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Bone Substitute Material in the Surgical Therapy of Peri-Implantitis—3-Year Outcomes of a Randomized Controlled Trial

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ABSTRACT

Objective: To evaluate the potential mid-term benefit of the use of a bone substitute material in the reconstructive surgical treatment of peri-implantitis.

Methods: A total of 120 subjects (127 implants) affected by peri-implantitis were followed over 3 years in a multicenter randomized clinical trial. Participants had been randomized to either control (access flap surgery) or test group (access flap surgery and bone substitute material). Clinical, radiographic, and patient-reported outcomes were assessed. The primary outcome was a composite measure including probing pocket depth ≤ 5 mm, absence of bleeding and suppuration on probing, soft tissue recession ≤ 1 mm, and implant neither reoperated nor lost. In an additional outcome (disease resolution), we allowed for one bleeding site and did not consider recession.

Results: While 14 implants (11%) were lost and a second surgical intervention had been performed at 3 implants (2.4%), pronounced improvements of clinical parameters were noted at remaining implants in both treatment groups at the 3-year follow-up. This was illustrated by a 3.2–3.5 mm reduction in probing pocket depth and a marginal bone level gain of 1.1–1.3 mm. The primary composite outcome, however, was only achieved at 14% of implants. The second composite outcome defining disease resolution was accomplished at 39% of implants. Patient-reported outcomes were generally favorable.

Conclusion: At 3 years, the use of a bone substitute material in the surgical therapy of peri-implantitis did not result in a clear benefit over access flap surgery alone.

Trial Registration: ClinicalTrials.gov identifier: NCT0307706

1 | Introduction

The guideline for the prevention and management of peri-implant diseases published by the European Federation of Periodontology (EFP; Herrera et al. 2023) suggested a clinical endpoint of therapy focusing on soft tissue inflammation. The suggestion was based on the fact that shallow probing pocket depth (PPD) and the presence of only minimal bleeding on probing were shown to be strong indicators of future stability of marginal bone levels (MBLs; Carcuac et al. 2020; Carcuac et al. 2017; Jepsen et al. 1996; Karlsson et al. 2019). In other words, if clinical signs of inflammation are resolved, the risk for continuing bone loss is low.

Current evidence shows that, in peri-implantitis, clinical endpoints are not consistently achieved by nonsurgical therapy, alone (Blanco et al. 2022; Hentenaar et al. 2021; Polymeri et al. 2022). Hence, in established cases, surgical intervention is typically required. Surgical exposure is meant to facilitate decontamination procedures of implant surfaces. It also offers the possibility to manage the intra-bony defect associated with the disease, typically encompassing the whole circumference of the implant (Monje et al. 2019).

The EFP guideline recognizes reconstructive techniques as an adjunctive measure to the surgical intervention with the aim to regenerate tissues lost during disease progression (Herrera et al. 2023). While available studies show positive treatment outcomes (Derks et al. 2022; Jepsen et al. 2016; Renvert et al. 2021; Renvert, Roos-Jansåker, and Persson 2018), benefits of reconstructive modalities over access flap alone in terms of established clinical endpoints remain to be demonstrated (Donos et al. 2023). Furthermore, evaluations of recurrence in long follow-up studies have rarely been reported for patient groups provided with reconstructive therapy (Renvert, Giovannoli, and Rinke 2024; Roccuzzo et al. 2020; Schwarz et al. 2017).

The aim of this study was to evaluate the potential benefit of the adjunctive use of a bone substitute material in the surgical therapy of peri-implantitis. Here, we report 3-year outcomes of a randomized controlled trial.

2 | Materials and Methods

Study design and 1-year outcomes of this multicenter, randomized controlled trial were previously reported (Derks et al. 2022; Ichioka et al. 2023). This manuscript describes outcomes over a 3-year follow-up. The study protocol was approved by authorities responsible for ethical evaluations (Gothenburg: 1192–16; Bilbao: 06/2017; Málaga: 27/09/2017; Perugia: 3173/18; Trento: 21390; Munich: 17028). Data were collected across six European centers. Reporting followed the CONSORT checklist (Data S1; Schulz et al. 2010). Research was conducted according to the principles outlined in the Declaration of Helsinki on human medical experimentation and we obtained written patient consent.

