessed.

1 | INTRODUCTION

Guided bone regeneration (GBR) is a surgical technique based on the application of barrier membranes, to create an adequate space for bone regeneration, in which the bone defect cannot be colonized by epithelial cells, but only by osteogenic and/or osteoprogenitor cells, coming from the bone tissue underneath the membrane.[1] Both resorbable and non-resorbable membranes can be used as barrier for GBR and when vertical ridge augmentation (VRA) is required by the clinical situation in order to guarantee the space making effect and to prevent membrane collapse: non-resorbable membranes are usually reinforced by a titanium frame, while collagen membranes are supported by titanium plates, screws or meshes.[2,3]

The efficiency and reliability of GBR for the reconstruction of vertical defects have been demonstrated in many studies in the literature[4–8] and according to a recent systematic review, GBR represents a predictable technique for VRA with a complication rate of 12.1%. Mean reported values of vertical bone gain after GBR ranged from 4.26 mm, when using resorbable membranes associated with space maintainers such as titanium mesh or osteosynthesis plates, to 4.42 mm, when using non-resorbable membranes. The aggregated mean implant survival was 98.95%, while the bone level changes from final to baseline were 0.99 mm for GBR with non-resorbable membranes and 0.58 mm with resorbable membranes.[9]

However, there are only a few randomized clinical trials in the literature reporting peri-implant bone levels (PBLs) and crestal bone loss after bone augmentation procedures.[5,10–12] There are no studies currently available which evaluate all the peri-implant soft tissue parameters, such as plaque index, fornix depth (FD), pocket depth, bleeding on probing, thickness and width of keratinized tissues after bone reconstruction procedures.[13] Indeed, reporting data regarding peri-implant bone and soft tissues is crucial to evaluate the behavior of alveolar bone after VRA using GBR over time.

The aims of this follow-up study were (i) to measure the marginal bone loss (MBL), (ii) to evaluate the soft tissue parameters, and (iii) to investigate any statistically significant differences of implants placed simultaneously at a VRA procedure with titanium (Ti)-reinforced dense polytetrafluoroethylene (d-PTFE) membranes compared with titanium (Ti)-meshes covered by cross-linked collagen membranes after 3 years of follow-up.

This is the report of a series presenting clinical and radiographic outcomes at 3-year follow up after functional loading. Previous publications reported the results of primary outcomes (complication rates and vertical bone gain),[8] secondary outcomes (histological and histomorphometric parameters)[14] and tertiary outcomes (peri-implant bone and soft-tissue parameters)[12] at 1-year follow up.

2 | MATERIALS AND METHODS

2.1 | Study design

The present study is reported according to the CONSORT statement (http://www.consort-statement.org). The study was conducted at the Unit of Oral and Maxillo-Facial Surgery, University of Bologna, Italy and was approved by the Ethical Committee of the St. Orsola-Malpighi Polyclinic (Protocol CMF 01/2013, Study code n. 30/2013/O/Disp). After a detailed explanation of the study protocol, all patients signed an informed consent for the experimental treatment and the processing of personal data. The investigation was conducted according to the principles in the Declaration of Helsinki (2014) guidelines for investigations involving human subjects. After enrollment, each patient received a unique identification number, in which all data were recorded accordingly. Patients had undergone bone augmentation and implant surgery between 2013 and 2015 according to the study protocol; subsequently, they received prosthetic rehabilitation between 2014 and 2017. Finally, follow-ups were carried out for a period of at least 3 years after functional loading.

The inclusion criteria for the study were reported in previous articles.[8,12,14] All patients showed a partial edentulism in posterior mandible with a vertical bone defect ≥2 mm, that requires a 3D bone augmentation in order to allow an implant-supported rehabilitation.

The sample size was calculated based on the primary outcome of the study protocol (surgical and healing complications). However, the primary endpoint of this follow-up study is the evaluation of specific peri-implant hard and soft tissue parameters.

Subsequently, 40 eligible patients were randomly assigned for treatment using either Ti-reinforced d-PTFE membrane (group A) or titanium mesh covered by cross-linked collagen membrane (group B). In both study groups, a simultaneous 3D prosthetically driven implant placement and a 50:50 mixture of autogenous bone and bone allograft were used. The random allocation of patients to each study group was based on a computer-generated sequence as simple randomization. Patient, clinicians and statistician were blinded to treatment allocation (surgeon was blinded until envelope opening). Therefore, the study was defined as double blind.

2.2 | Operative protocol

All the patients included in the present study received a well-established surgical and prosthetic protocol, as described in previous publications.[8] The first surgical step (T0) included the procedures of bone augmentation and implant placement. Surgical flaps were elevated and mobilized, then tapered implants (BT SAFE; Biotec SRL, Vicenza, Italy) were placed in the "ideal" position and axis: the protrusion of the most coronal portion of the implants from the alveolar ridge showed the amount of vertical bone regeneration. After cortical bone perforation, a mixture of 50% autogenous bone and 50% bone allograft (EnCore; Osteogenics Biomedical, Lubbock, Texas, USA) was created. According to the randomized sequence, the grafting material was used to fill a PTFE membrane (Cytoplast Ti-250XL; Osteogenics Biomedical) in Group A; or a Ti-mesh (Trinon Titanium; Karlsruhe, Germany) which was covered with a cross-linked collagen membrane (Osseoguard; Zimmer Biomet, Warsaw, Indiana, USA) in Group B. The barrier membrane was fixed using osteosynthesis mini-screws (Pro-fix Membrane Fixation Screws, Osteogenics Biomedical), then a double suture was used to ensure primary closure of the surgical wound using PTFE (Cytoplast sutures 250XL; Osteogenics Biomedical).

After 9 months (T1) the treated sites were reopened, the barrier membrane was removed, implants were uncovered, and healing screws were placed. If the amount of keratinized mucosa was less than 2 mm, soft tissue management was performed immediately. All the sites included in this follow-up study were treated with a subepithelial connective tissue graft (thickness 1–2 mm) from the lateral palate and/or the tuberosity area.

After about 3 months (T2) patients received the implant-supported fixed metal-ceramic restoration and were advised to follow both home oral hygiene procedures and a professional maintenance protocol. After 1 year (T3) and 3 years (T4), all clinical and radiographic parameters were collected according to the study protocol. In case of inflammation around implants (mucositis or peri-implantitis), an additional connective tissue graft was performed to reduce bacterial infiltration. (Figures 1–6)

2.3 | Follow-up and outcomes

All clinical and radiographic outcomes were collected by a blinded examiner, using a specific data collection form (CRF). The mean values resulting from the measurements were used for the statistical analysis.

The periapical radiographs were collected for each augmented site using a parallel technique. Close attention was paid to proper positioning of the receptor and x-ray tube to obtain radiographs with the same field of view, the same projection and angulation, and the least possible amount of distortion/deformation. If evidence of distortion, deformation, or other alterations was present, a new radiograph was taken to achieve an adequate image overlapping with previous images. All radiographs were scanned, digitized in JPG format, converted to 600 dpi resolution TIFF images, then analyzed to measure the values through an image analysis software (ImageJ 1.53a NIH) (Figures 7–10).

Implant success and survival rates were calculated according to the criteria suggested by Buser and colleagues in 1990[15] and modified by Zarb and Albrektsson in 1998,[16] which included: (i) no persistent pain, dysesthesia or paresthesia in the implant area; (ii) no peri-implant infection, with or without suppuration; (iii) no perceptible implant mobility; (iv) no persistent peri-implant bone resorption >1.5 mm during the first year of loading and >0.2 mm/year thereafter. Implants were considered "successful" when these criteria were satisfied, otherwise functioning implants were classified as "surviving."

The peri-implant bone and soft tissue parameters recorded were previously described in detail by Cucchi et al,[12] briefly the evaluation of surgical and healing complications was performed during postoperative visits, from T0 to T1. Vertical bone gain (VBG) was calculated as the difference between IBD (initial peri-implant bone defect), evaluated at T0, and FBD (final peri-implant bone defect), assessed at T1. After functional loading of implants (T2, T3, T4), the following peri-implant outcomes were measured as previously reported: probing pocket depth (PPD),[17] modified plaque index (mPI),[18] bleeding on probing (BoP),[19] modified gingival index (mGI),[20] thickness of keratinized tissue (tKT)[21] and width of keratinized tissue (wKT),[22,23] FD,[24,25] PBL, and interproximal bone peaks (IBP).[12] MBL was calculated from the difference between PBL at the follow-up (T3 and T4) and PBL at the baseline (T2). Interproximal bone loss (IBL) was similarly measured comparing IBP at the follow-ups (T3 and T4) with IBP at the baseline (T2).

2.4 | Statistical analysis

An Excel data collection form and data management system were used (Microsoft Excel 2011; Windows, ver. 14.0.0; Microsoft Corp., Redmond, WA, USA). All data were entered by a single blinded operator. Prior to entry, all data were evaluated in terms of accuracy and completeness: logical consistency was verified, and the ranges of quantitative data were computed. Data analysis was performed with STATA/IC software (StataCorp LLC, College Station, TX, USA).

This study was based on the hypothesis that Group B (titanium-meshes plus collagen membranes) would not be inferior to Group A (reinforced-PTFE membranes). The non-inferiority margin was set at 0.51 mm (delta—as largest difference that was clinically acceptable). Non-Inferiority test was performed for the PBL and IBP outcomes only (one-sided confidence interval approach). The null hypothesis is that the experimental treatment (Group B) is inferior to the standard treatment (Group A).