2.1 | Study Sample and Interventions

Study participants presented with severe peri-implantitis (PPD ≥ 7 mm; presence of bleeding/suppuration on probing (BOP/SOP) and radiographically documented bone loss ≥ 3 mm). Only circumferential peri-implant osseous defects with a depth of ≥ 3 mm were considered. No minimum number of bony walls was required. In total, 138 subjects (147 implants) were included. Surgical therapy consisting of elevation of soft tissue flaps, removal of inflamed tissues, and implant surface decontamination was performed. The cleaning protocol was based on the use of titanium curettes and a rotating titanium brush (Nano NiTi Brush, HANS KOREA CO. Ltd) under irrigation with saline. Following surface decontamination, subjects were randomly allocated to either open-flap debridement alone or combined with application of a bone substitute material (Bio-Oss Collagen, Geistlich, Lucerne, Switzerland). Mucosal flaps were resutured as part of the transmucosal healing protocol. Systemic antibiotics (Amoxicillin 750 mg, twice daily) were prescribed for a period of 10 days. The surgical interventions were performed between July 2017 and February 2021.

During the first year following surgery, individuals were recalled on a 3-month basis to reinforce self-performed plaque control. From year 1 and onward, the recall interval was individualized.

2.2 | Evaluations and Outcomes

The clinical evaluations were performed at baseline, 6 months, 1, 2, and 3 years. Registrations included PPD, BOP/SOP, and plaque at four aspects per implant. The width of keratinized mucosa (KM) and the soft tissue level (REC) were measured on the buccal aspect. Assessments were made with a metal periodontal probe. Intra-surgical assessments of the defect geometry included measurements of the defect width and depth relative to the bony crest.

Intraoral radiographs were obtained at baseline, 1 and 3 years. Two examiners (Y.I. and L.A.) measured the distance between a fixed reference landmark and the MBL on the mesial and distal aspects of each target implant (ImageJ 2.0.0-rc-69/1.52n; National Institutes of Health, Maryland, USA) using a known distances (thread pitch or implant length/diameter) for calibration. Measurements were repeated (30 implant sites) for evaluations of intra- and inter-rater agreement. Mean measurement error was expressed by the absolute difference between the two assessments, showing values of 0.33 ± 0.37 and 0.34 ± 0.33 mm for intra- and inter-rater comparisons, respectively. The respective intraclass correlation coefficients were 0.98 (95% CI 0.96, 0.99) and 0.99 (95% CI 0.98, 0.99). Questionnaires were used to evaluate patient-reported outcomes (PROs) at baseline, 2 weeks, 1 and 3 years.

The primary outcome was a composite of the following criteria: PPD ≤ 5 mm, absence of BOP/SOP, buccal REC ≤ 1 mm, implant neither reoperated nor lost. Secondary outcomes included PPD, BOP/SOP, buccal KM, buccal REC, MBL, and changes thereof as well as PROs. A second composite outcome termed "disease resolution" was defined by PPD ≤ 5 mm, BOP at ≤ 1 site, absence of SOP, implant neither reoperated nor lost (Herrera et al. 2023).

We also evaluated disease recurrence, repeated surgical intervention, and implant loss. Recurrence, defined as either PPD

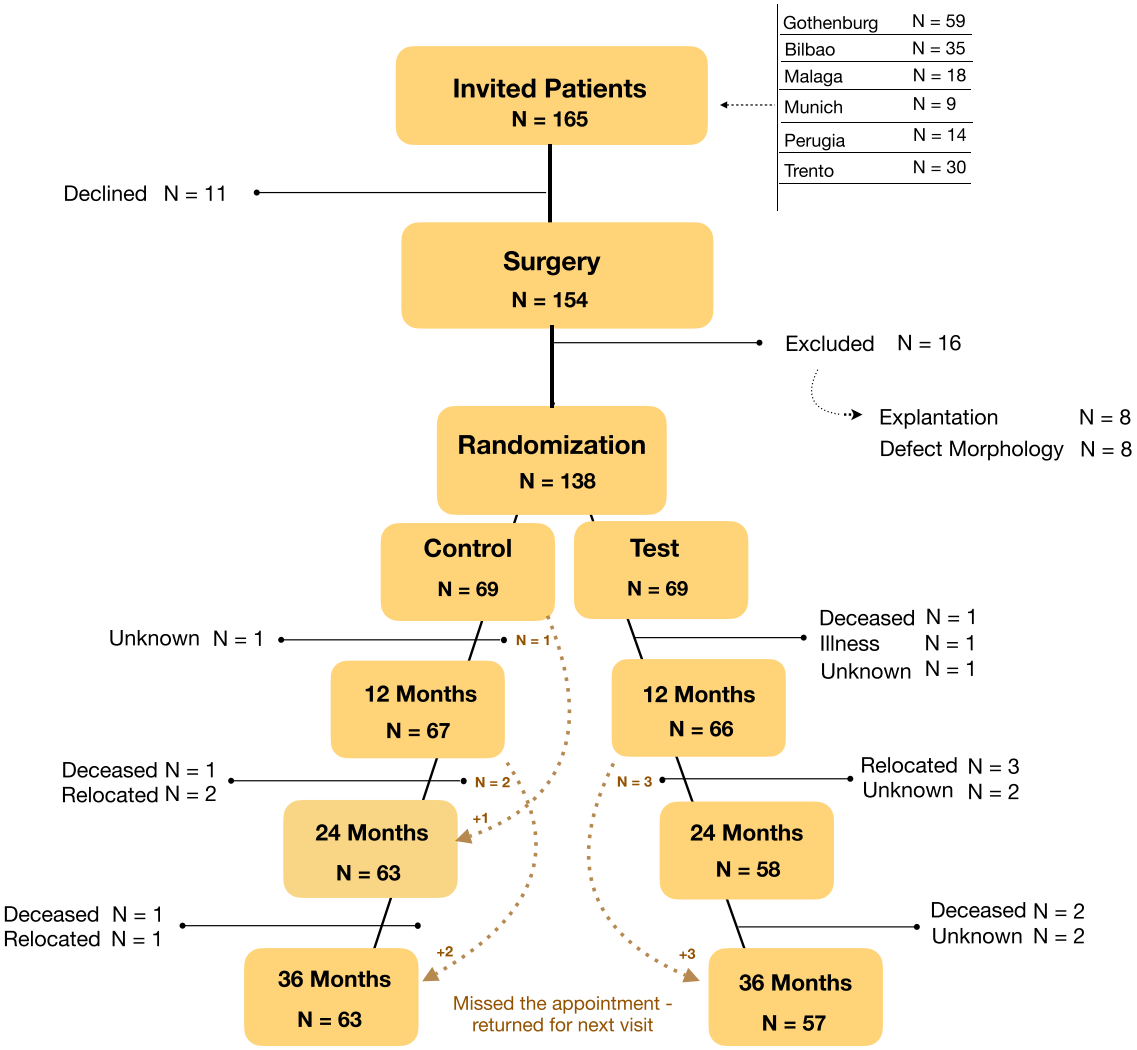

FIGURE 1 | Flowchart illustrating the number of participants throughout the study period.

> 5 mm, implant loss, or re-surgery by year 3, was assessed among implants displaying favorable outcomes (PPD ≤ 5 mm) at year 1.

Assessors were not blinded to initial group allocation.

2.3 | Data Analysis

We applied a per-protocol approach using the implant as the unit of analysis. Simple linear and logistic regression models with robust variance estimates were utilized to evaluate differences between groups.