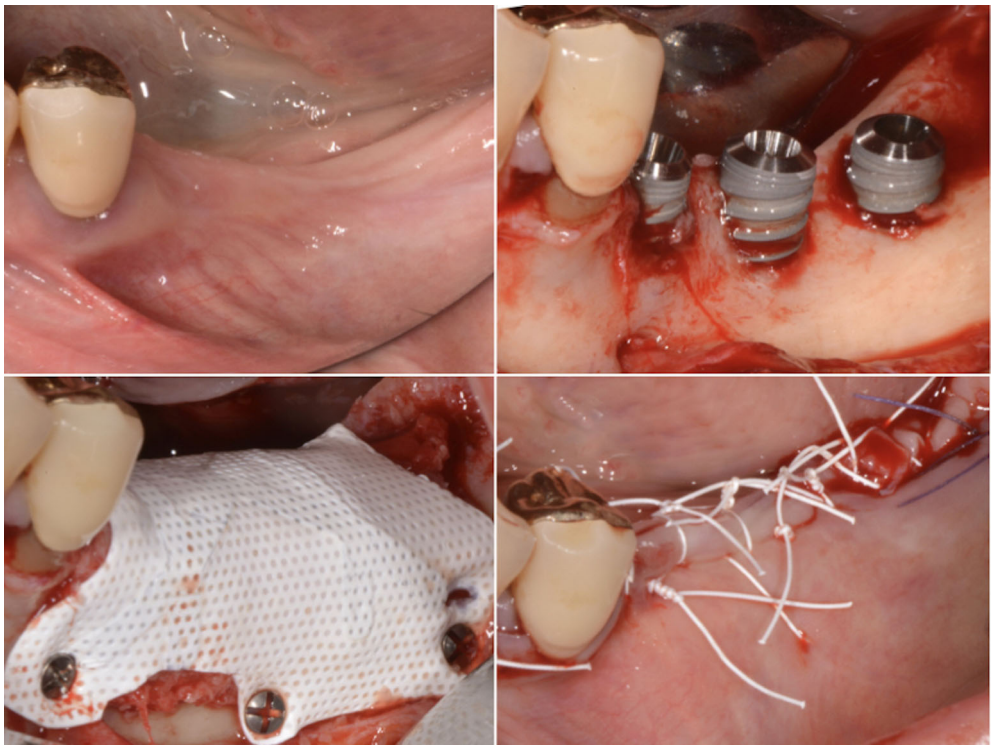

FIGURE 1 Clinical case (group A, T0): preoperative view; implants placement; bone augmentation procedure; primary wound closure.

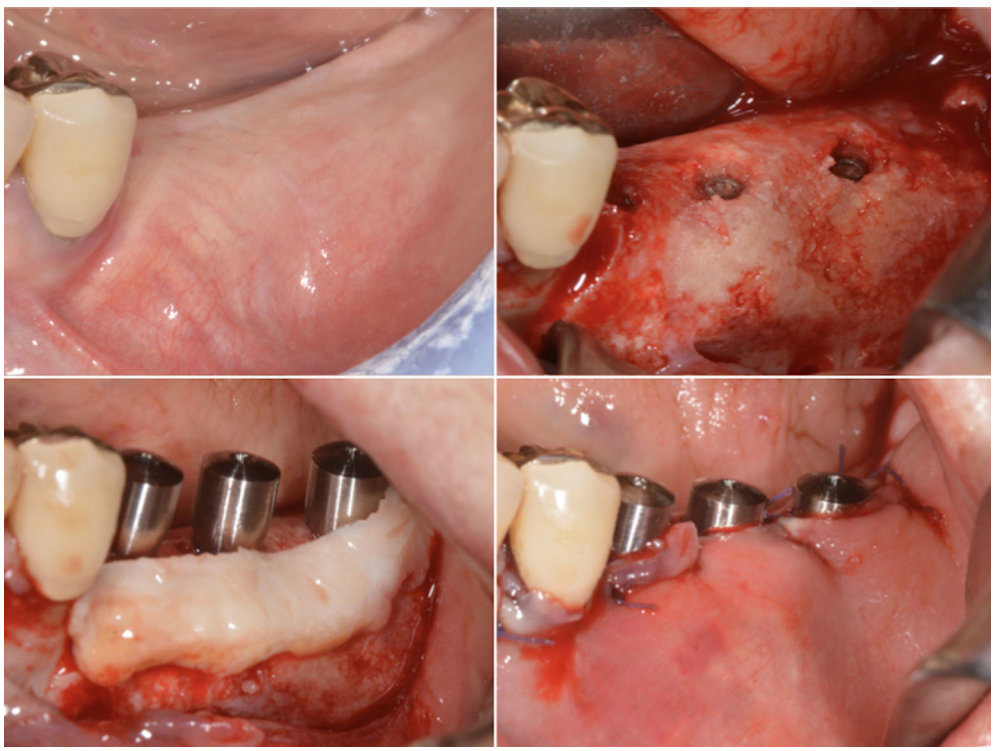

FIGURE 2 Clinical case (group A, T1): preoperative view; barrier membrane removal and implants uncovering; healing screws and connective tissue graft placement; primary wound closure.

A secondary statistical analysis was performed with a superiority approach on all variables. The null hypothesis is that the experimental treatment (Group B) was superior to the standard treatment (Group A). For each variable the following values were reported: the mean, median, standard deviation (SD), interquartile range (IQR) and the confidence intervals (CIs). Hypothesis of normality was tested with the Skewness/Kurtosis tests (normal distribution if p-value >0.05). The Statistic significance of the differences between the variables were evaluated by t-test, Wilcoxon rank sum test and Wilcoxon matched-pairs and signed-ranks test where necessary. The possible correlation between the different periodontal anatomical variables (PPD, wKT, tKT, and FD) and periodontal health parameters (BoP, mGI, and mPI) were investigated

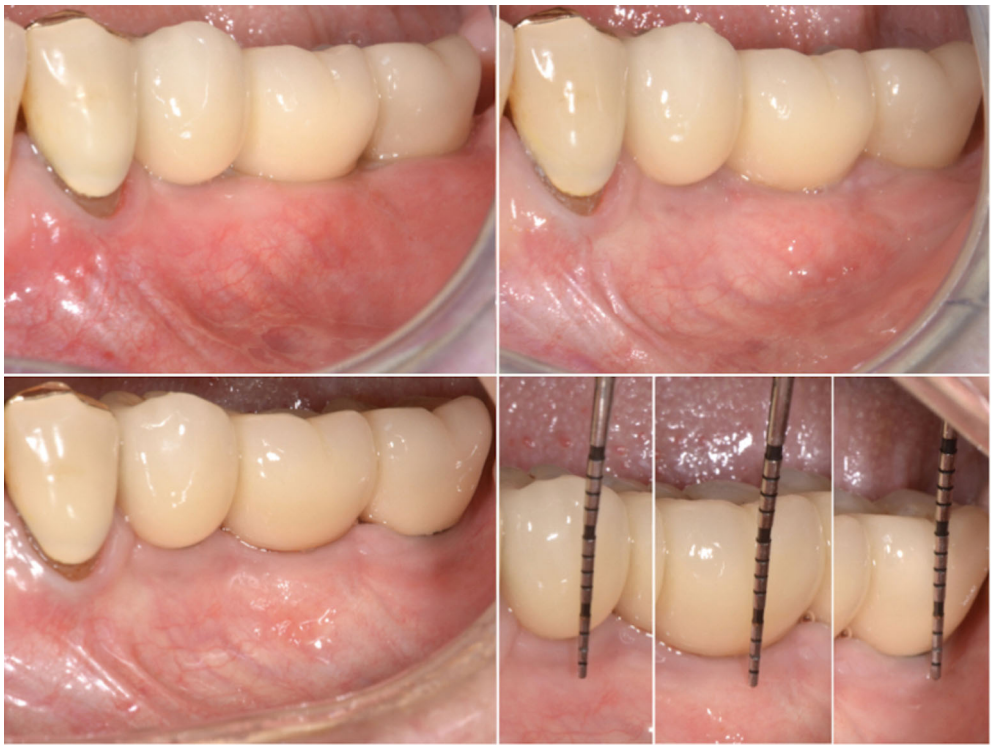

FIGURE 3 Clinical case (group A): implant-supported fixed metal-ceramic restoration at the baseline (T2); after 1 year of follow-up (T3); after 3 years of follow-up (T4); width of keratinized tissue (wKT) evaluation after 3 years of follow-up.

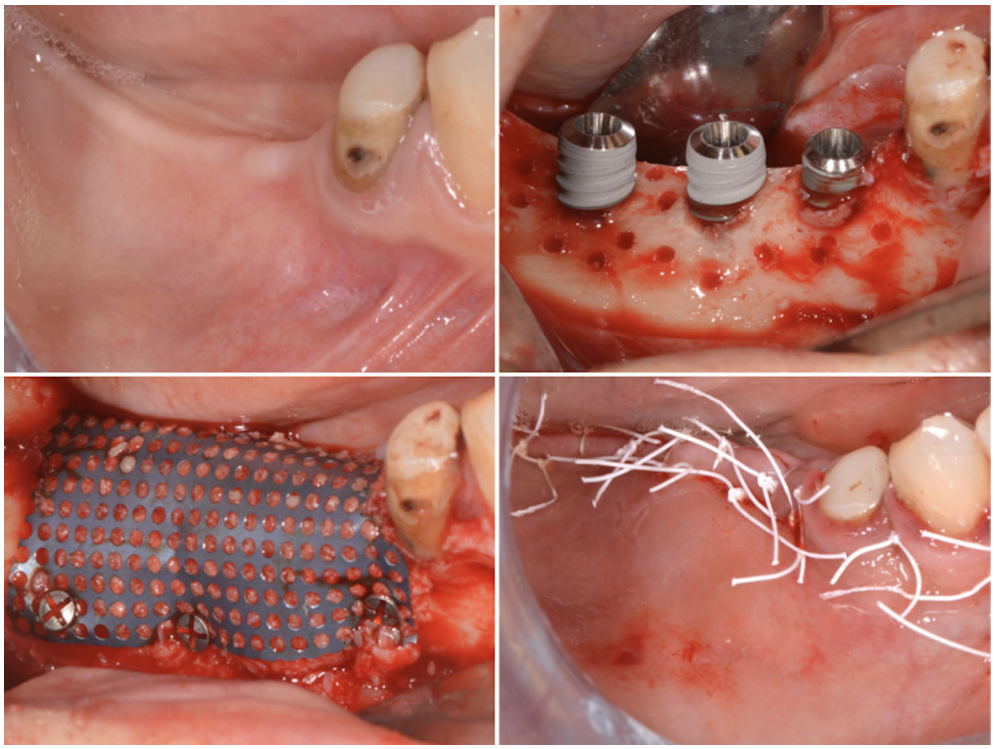

FIGURE 4 Clinical case (group B, T0): preoperative view; implants placement; bone augmentation procedure; primary wound closure.

by applying the Pearson's test. Spearman's correlation test was applied when the variables did not have a normal distribution or a non-linear relationship. Correlations were reported specifying the *p*-value and the Pearson (R) or Spearman (Rs) correlation coefficient.

A linear regression and predicting analysis were carried out to understand the PBL and IBP variation (dependent variable) according to the years of follow up (independent variable). Before carrying out the regression analysis, the following were verified:

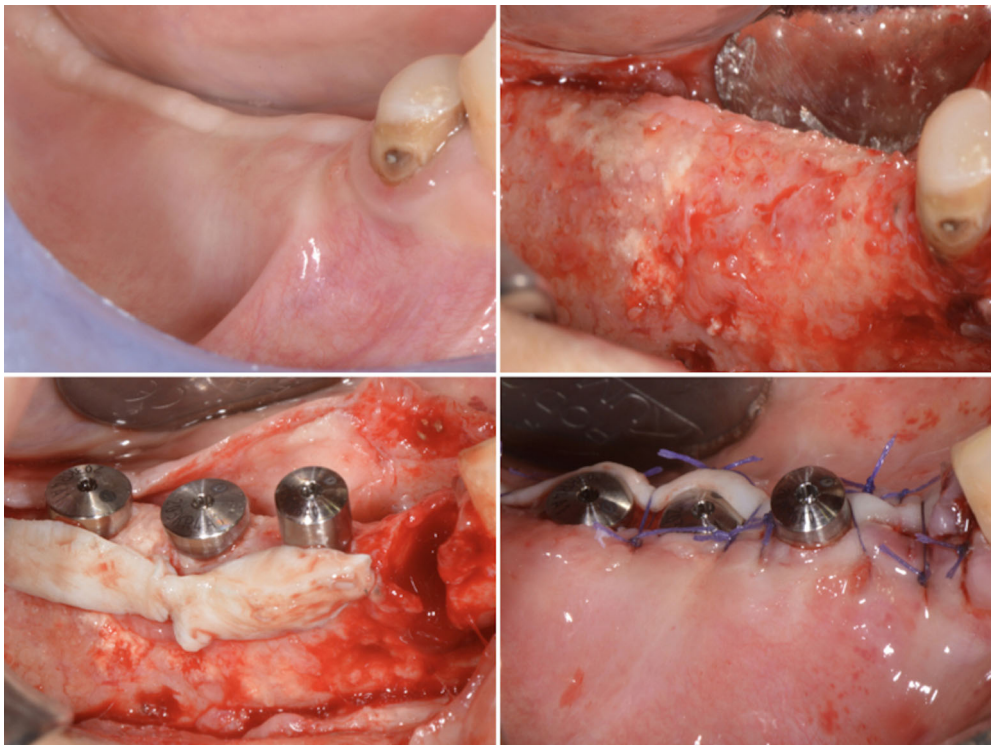

FIGURE 5 Clinical case (group B, T1): preoperative view; barrier membrane removal and implants uncovering; healing screws and connective tissue graft placement; primary wound closure.

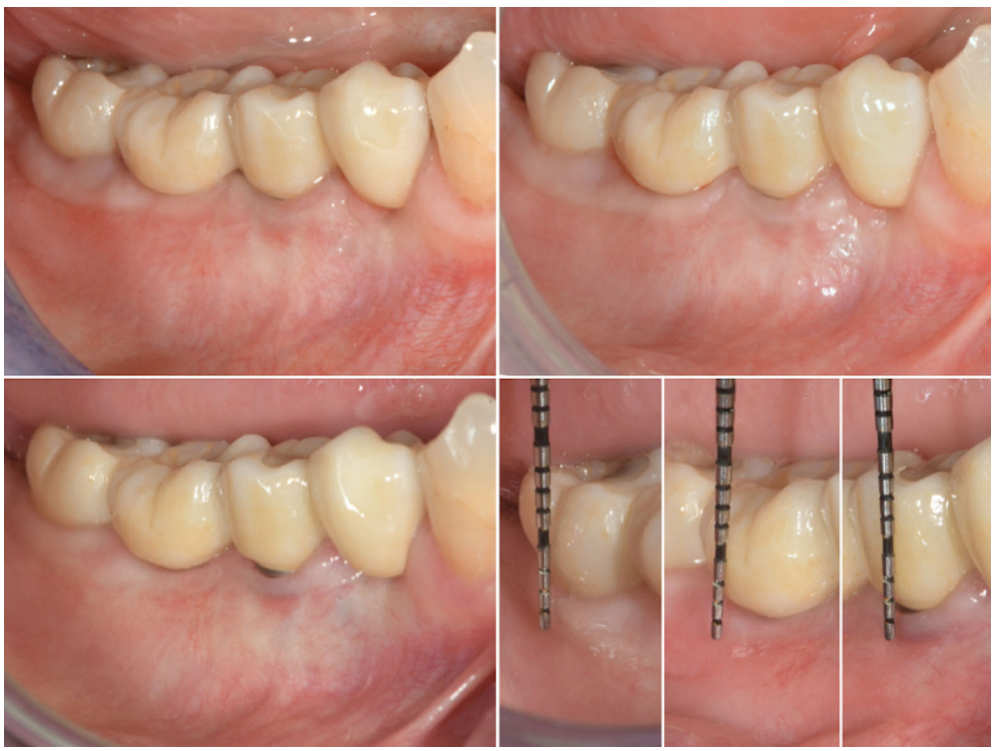

FIGURE 6 Clinical case (group B): implant-supported fixed metal-ceramic restoration at the baseline (T2); after 1 year of follow-up (T3); after 3 years of follow-up (T4); width of keratinized tissue (wKT) evaluation after 3 years of follow-up.

- The independence of observations using the Durbin-Watson statistic
- The linear relationship between the dependent and independent variables
- Absence of significant outliers
- Presence of homoscedasticity

For regression analysis the obtained *F*-value, adjusted R^2 and *p*-value were reported. The threshold value essential in determining the statistical significance, corresponds to a *p*-value <0.05 (5%). The statistician was blinded and external to working group.

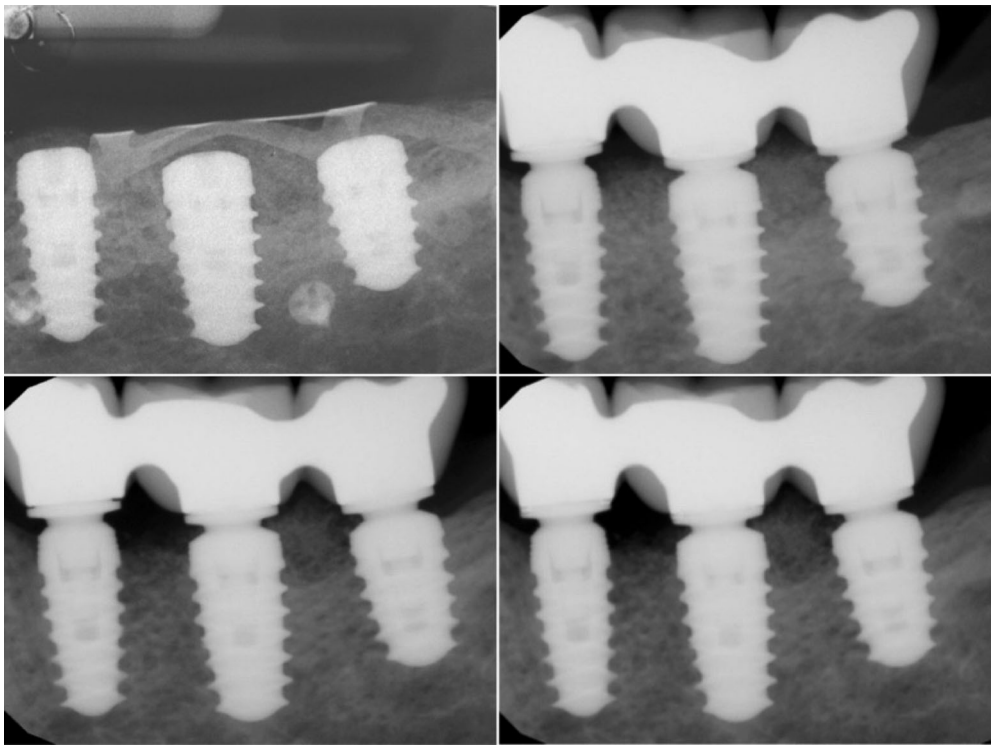

FIGURE 7 Radiographic follow-up using intraoral radiographs in a patient treated with Ti-reinforced d-PTFE membrane (group A): immediately after surgical step (T0); baseline (T2); 1 year of follow-up (T3); 3 years of follow-up (T4).