Predictors of disease recurrence were explored using logistic regression, adjusting for treatment allocation. The following potential parameters were considered: gender, age, smoking status, implant brand, type of prosthetic retention, and status at year 1 (number of BOP+/SOP+ aspects, MBL, buccal KM and buccal REC). When independent variables were correlated, one was selected based on coefficients, *p*-values and Akaike's information criterion. The Hosmer–Lemeshow goodness-of-fit test and area under the ROC curve were used as measures of model fit.

PROs were compared by Wilcoxon rank-sum testing at patient level.

All statistical analyses were performed using Stata 18 (StataCorp, College Station, Texas, USA). Results were presented as coefficients and odds ratios (ORs) with 95% confidence intervals (95% CI).

3 | Results

Of the initially allocated 138 participants, 18 were lost to follow-up (Figure 1). Out of the remaining 120 patients (Table A1; 127 implants), 12 experienced implant loss (14 implants) and a second surgical intervention was performed at 3 implants in 3 patients. Figure 2 illustrates implant status over time for each study arm. Differences in terms of implant loss (control: 11 of 67; test: 3 of 60; $p = 0.062$) and re-surgery (control: 2 of 56; test: 1 of 57; $p = 0.558$) were not statistically significant between groups.

Clinical outcomes are presented in Tables 1 and 2, Figure A1, and exemplified in Figure 3. Changes in PPD, MBL, buccal REC, and buccal KM were similar in both groups, while reduction in