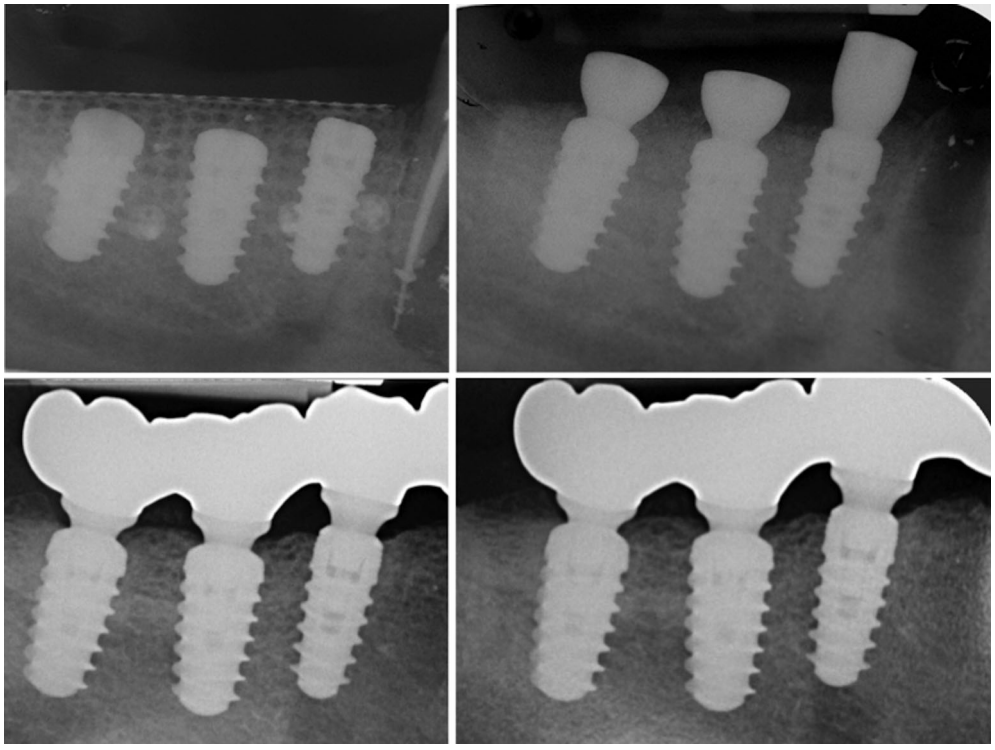

FIGURE 8 Radiographic follow-up using intraoral radiographs in a patient treated with titanium mesh covered by cross-linked collagen membrane (group B): immediately after surgical step (T0); healing screws before functional loading (T2); 1 year of follow-up (T3); 3 years of follow-up (T4).

3 | RESULTS

3.1 | Patients and implants

In total, 40 patients (13 males, 27 females; mean age 52 years) requiring implant-supported rehabilitation in a posterior atrophic mandible were treated by means of a bone augmentation procedure and simultaneous placement of 108 implants. Amongst the total number of patients, 35 had no complications during the entire study protocol with the definitive restoration of 96 implants.

During the follow-up period after functional loading (T2–T4), three patients dropped-out for personal reasons (job traveling or

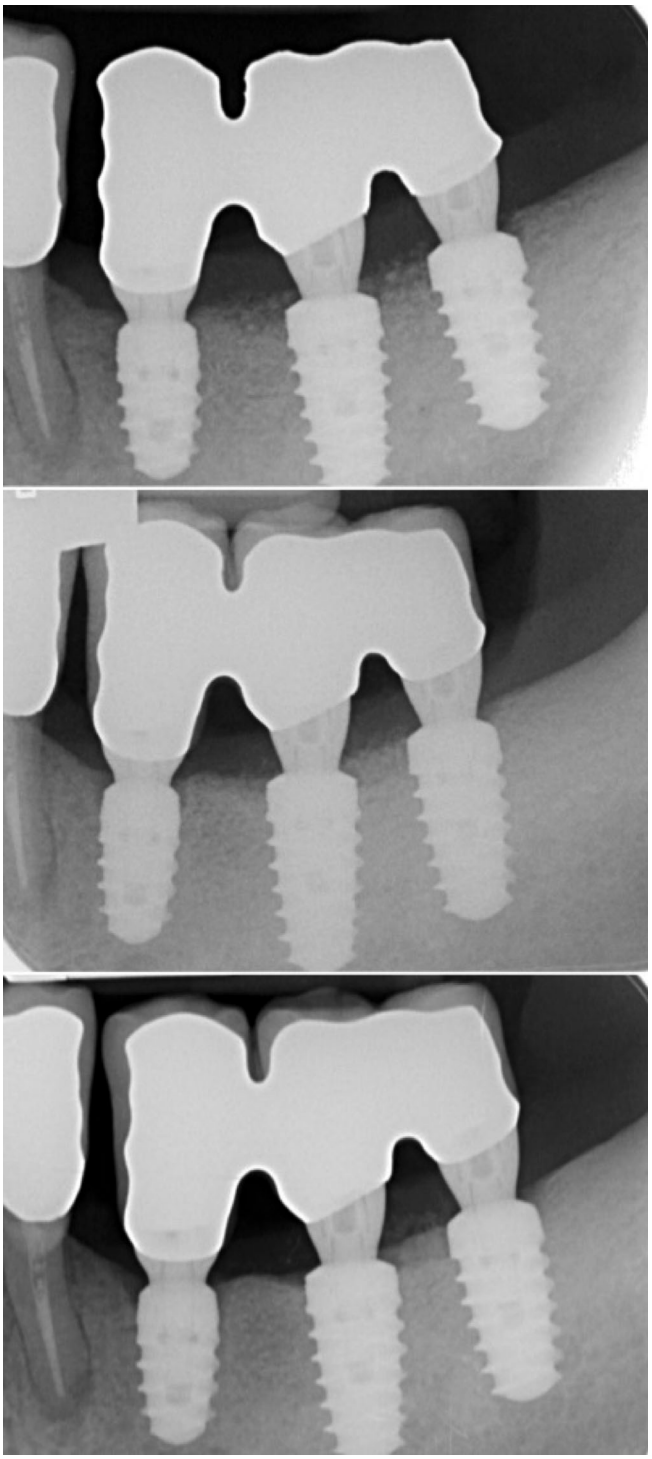

FIGURE 9 Radiographic follow-up using intraoral radiographs in a patient treated with Ti-reinforced d-PTFE membrane (group A): baseline (T2); 1 year of follow-up (T3); 3 years of follow-up (T4).

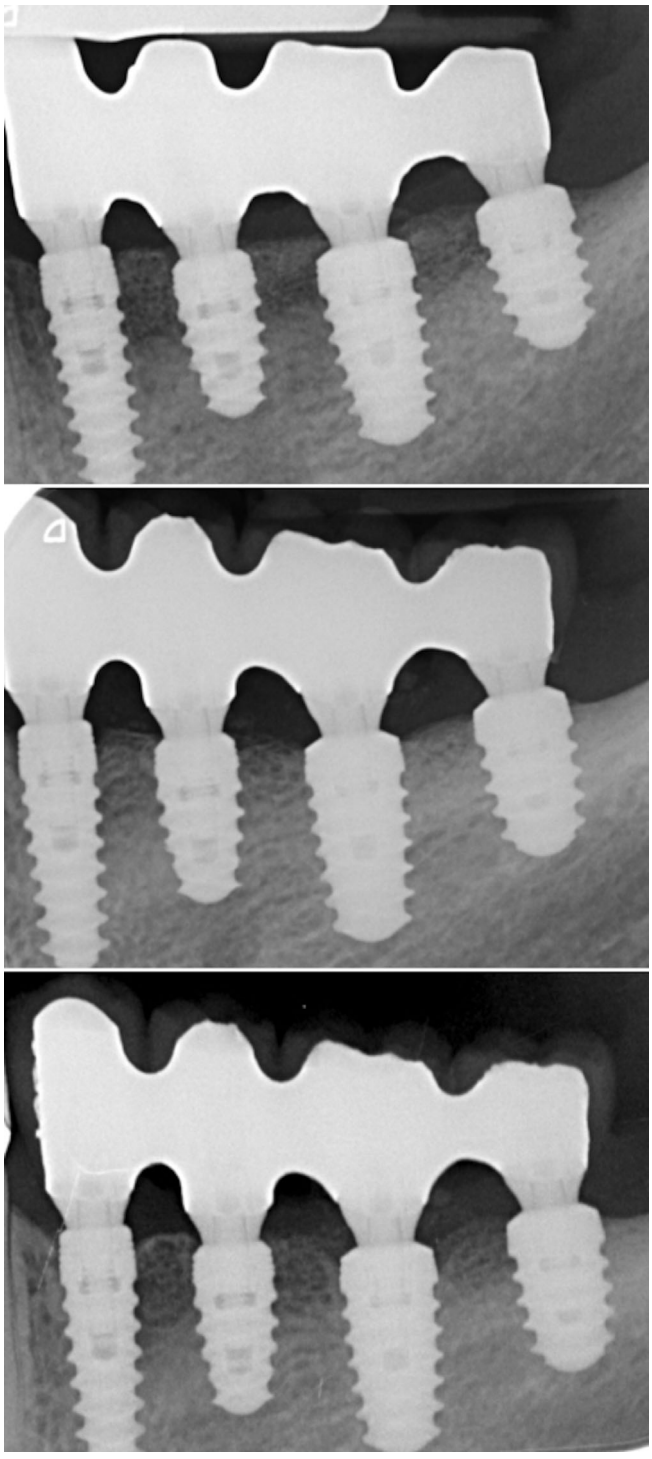

FIGURE 10 Radiographic follow-up using intraoral radiographs in a patient treated with titanium mesh covered by cross-linked collagen membrane (group B): baseline (T2); 1 year of follow-up (T3); 3 years of follow-up (T4).

health problems) and four patients refused to undergo radiological and clinical evaluations. The dropout rate thereby increased from 12.5% at the functional loading to 30% after 3 years of follow-up. In total, the final sample size of this 3-year follow-up study included 28 patients with 79 implants and this sample was used for data collection and statistical analysis: group A was comprised of 15 patients with 45 implants whereas group B was composed of 13 patients with 34 implants. Considering PBL mean values, standard deviation,

sampling ratio and the non-inferiority margin at 3-year follow-up, the post-hoc power was 59.79%.

Soft tissue augmentation was performed in 21 patients (75%) with 56 implants (71%): 26 implants in 10 patients of group A (58%) and 30 implants in 11 patients belonging to group B (88%).

All parameters evaluated between T0 and T3 were reported in the previous publication.[12] Surgical and healing complications rates in group A were 5.0% and 15.0%; while in group B, the rates were 15.8% and 21.1%, respectively. Mean values of peri-implant bone defects in group A were: IBD = 3.8 ± 0.7 mm and FBD = 20.5 ± 0.6 mm in group A; IBD = 4.0 ± 0.8 mm and FBD = 20.2 ± 0.7 mm in group B. Consequently, VBG was 4.2 ± 1.0 mm in group A and 4.1 ± 1.0 mm in group B. No statistically significant difference was observed between the two study groups regarding IBD, FBD or VBG parameters.

All implants that were analyzed after a 3-year follow-up were osseointegrated and clinically stable. During the entire period of follow-up, there was no prostheses failure, and none of the patients experienced prosthetic complications, with the exception of a retaining-screw loosening in one patient and three crowns chipping in other patients. During the follow-up visit two patients showed mucositis (7.1%) and one patient had a peri-implantitis (3.6%) around three different implants that were treated with non-surgical therapy. The mean values of PBL were compared at 3-year follow-up to the respective values reported at 1-year follow-up: in group B, four implants (three in one patient and one in another patient) and in group A, two implants (in one patient) showed a mean MBL > 1.9 mm/year. Resulting in implant survival rate at 100% in both group A and group B, while success rates were 95.6% in group A and 88.2% in group B, without statistically significant differences ($p = 0.394$).

3.2 | Overall measurements

According to radiographic evaluations performed in the entire population, the mean PBL was 0.12 ± 0.76 mm at the baseline (T2), 0.76 ± 0.77 mm at 1-year follow-up (T3) and 0.82 ± 0.68 mm at 3-year follow-up (T4). Statistically significant changes were observed from T3 to T2 and from T4 to T2, however, were not observed between 1- and 3-year follow-ups. The resulting mean MBL after 3 years of follow up was 0.70 ± 0.52 mm from the baseline. Median, CI, and *p* values of the above-mentioned variables were reported in Table 1.

Interproximal bone peaks (IBP) values were 0.10 ± 0.78 mm at the baseline (T2), 0.34 ± 0.82 mm at 1-year follow-up (T3) and 0.64 ± 0.84 mm at 3-year follow-up (T4). Regarding these measures, statistically significant changes were observed from T3 to T2, from T4 to T2 and from T4 to T3. The resulting mean IBL after 3 years of follow up was 0.54 ± 0.56 mm from the baseline. Median, CI, and *p* values of the above-mentioned variables were reported in Table 1.

The BoP rate changed from 16.8% at T2 to 18.2% at T4. The PPD values were 2.0 ± 0.5 mm at the baseline and 2.0 ± 0.5 mm after 3 years of follow up. While the results obtained at 1-year follow-up, BoP and PPD changes showed no statistically significant differences when comparing the baseline to T4.

The tKT varied from 2.6 ± 1.0 mm at the baseline to 4.5 ± 1.0 mm after 3 years, while the wKT was 2.0 ± 1.1 mm at T2 and 3.7 ± 0.9 mm at T4. According to these outcomes, statistically significant changes were observed at the 3-year follow up, both from the baseline and from the 1-year follow up.

The FD changed from 6.6 ± 2.2 mm at T2 to 7.4 ± 1.2 mm at T4. Although no statistically significant difference was observed between T2 and T3, the analysis showed a significance equal to $p = 0.02$ between the 3-year follow-up and the baseline (T2–T4).

The other variables showed no significant differences. The total values measured in the entire population were reported in Table 1.

Finally, correlation between PBL and IBP was confirmed after a 3-year follow-up, with $Rs = 0.7455$ ($p = 0.0001$). No other significant correlations resulted using the mean values at baseline and after 1- to 3-year follow-ups. (Figure 11).

A linear regression established that PBL and IBP variation demonstrated not to be statistically significant during the years of follow up (excluding the interval between T2 and T3) (Table 2).

Predictions were made to determine the mean PBL and IBP values after 5, 7, and 10 years of follow-up (Figure 12 and Table 2).

3.3 | Comparison between study groups

Regarding the non-inferiority analysis, the mean change in PBL from baseline to 3 years of follow-up in the study population demonstrated that group B treatment was not inferior, however, it was clinically like group A. The estimated treatment difference of PBL mean values was −0.17 (CI: −0.58 to 0.23). Unlike PBL, the IBP mean values with an estimated value of −0.47 (CI: −0.87 to −0.07) confirmed the statistical but not clinical superiority of group B to group A (Figure 13).

In group A, the mean values of PBL were − 0.01 ± 0.75 mm at the baseline and 0.72 ± 0.66 mm at T4 ($p = 0.0001$), resulting in a MBL of 0.73 ± 0.42 mm after 3 years of follow up. The values of IBP were − 0.02 ± 0.71 mm at T2 and 0.61 ± 0.82 mm at T4 ($p = 0.0001$), resulting in an IBL of 0.64 ± 0.63 mm after 3 years of follow up.

In group B, the mean values of PBL and IBP changed similarly to group A. The PBL varied from 0.22 ± 0.76 mm at the baseline to 0.92 ± 0.73 mm at T4 ($p = 0.0046$), resulting in a MBL of 0.71 ± 0.65 mm after 3 years of follow up. The values of IBP were 0.26 ± 0.86 mm at T2 and 0.66 ± 0.90 mm at T4, resulting in a mean IBL of 0.40 ± 0.45 mm after 3 years of follow up.

The values showed no statistically significant differences between the two study groups neither at baseline nor at 3-year follow-up. Neither were there any differences regarding the MBL after 3 years. In contrast, the mean values of IBL showed a statistically significant

TABLE 1 Mean values of alveolar and peri-implant parameters in the entire population at the baseline, after 1 year and after 3 years of follow-up

Variable	Baseline		Intra baseline vs. 1 year *p*-value	1 Year follow-up		Intra 1 year vs. 3 years *p*-value	3 Years follow-up		Intra baseline vs. 3 years *p*-value
	Mean ± SD (IQR)	Median (95% CI)		Mean ± SD (IQR)	Median (95% CI)		Mean ± SD (IQR)	Median (95% CI)	
PBL (mm)	0.12 ± 0.76 (1.29)	0.27 (−1.16; 0.40)	0.00001*	0.76 ± 0.77 (1.10)	0.69 (0.48; 1.05)	0.6295	0.82 ± 0.68 (0.72)	0.75 (0.55; 1.08)	0.0001**
IBP (mm)	0.10 ± 0.78 (1.01)	0.11 (−1.19; 0.39)	0.00001*	0.34 ± 0.82 (1.03)	0.19 (0.03; 0.65)	0.0088*	0.64 ± 0.84 (1.03)	0.49 (0.31; 0.96)	0.0001**
PPD (mm)	2.04 ± 0.46 (0.58)	2 (1.87; 2.21)	0.0276*	1.88 ± 0.49 (0.47)	1.81 (1.69; 2.06)	0.1955	2.02 ± 0.51 (0.50)	2 (1.82; 2.22)	0.9687
tKT (mm)	2.63 ± 1.03 (1.25)	2.58 (2.25; 3.02)	0.1439	2.12 ± 1.00 (1,67)	2 (1.74; 2.49)	0.0001**	4.51 ± 0.95 (1.13)	4.51 (4.14; 4.88)	0.0001**
wKT (mm)	2.06 ± 1.07 (1.63)	2.33 (1.66; 2.46)	0.0009*	2.61 ± 1.11 (1.50)	2.88 (2.20; 3.03)	0.0003**	3.67 ± 0.94 (1.67)	3.67 (3.30; 4.03)	0.0001**
FD (mm)	6.63 ± 2.21 (3.33)	6.83 (5.98; 7.87)	0.9401	6.83 ± 1.89 (2.50)	7.13 (6.10; 7.56)	0.0961	7.44 ± 1.24 (1.33)	7.33 (6.96; 7.92)	0.0201*
BoP (%)	16.76 ± 16.82 (33.33)	13.89 (10.48; 20.04)	0.0114*	9.30 ± 13.12 (16.67)	5.55 (4.40; 14.20)	0.1306	18.16 ± 20.94 (27.88)	12.5 (10.03; 26.28)	0.8173
mGI 0–1 (%)	49.58 ± 2.28 (0)	50 (48.73; 50.44)	0.5773	49.40 ± 2.47 (0)	50 (48.48; 50.32)	1.0000	49.40 ± 2.19 (0)	50 (48.56; 50.25)	1.0000
mGI 2–4 (%)	0.42 ± 2.28 (0)	0 (−0.44; 1.27)	0.5773	0.60 ± 2.47 (0)	0 (−0.32; 1.52)	1.0000	0.40 ± 1.46 (0)	0 (−0.17; 0.96)	1.0000
mPI 0–1 (%)	47.85 ± 3.91 (5.55)	50 (46.39; 49.31)	0.0760	49.38 ± 2.39 (0)	50 (48.47; 50.29)	0.0227*	46.55 ± 9.54 (4.17)	50 (42.85; 50.25)	0.9134
mPI 2–3 (%)	2.15 ± 3.91 (5.55)	0 (0.69; 3.61)	0.1053	0.62 ± 2.39 (0)	0 (−0.29; 1.53)	0.0093**	3.45 ± 9.54 (4.17)	0 (−0.25; 7.15)	0.9617

Note: Values are expressed as mean ± standard deviation (SD), interquartile range (IQR), median and confidence interval (CI). MBL and IBL are measured as average difference between follow-up and baseline (from PBL and IBP values, respectively).

Abbreviations: BoP, bleeding on probing; FD, fornix depth; IBP, interproximal bone peaks; mGI 0-1, modified gingival index (value 0–1); mGI 2-4, modified gingival index (value 2–4); mPI 0-1, modified plaque index (value 0–1); mPI 2-3, modified plaque index (value 2–3); PBL, peri-implant bone level; PPD, probing pocket depth; tKT, thickness of keratinized tissue; wKT, width of keratinized tissue.