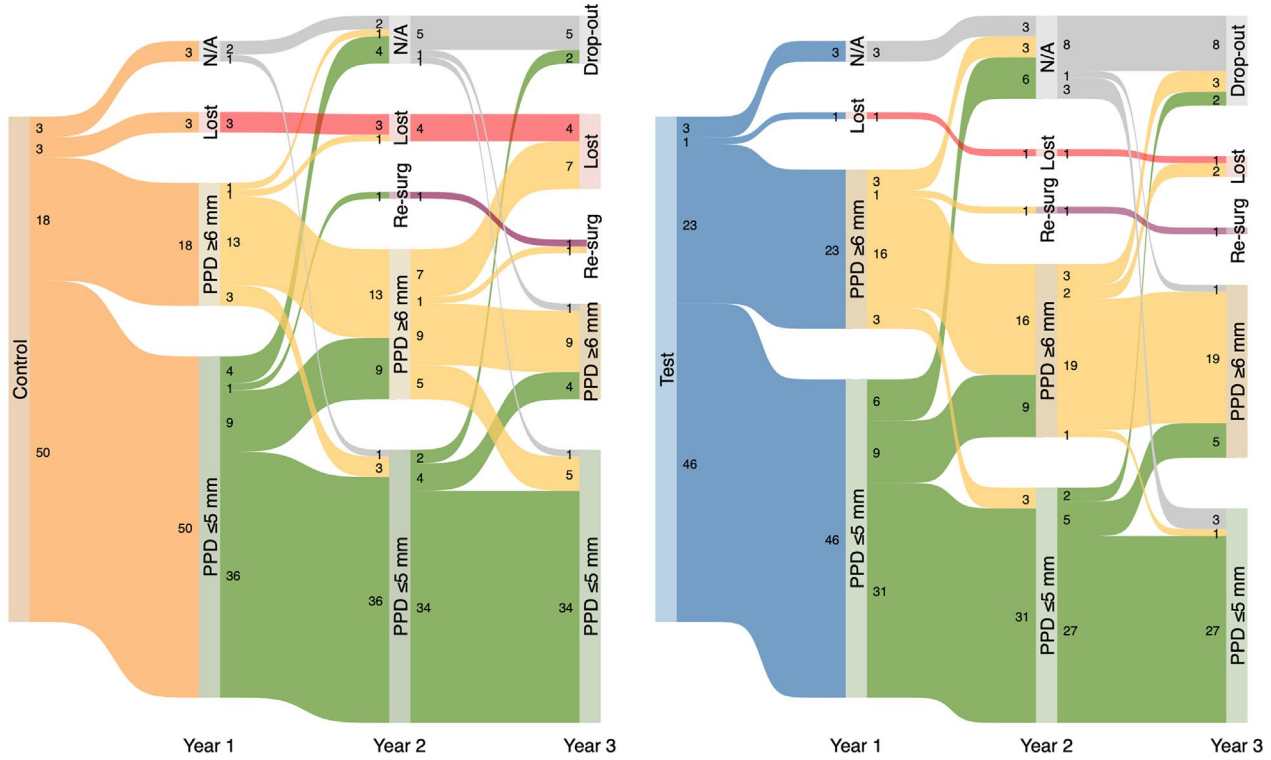

FIGURE 2 | Alluvial plots illustrating implant status by study arm over the 3-year follow-up period.

BOP scores was more pronounced in controls ($p = 0.013$). The composite outcome (primary outcome) was met in 14.2% of implants (control: 13 of 67; test: 5 of 60; $p = 0.086$). Disease resolution was achieved at 38.6% of implants (control: 31 of 67; test: 18 of 60; $p = 0.081$).

Among the 82 implants with shallow PPD (≤5 mm) at 1 year, recurrence was detected at 18 implants (control: 7 of 46; test: 11 of 41; $p = 0.222$). According to the adjusted model, treatment allocation (control: OR 0.14; 95% CI 0.02, 0.79; $p = 0.026$), smoking (OR 10.51; 95% CI 1.71, 64.40; $p = 0.011$), bleeding on probing at year 1 (OR 1.68; 95% CI 1.06, 2.66; $p = 0.028$), and MBL at year 1 (OR 1.56; 95% CI 1.07, 2.29; $p = 0.022$) had a significant effect on the risk of recurrence (Tables A2a & A2b, Figure A2).

We observed only minor differences between groups in terms of PROs, with slightly higher scores for "pain on chewing" in the control group ($p = 0.035$). Patient-reported satisfaction at 3 years was high (median ≥90 in both groups; Table A3).

4 | Discussion

Three-year outcomes of a multicenter, randomized controlled trial on surgical treatment of peri-implantitis were analyzed. While 14 implants were lost and a second surgical intervention had been performed at three implants, pronounced improvements of clinical parameters were noted at remaining implants in both treatment groups. This was illustrated by a 3.2–3.5 mm reduction in PPD and an MBL gain of 1.1–1.3 mm. The primary composite outcome, consisting of shallow probing, absence of BOP/SOP, and limited soft tissue recession, however, was only achieved at 14% of implants. The second composite outcome defined as disease resolution (shallow probing, bleeding on probing at ≤1 site, no suppuration) was accomplished at 39% of implants. PROs were generally favorable. The addition of a bone substitute material did not result in any clear benefit over open-flap debridement alone.

For implants in situ at the 3-year evaluation, the favorable changes in PPD, bleeding on probing and MBLs were in line with the initial response to surgical therapy of peri-implantitis observed at 12 months (Derks et al. 2022). In our earlier report, we highlighted more favorable esthetic outcomes in the test group, expressed by significantly less soft tissue recession. This benefit, however, was not observed in the mid-term (Figure A2). Overall, the magnitude of improvements was in line with mid-term data recently reported by Renvert, Giovannoli, and Rinke (2024). The authors evaluated 3-year outcomes of reconstructive surgical therapy of peri-implantitis in 50 patients. While changes in MBLs and soft tissue recession were similar, a somewhat more pronounced reduction in PPD was observed in the present study. This difference may be explained by variations in inclusion criteria and baseline conditions.

In the interpretation of the present clinical and radiographic outcomes, it needs to be emphasized that implants in situ at the final evaluation represent a positive selection. In other words, failing implants will eventually be exposed to either renewed surgery or removed. The focus of mid- and long-term evaluations should therefore lie on robust and clinically relevant

TABLE 1 | Continuous outcomes at baseline and 3 years by group (per protocol).

	Control						Test					
	Baseline			3 years (or latest for lost/re-surgery)			Baseline			3 years (or latest for lost/re-surgery)		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
Implants in situ during entire follow-up												
PPD (mm)	54	8.4	(1.5)	54	4.9	(2.0)	56	8.7	(1.5)	56	5.5	(2.5)
BOP+ (number of aspects)	54	3.6	(0.9)	54	1.3	(1.5)	56	3.5	(0.9)	56	2.1	(1.5)
SOP+ (number of aspects)	54	1.2	(1.5)	54	0.2	(0.8)	56	1.4	(1.7)	56	0.3	(0.8)
Plaque+ (number of aspects)	54	0.6	(1.2)	54	0.7	(1.2)	56	0.8	(1.5)	55	0.9	(1.4)
Soft tissue REC (mm)	54	0.6	(1.4)	54	1.4	(1.8)	56	0.3	(1.3)	56	1.2	(1.4)
Keratinized mucosa (mm)	54	2.1	(1.7)	53	1.7	(1.6)	56	2.0	(1.7)	55	1.9	(1.6)
Marginal bone level (mm)	54	6.1	(2.0)	54	4.8	(2.5)	56	5.7	(1.8)	56	4.6	(2.6)
Implants subjected to re-surgery												
PPD (mm)	2	11.0	(1.4)	1	7.0	(.)	1	9.0	(.)	1	7.0	(.)
Marginal bone level (mm)	2	6.7	(0.1)	2	6.9	(0.4)	1	6.4	(.)	1	6.1	(.)
Implants lost during follow-up												
PPD (mm)	11	8.7	(1.6)	8	10.2	(2.0)	3	9.3	(2.1)	3	9.3	(1.5)
Marginal bone level (mm)	11	7.2	(2.1)	10	9.1	(2.5)	3	7.9	(2.1)	3	8.3	(2.1)

Note: In situ: implant not lost, no re-surgery. Plaque and KM data missing at 3 years for one implant in the test group. KM data missing at 3 years for one implant in the control group. PPD and MBL are presented for implants that were reoperated and/or lost if data were available from within 6 months of the event; complete data available for eight of 14 lost implants and for two of three reoperated implants.

outcomes. In all, 11% of treated implants were removed over the 3 years. Renvert, Giovannoli, and Rinke (2024) noted a considerably lower value of 3%, whereas Roccuzzo et al. (2021) with a longer follow-up of 5 years reported a loss rate of 20%. In the study by Renvert, Giovannoli, and Rinke (2024), however, events occurring during the first year of follow-up were disregarded in the calculations. In the present study, the incidence of implant loss was unbalanced, favoring the test group. Although not statistically significant, this discrepancy needs to be considered when evaluating primary and secondary composite outcomes. Disease resolution was achieved at 46% and 30% of implants in control and test groups, respectively. This is largely in line with 5-year data presented by Heitz-Mayfield et al. (2018) (42%) and with 3-year data reported by Isler et al. (2022) (27%–35%).

While the percentages of implants fulfilling the criteria for the two composite outcomes were higher in the control than in the test group, implant loss was more frequent among controls. The imbalance in implant loss is not understood, but probably directly linked to the more favorable composite outcomes. As our study protocol left decisions on renewed surgery and implant removal to the clinician without specific thresholds, it is possible that, given the lack of blinding, group allocation affected treatment decisions during follow-up. While we recognize this as a limitation of our study, we consider this bias as unlikely, given similar clinical and radiographic conditions at time of implant removal across groups (Table 1).