*Statistical significance.

**Strong statistical significance.

difference between the two study groups after 3 years of follow up, favoring group B which confirmed the results of the non-inferiority analysis.

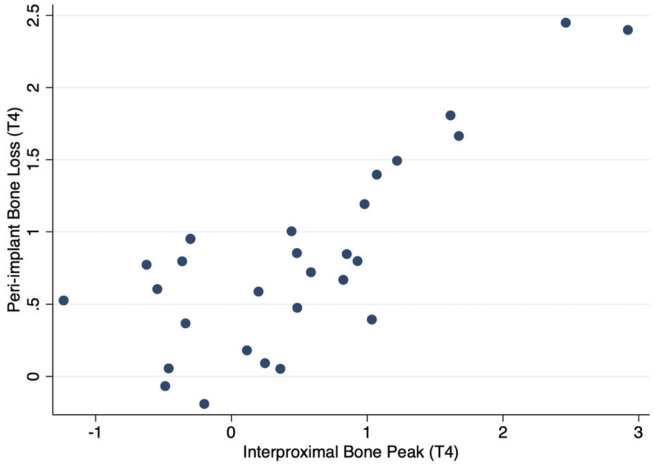

FIGURE 11 Scatter plots that show the strong positive linear correlation between peri-implant bone levels (PBL) and Interproximal Bone Peaks (IBP) after 3 years of follow-up. P-value = 0.0001. Spearman's rho = 0.7455.

Regarding peri-implant variables, BoP rate at baseline showed significant differences between the two study groups (9.7% for group A and 24.8% for group B), while no significant correlations were observed at 3-year follow-up.

The two study groups showed a significant increase of tKT after 3 years of follow up, both in respect to the baseline and at 1-year follow-up. The same significant differences were observed regarding wKT, comparing the values at T4 to baseline and to T3.

No other statistically significant differences were noted between group A and group B (Table 3).

A linear regression established that PBL and IBP variation (excluding the first year after functional loading) in both groups is not statistically significant (p value >0.05). (Table 2).

In each group, predictions were made to determine the mean PBL and IBP values after 5, 7, and 10 years of follow up (Figure 12 and Table 2).

4 | DISCUSSION

The present study is a 3-year follow-up report of a series aimed at comparing clinical and radiographic parameters surrounding implants placed simultaneously to VRA with Ti-reinforced non-resorbable

TABLE 2 Analysis of linear regression in the whole population and divided in group A and B

Linear regression: overall							
	PBL				**IBP**		
Time point	5 years	7 years	10 years	Time point	5 years	7 years	10 years
Predicted 95% CIs	0.26; 1.51	−0.06; 1.96	−0.54; 2.64	Predicted 95% CIs	0.20; 1.63	0.04; 2.34	−0.22; 3.42
F (1;54)		0.11		*F* (1;54)		1.51	
Adj. R^2		−0.0164		Adj. R^2		0.0091	
p-Value		0.7395		*p*-Value		0.2249	
Linear regression: by group							
	Group A PBL				**Group B PBL**		
Time point	5 years	7 years	10 years	Time point	5 years	7 years	10 years
Predicted 95% CIs	−0.10; 1.65	−0.58; 2.24	−1.32; 3.14	Predicted 95% CIs	0.04; 1.97	−0.47; 2.64	−1.25; 3.66
F (1;28)		0.04		F (1;24)		0.07	
Adj. R^2		−0.0342		Adj.R^2		−0.0386	
p-Value		0.8411		*p*-Value		0.7914	
	IBP				**IBP**		
Time point	5 years	7 years	10 years	Time point	5 years	7 years	10 years
Predicted 95% CIs	0.06; 1.94	−0.13; 2.91	−0.43; 4.37	Predicted 95% CIs	−0.36; 1.98	−0.92; 2.85	−1.80; 4.16
F (1;28)		1.78		*F* (1;24)		0.17	
Adj. R^2		0.0263		Adj. R^2		−0.0343	
p-Value		0.1925		*p*-Value		0.6829	

Note: Peri-implant bone levels and interproximal bone peaks values after 5, 7, and 10 years of follow-up are predicted. Values are expressed using Confidence Intervals (CIs), *F*-value (*F*), Adjusted R^2 (Adj. R^2), *p*-value.

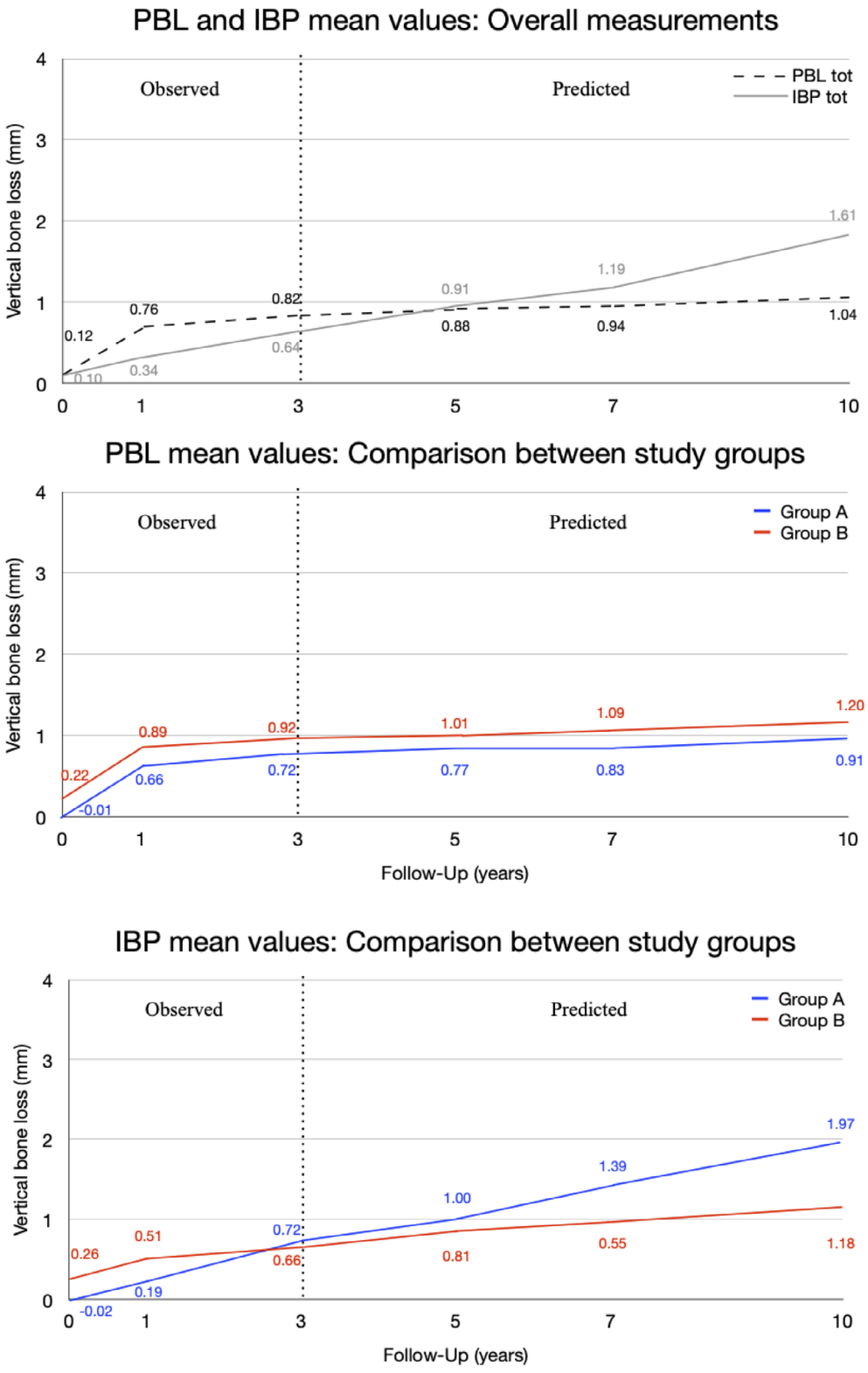

FIGURE 12 Analysis of linear regression in the entire population and comparing study groups. Peri-implant bone levels (PBL) and Interproximal Bone Peaks (IBP) mean values were observed at the baseline, after 1 year and after 3 years of follow-up, while mean values after 5,7 and 10 years of follow-up were predicted.

membranes or titanium meshes covered with resorbable membranes in the posterior mandibles.

The values measured in the present study showed a MBL around implants of 0.73 mm for the PTFE group and 0.71 for the titanium mesh group, after a 3-year follow up. The efficacy of both techniques for VRA in the posterior mandible was confirmed as no statistically significant differences were noted in MBL between group A and group B.