We investigated disease recurrence at implant sites demonstrating initially favorable outcomes (18 of 87 implants; 21%). One of the relevant predictors was tobacco smoking, which is in line with otherwise reported data on the effect of smoking on treatment outcomes of peri-implantitis (Ichioka et al. 2023; Koldsland, Wohlfahrt, and Aass 2018; Waal et al. 2016). In this context, it is noteworthy that smoking patients were somewhat overrepresented in the control group (33% vs. 21%) at baseline. This observation represents another limitation of our dataset. Other authors have addressed the risk for confounding by stratifying the randomization by smoking status

TABLE 2 | Composite outcomes and changes in continuous measures by group (per protocol).

	Control		Test		
	Mean/frequency	**SD/%**	**Mean/frequency**	**SD/%**	***p***
Implant failure (implant lost or reoperated)					
No	54	(80.6%)	56	(93.3%)	
Yes	13	(19.4%)	4	(6.7%)	0.052
Composite outcome (PPD ≤5 mm, no BOP/SOP, REC ≤1 mm, implant neither reoperated nor lost)					
No	54	(80.6%)	55	(91.7%)	
Yes	13	(19.4%)	5	(8.3%)	0.086
Disease resolution (PPD ≤5 mm and BOP ≤1 site, implant neither reoperated nor lost)					
No	36	(53.7%)	42	(70.0%)	
Yes	31	(46.3%)	18	(30.0%)	0.081
Changes for implants in situ at year 3 (between baseline and year 3)					
PPD (mm)[a]	−3.5	(2.2)	−3.2	(2.8)	0.493
BOP+ (number of sites)[a]	−2.3	(1.8)	−1.4	(1.7)	0.013
Soft tissue REC (mm)	0.8	(1.3)	0.8	(1.0)	0.886
Keratinized mucosa (mm)	−0.3	(1.2)	−0.0	(1.4)	0.245
Marginal bone level (mm)	1.3	(1.4)	1.1	(1.8)	0.576
Categorization according to clinical outcomes for implants in situ at year 3[b]					
PPD ≤5 mm	40	(74.1%)	31	(55.4%)	0.051
BOP ≤1 site per implant	35	(64.8%)	21	(37.5%)	0.007
REC ≤1 mm	36	(66.7%)	39	(69.6%)	0.736
Disease recurrence (PPD ≥6 mm, lost or re-surgery at year 3) for implants with PPD ≤5 mm at year 1					
No	39	(84.8%)	30	(73.2%)	0.222
Yes	7	(15.2%)	11	(26.8%)	

Note: p-values from unadjusted logistic/linear regression analyses.
[a]Negative values indicate an improvement.
[b]$N = 110$ implants (56 test, 54 control).

FIGURE 3 | Clinical photographs and radiographs depicting two cases showing favorable outcomes (examples 1 and 2) and one case (example 3) displaying pronounced disease progression.

(Carcuac et al. 2016). The estimated lower risk for disease recurrence among controls was only evident when simultaneously considering all relevant factors, in particular "smoking."

Strengths of the present study include the relevant sample size, a low drop-out rate and a high external validity, given the multicenter and multinational set-up. While the sample size was

deemed appropriate to address the aim of the study, it may not have been sufficiently powered to fully explore secondary outcomes. This is reflected in large confidence intervals in the analysis on risk factors for disease recurrence. The individualized maintenance protocol subsequent to the 1-year examination implies a heterogeneity, which is inherent to clinical trials with mid- and long-term follow-ups but also to clinical reality. The fact that we did not record adherence to recommended maintenance intervals, however, represents a limitation. The importance of regular supportive care in preventing peri-implantitis has been demonstrated (Leone et al. 2024; Monje, Wang, and Nart 2017; Roccuzzo et al. 2021).

A final consideration is the adjunctive use of systemic antibiotics as part of the surgical protocol in both study arms. This indiscriminate prescription of antibiotics stands in conflict with the latest guideline on the management of peri-implant diseases published by the EFP (Herrera et al. 2023; Teughels et al. 2023).