Similar values of MBL were reported by Merli and colleagues[5,10] comparing GBR with resorbable collagen membranes supported by

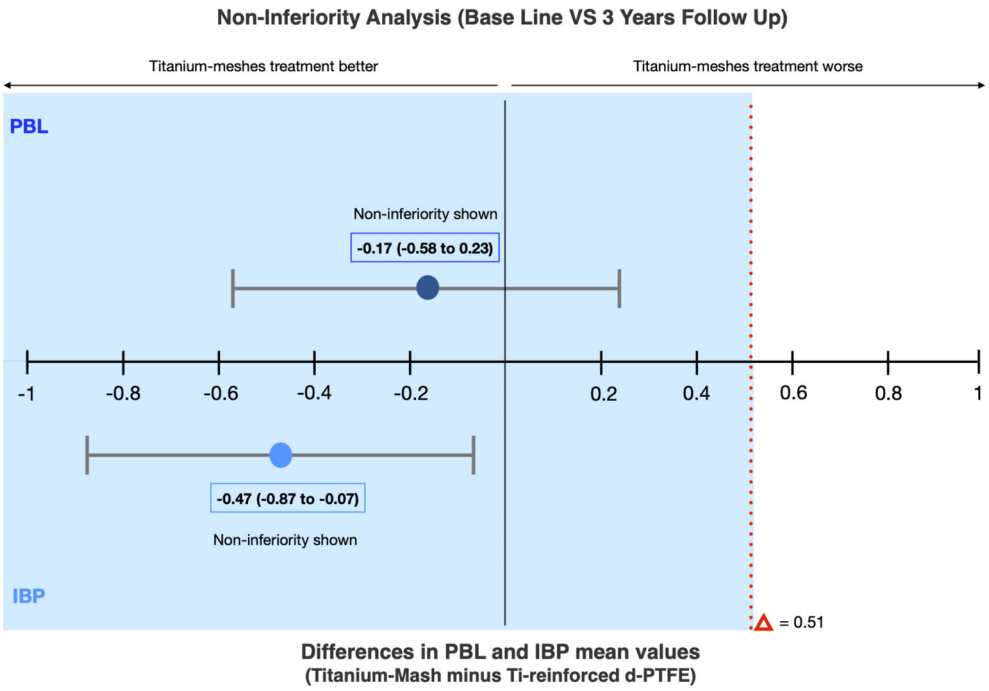

FIGURE 13 Error bars indicated mean values and one-sided 95% confidence intervals of the difference in peri-implant bone level (PBL) and Interproximal Bone Peaks (IBP) mean values between group A and group B (B - A). The red broken line delineating the difference in the score shows the non-inferiority margin ($\Delta = 0.51$ mm). The tinted area indicates the zone of inferiority. Since the PBL mean value (-0.17 mm) lie to the left of the non-inferiority margin, then the non-inferiority of group B in relation to group A was demonstrated (clinically similar). The mean value of IBP (-0.47 mm) shows that group B is significantly different (statistical superiority) and not inferior to group A (clinically similar).

osteosynthesis titanium plates and non-resorbable Ti-reinforced PTFE membranes (0.66 mm and 0.53, respectively), after a 6 year follow-up. To the best of our knowledge, no other randomized clinical studies in the literature have evaluated MBL outcome, analyzing different techniques for VRA.

Comparing the values of MBL reported in different scientific studies is difficult due to the presence of many confounding factors, namely the implant surface, grafted biomaterial, implant-abutment connections.[26] According to Caricasulo and colleagues, the use of internal interface in particular conical connections, positively influence crestal bone levels around implants in the short-medium term.[27]

MBL around implants placed in reconstructed alveolar ridges has been evaluated by many authors in non-randomized clinical trials. The mean values of MBL reported in the literature after GBR with PTFE membranes ranged from 1.0 mm in the first year[28] to 1.7 mm after 7 years.[29] Values of mean peri-implant bone loss after GBR with titanium meshes ranged from 0.6 mm after 1 year[30] to 1.6 mm after 3–8 years.[31] After inlay bone grafting the MBL was also measured around placed implants, reporting a mean value of 1.7 mm after 5 years[32]; after autogenous onlay bone graft technique, the reported mean MBL showed similar mean values.[33,34]

According to a recent systematic review, the values of MBL after loading around implants placed in augmented bone varied from 0.0 to −1.5 mm and most of the included studies reported no statistically significant differences when compared to short implants.[35] The values of MBL observed in the present study are exactly in the middle of the above-mentioned range of values.

The measurement of IBP led to the clinical evaluation of the amount of bone loss caused by the remodeling of the augmented ridge, relating this outcome to the PBL. The mean values of IBL were 0.64 and 0.40 mm for group A and group B, respectively. It is interesting to emphasize that the difference between these measures nearly coincide with the difference between PBL mean values at the baseline. A statistically significant difference in IBL was observed between the two study groups. According to these findings, the use of a titanium mesh covered with a cross-linked collagen membrane led to more favorable results when compared to a PTFE membrane. Thus, it is important to note that non-resorbable membranes achieve a thinner pseudo-periosteum layer above the newly formed bone, when compared to Ti-mesh covered by collagen membranes.[36]

Overall, PTFE membranes have been shown to produce a higher bone augmentation, lower pseudo-periosteum formation and higher bone resorption, while titanium meshes showed a reduction in bone obtained which is associated to thicker pseudo-periosteum and less bone reduction over time.

In a recent clinical trial, the role of resorbable membranes covering customized titanium meshes was assessed which evaluated soft tissue healing and bone regeneration using only titanium meshes or using titanium meshes with cross-linked collagen membranes. Even though no statistical significant differences were observed, all the measured variables showed superior results in the group treated with titanium meshes covered with collagen membranes.[37] On the other hand, a novel titanium reinforced PTFE mesh with macropores has been recently introduced to combine the advantages of titanium meshes and PTFE membranes in bone regeneration. In fact, the perforation of the membrane led to direct contact between periosteum and bone grafts which improved graft vascularization and enhanced bone maturation.[38,39]

The mean value of VBG reported in this study match the average gain of 4.2 mm of bone after VRA procedures that were reported in

TABLE 3 Analysis of alveolar and peri-implant variables in group A and in group B at the baseline, after 1 year and after 3 years of follow-up

Variable		Baseline	Average Difference baseline vs. 1 year	1 year follow-up	Average difference 1 year vs. 3 years	3 year follow-up	Average difference baseline vs. 3 years
		Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)
PBL (mm)	A	−0.01 ± 0.75 (−0.41; 0.39)	−0.01 ± 0.75 (−0.41; 0.39)	0.66 ± 0.80 (0.23; 1.08)	0.12 ± 0.11 (−0.12; 0.33)	0.78 ± 0.66 (0.41; 1.14)	0.80 ± 0.39 (0.59; 1.02)
	B	0.27 ± 0.76 (−0.17; 0.71)	0.27 ± 0.76 (−0.17; 0.71)	0.89 ± 0.75 (0.45; 1.31)	−0.02 ± 0.49 (−0.28; 0.32)	0.87 ± 0.72 (0.43; 1.30)	0.63 ± 0.65 (0.24; 1.02)
	Inter group *p*-value	0.2124	0.2124	0.3390	0.5963	0.7510	0.6177
IBP (mm)	A	−0.04 ± 0.71 (−0.42; 0.33)	−0.04 ± 0.71 (−0.42; 0.33)	0.19 ± 0.75 (−0.21; 0.59)	0.42 ± 0.42 (0.26; 0.72)	0.61 ± 0.82 (0.16; 1.07)	0.64 ± 0.63 (0.29; 0.98)
	B	0.26 ± 0.86 (−0.24;0.76)	0.26 ± 0.86 (−0.24;0.76)	0.51 ± 0.89 (−0.01; 1.02)	0.15 ± 0.66 (−0.68; 0.13)	0.66 ± 0.90 (0.12; 1.21)	0.40 ± 0.45 (0.13; 0.67)
	Inter group p-value	0.2529	0.2529	0.2987	0.003*	0.3450	0.0092*
PPD (mm)	A	2.13 ± 0.44 (1.89; 2.36)	2.13 ± 0.44 (1.89; 2.36)	1.85 ± 0.36 (1.66; 2.04)	0.09 ± 0.58 (−0.23; 0.42)	1.94 ± 0.45 (1.69; 2.19)	−0.19 ± 0.59 (−0.52; 0.14)
	B	1.94 ± 0.48 (1.67; 2.22)	1.94 ± 0.48 (1.67; 2.22)	1.91 ± 0.61 (1.55; 2.26)	0.20 ± 0.79 (−0.21; 0.74)	2.11 ± 0.57 (1.76; 2.45)	0.21 ± 0.82 (−0.29; 0.70)
	Inter group *p*-value	0.1394	0.1394	0.4919	0.5340	0.2296	0.0700
tKT (mm)	A	2.33 ± 0.83 (1.89; 2.77)	2.33 ± 0.83 (1.89; 2.77)	1.90 ± 0.83 (1.46; 2.35)	2.41 ± 1.64 (1.51; 3.33)	4.31 ± 1.04 (3.73; 4.89)	1.96 ± 1.06 (1.37; 2.55)
	B	2.98 ± 1.15 (2.32; 3.64)	2.98 ± 1.15 (2.32; 3.64)	2.36 ± 1.15 (1.70; 3.03)	2.37 ± 1.88 (1.21; 3.48)	4.73 ± 0.82 (4.24; 5.23)	1.64 ± 1.07 (0.99; 2.29)
	Inter group *p*-value	0.0713	0.0713	0.2759	0.9186	0.2382	0.6081
wKT (mm)	A	2.16 ± 1.12 (1.56; 2.76)	2.16 ± 1.12 (1.56; 2.76)	2.51 ± 1.08 (1.94; 3.09)	0.98 ± 1.08 (0.41; 1.61)	3.49 ± 0.84 (3.03; 3.96)	1.39 ± 1.25 (0.70; 2.08)
	B	1.94 ± 1.02 (1.35; 2.54)	1.94 ± 1.02 (1.35; 2.54)	2.73 ± 1.18 (2.04; 3.41)	1.13 ± 1.48 (0.15; 1.94)	3.86 ± 1.03 (3.24; 4.49)	1.85 ± 1.20 (1.13; 2.57)
	Inter group *p*-value	0.6602	0.6602	0.5590	0.9448	0.3194	0.3435
FD (mm)	A	6.52 ± 2.18 (5.35; 7.68)	0.13 ± 2.29 (−1.1; 1.35)	6.64 ± 2.05 (5.55; 7.73)	0.62 ± 1.69 (−0.22; 1.65)	7.26 ± 1.44 (6.46; 8.06)	0.57 ± 1.93 (−0.49; 1.64)
	B	7.39 ± 2.88 (5.72; 9.05)	−0.07 ± 2.62 (−1.58; 1.44)	7.32 ± 1.70 (6.33; 8.30)	0.32 ± 1.79 (−0.59; 1.57)	7.64 ± 0.97 (7.06; 8.23)	1.07 ± 1.89 (−0.07; 2.21)
	Inter group *p*-value	0.4170	0.7550	0.3817	0.6777	0.3185	0.8471
BoP (%)	A	9.72 ± 12.09 (3.28; 16.16)	−2.17 ± 6.79 (−5.79; 1.45)	7.55 ± 10.47 (1.98; 13.13)	9.86 ± 23.68 (−3.76; 22.46)	17.41 ± 21.98 (5.23; 29.58)	7.04 ± 25.13 (−6.88; 20.95)
	B	24.80 ± 18.21 (14.29; 35.31)	−13.5 ± 17.02 (−23.32; −3.67)	11.30 ± 15.80 (2.18; 20.43)	7.72 ± 21.26 (−6.00; 19.69)	19.02 ± 20.53 (6.61; 31.43)	−5.55 ± 25.78 (−21.14; 10.03)
	Inter group *p*-value	0.0183*	0.0360*	0.7921	0.8349	0.7674	0.1436
mGI 0–1 (%)	A	49.22 ± 3.12 (47.55; 50.88)	0.78 ± 3.13 (−0.88; 2.45)	50 ± 0 (50; 50)	0 ± 0 (0; 0)	50 ± 0 (50; 50)	0.83 ± 3.23 (−0.95; 2.62)
	B	50 ± 0 (49.99; 50)	−1.29 ± 3.55 (−3.34; 0.76)	48.71 ± 3.13 (46.66; 50.76)	0.01 ± 4.41 (−2.56; 2.77)	48.72 ± 3.13 (46.83; 50.61)	−1.28 ± 3.13 (−3.17; 0.61)
	Inter group *p*-value	0.9617	0.0791	0.1241	0.5200	0.4127	0.2381
mGI 2–4 (%)	A	0.78 ± 3.13 (−0.88; 2.45)	−0.78 ± 3.12 (−2.45; 0.88)	0 ± 0 (0; 0)	0 ± 0 (0; 0)	0 ± 0 (0; 0)	−0.83 ± 3.23 (−2.62; 0.95)
	B	0 ± 0 (0; 0)	1.29 ± 3.54 (−0.76; 3.34)	0.85 ± 2.09 (− 0.76; 3.34)	0 ± 3.91 (−2.89; 1.83)	0.85 ± 2.09 (−0.41; 2.12)	0.85 ± 2.09 (−0.41; 2.12)
	Inter group *p*-value	0.3496	0.0791	0.1241	0.5202	0.4127	0.2381

(Continues)

TABLE 3 (Continued)

Variable		Baseline	Average Difference baseline vs. 1 year	1 year follow-up	Average difference 1 year vs. 3 years	3 year follow-up	Average difference baseline vs. 3 years
		Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)
mPI 0–1 (%)	A	47.83 ± 4.09 (45.65; 50.01)	2 ± 4.24 (−2.26; 4.26)	44.58 ± 12.69 (49.66; 50.20)	0.28 ± 2.85 (−2.85; 0.77)	44.86 ± 12.77 (37.55; 51.61)	−3.10 ± 11.73 (−9.60; 3.40)
	B	47.87 ± 3.86 (45.64; 50.09)	1.12 ± 5.81 (−2.39; 4.63)	48.82 ± 2.52 (46.72; 50.93)	−0.32 ± 12.80 (−12.31; 1.85)	48.50 ± 2.63 (47.30; 50.35)	1.12 ± 4.39 (−1.52; 3.77)
	Inter group *p*-value	0.9407	0.9804	0.4239	0.3171	0.1305	0.1889
mPI 2–3 (%)	A	2.17 ± 4.09 (−0.01; 4.35)	−2 ± 4.24 (−4.26; 0.26)	5.41 ± 12.69 (−0.20; 0.54)	−0.27 ± 12.80 (−1.86; 12.32)	5.14 ± 12.77 (−1.61; 12.44)	3.10 ± 11.73 (−3.40; 9.60)
	B	2.13 ± 3.86 (−0.09; 4.36)	−1.12 ± 5.81 (−4.63; 2.39)	1.18 ± 2.53 (−0.93; 3.28)	0.32 ± 2.85 (−0.77; 2.85)	1.50 ± 2.63 (−0.35; 2.70)	−1.12 ± 4.39 (−3.77; 1.53)
	Inter group *p*-value	0.9149	0.8406	0.4067	0.2591	0.1991	0.2482

Note: Values are expressed as mean ± standard deviation (SD) and confidence interval (CI). MBL and IBL are measured as average difference between follow-up and baseline (from PBL and IBP values, respectively).
Abbreviations: BoP, bleeding on probing; FD, fornix depth; IBP, interproximal bone peaks; mGI 0–1, modified gingival index (value 0–1); mGI 2–4, modified gingival index (value 2–4); mPI 0–1, modified plaque index (value 0–1); mPI 2–3, modified plaque index (value 2–3); PBL, peri-implant bone level; PPD, probing pocket depth; tKT, thickness of keratinized tissue; wKT, width of keratinized tissue.
*Statistical significance.

the last consensus report of the 15th European Workshop on Periodontology on Bone Regeneration.[40] This correlation may be associated to the maintenance of the vertically augmented bone reported in this study. On the other hand, these results confirm the previously cited consensus report.

As previously reported, few studies reported peri-implant soft tissue changes after bone reconstruction procedures. The results observed in the present study are in accordance with those reported in the literature, confirming that both surgical approaches are suitable to obtain a soft tissue stability after VRA. Mean values of BOP reported around implants placed in vertically augmented bone ranged from 8% to 18.2%.[41,42]

The mean values reported in the present study ensured the stability of soft tissues around implants placed after VRA. The management of soft tissues played an important role in peri-implant health. The presence of keratinized mucosa (KM) around implants was recently evaluated as a crucial factor: KM ≥2 mm had a protective effect on peri-implant tissues, while KM <2 mm increased MBL, plaque accumulation, tissue inflammation and brushing discomfort.[43–45]

The association between BoP and soft tissues has been confirmed in the present study. In fact, BoP rates showed a significant difference at baseline ($p = 0.0183$), but do not at 3-year follow-up. This may be related to the need of soft tissue augmentation, performed in 75% of patients (58% of implants in group A, 88% of implants in group B), in order to increase the amount of keratinized mucosa.[12] The influence of soft tissue augmentation on PBLs at 3-year follow-up was also evaluated with a descriptive analysis. Higher mean MBL values (0.41 vs. 0.90 mm) and IBL values (0.37 vs. 0.59 mm) were found after soft tissue augmentation, when compared to sites without soft tissue management. This may suggest a role of soft tissue biotype (thickness and width) on the maintenance of crestal bone levels after alveolar ridge augmentation.

The peri-implant tissues health was well maintained for 3 years after loading, thanks to a rigid professional protocol of oral hygiene. Even though an adequate peri-implant ridge remodeling occurred, a small rate of biological complications (i.e., mucositis and peri-implantitis) was observed. According to a recent systematic review, mean implant-based and subject-based peri-implantitis prevalence were 9.25% and 19.83%, while the same mean values regarding peri-implant mucositis were 29.48% and 46.83% respectively.[46]

The most notable finding regarding soft tissue is the increase of KT, both in thickness and in width, observed during the 3-year follow-up.

In a recent review, Tavelli and colleagues, in 2021, reported that the bilaminar approach involving connective tissue graft obtained the highest amount of mucosal thickness gain, whereas apically positioned flap approach in combination with free gingival graft was the most effective technique for increasing the width of the keratinized mucosa. While the first showed beneficial effects on marginal bone level stability, the latter was associated with a significant reduction in probing depth, soft tissue dehiscence, and plaque index.

In the present study, the main reason of the KT increase observed during the follow-up is the soft tissue management based on connective tissue graft with bilaminar approach which was performed in the majority of the cases before prosthetic restoration.[47–49] Other

reasons could be (i) the reduction of alveolar bone width in favor to soft tissue and (ii) the increase of alveolar bone height and related re-establishment of the genetically determined muco-gingival junction.[50,51] Further investigation is required in randomized clinical trials to understand the relation between alveolar ridge and soft tissues.

The major strengths of the present study are the randomized and blinded design of the protocol, that all treated sites were in the posterior mandible and were managed using the same surgical procedures (with exception of the medical devices PTFE membrane or Titanium mesh) and the analysis of both hard and soft tissues around implants at 3-year follow-up.

The main limitations are the limited number of patients, due to the drops-out and the consequent post-hoc power of analysis, the simultaneous approach (GBR and immediate implants). It is worth mentioning that the primary outcome of the original study protocol, which has impacted the statistical power of the trial, was to analyze healing complications. The present follow-up study aimed instead to evaluate the stability of peri-implant hard and soft tissues: the parameters described may in fact be more relevant for a longer follow-up. Nonetheless, due to the change in the outcome and some dropouts, the negative results of the study (absence of statistically significant findings) should be read with caution. Finally, in the present study authors compared two conventional devices. In this regard, further studies are needed to evaluate similar parameters using the most recently introduced devices, such as titanium-reinforced PTFE meshes and customized CAD-CAM titanium meshes.[30,37,38]

5 | CONCLUSIONS

The medium-term results of this RCT showed the stability of PBLs and interproximal bone levels up to 3 years after VRA in the posterior mandible, using both Ti-reinforced PTFE membrane and titanium mesh with collagen membrane. The study confirmed the feasibility and the importance of a correct maintenance protocol (control of accumulation of plaque and peri-implant inflammation) after GBR to preserve peri-implant health. The outcome of 5- and 10-year follow-ups is required in order to report long-term results.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the study and have agreed to the final submitted version of the manuscript. Alessandro Cucchi conceived the idea and the design of the study and contributed to data interpretation and drafting of the paper. Sofia Bettini has been involved in data analysis, data interpretation and drafting of the paper. Paolo Ghensi contributed with a critical revision of the work for important intellectual content. Antonino Fiorino has been involved in data acquisition, analysis and interpretation. Giuseppe Corinaldesi has given final approval of the version to be published.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

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