In conclusion, neither of the two treatment modalities demonstrated a clear superiority. Surgical therapy of peri-implantitis resulted in relevant improvements at 3 years. Composite outcomes, including disease resolution, were, however, not consistently achieved and disease recurrence was not infrequent. Tobacco smoking increased the risk for disease recurrence.

5 | Clinical Relevance

5.1 | Scientific Rationale

Evidence on reconstructive therapy of peri-implantitis is limited. Specifically, potential mid- and long-term benefits of reconstructive modalities have rarely been explored.

5.2 | Principal Findings

While surgical therapy resulted in pronounced improvements at 3 years, complete disease resolution was achieved at less than half of the treated implants. The reconstructive technique did not result in clear benefits over the access flap surgery alone.

5.3 | Practical Implications

Despite the application of a structured treatment protocol including surgical therapy of peri-implantitis, mixed outcomes were noted in the mid-term.

Author Contributions

Lamija Alibegovic: writing – original draft, formal analysis, data curation, validation, visualization, software, project administration. **Anna Trullenque-Eriksson:** writing – original draft, formal analysis, methodology. **Alberto Ortiz-Vigón:** data curation, writing – review and editing. **Adrián Guerrero:** writing – review and editing, data curation. **Mauro Donati:** writing – review and editing, data curation. **Eriberto Bressan:** writing – review and editing, data curation. **Karolina Karlsson:** writing – review and editing, data curation. **Carlotta Dionigi:** writing – original draft, methodology, project administration, visualization. **Erik Regidor:** writing – review and editing, data curation. **Yuki Ichioka:** writing – original draft, methodology, validation, data curation. **Cristiano Tomasi:** writing – review and editing, data curation, supervision. **Paolo Ghensi:** writing – review and editing, data curation. **Dennis Schaller:** writing – review and editing, data curation. **Ingemar Abrahamsson:** writing – review and editing, data curation. **Tord Berglundh:** conceptualization, investigation, funding acquisition, writing – original draft, methodology, project administration, resources, supervision. **Jan Derks:** writing – original draft, funding acquisition, conceptualization, investigation, methodology, project administration, supervision, data curation, resources, formal analysis.

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The authors have nothing to report.

Conflicts of Interest

Drs. Alibegovic, Trullenque-Eriksson, Ichioka, Dionigi, and Regidor report no conflict of interest. Dr. Ortiz-Vigón reports speakers honoraria from Straumann Group and Arrow Development research and financial support from ThinkingPerio research. Dr. Guerrero reports honoraria from Inibsa and Dentsply Sirona Implants. Dr. Donati reports speakers honoraria from Dentsply Sirona Implants and research grants from Dentsply Sirona Implants. Dr. Bressan reports speakers honoraria from Dentsply Sirona Implants and Sweden & Martina. Dr. Ghensi reports speakers honoraria from Geistlich Pharma AG and BioHorizons Camlog. Dr. Schaller reports speakers honoraria from Zimmer Biomet. Dr. Tomasi reports speakers honoraria from Dentsply Sirona Implants, Straumann Group, Geistlich Pharma AG, and Sweden & Martina. Dr. Karlsson reports speakers honoraria from Dentsply Sirona Implants. Dr. Abrahamsson reports research grants from Dentsply Sirona Implants. Dr. Berglundh reports honoraria from Dentsply Sirona Implants, speakers honoraria from Osteology Foundation and research grants from Dentsply Sirona Implants, Osteology Foundation and Geistlich Pharma AG. Dr. Derks reports speakers honoraria from Osteology Foundation, Dentsply Sirona Implants, Straumann Group and research grants from Eklund Foundation and Electro Medical Systems.

Data Availability Statement

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

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Supporting Information

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

Appendix A

TABLE A1 | Patient characteristics at baseline (not considering drop-outs).

	Control					Test				
	n	**%/Mean**	**SD**	**Min**	**Max**	***n***	**%/Mean**	**SD**	**Min**	**Max**
Number of implants included per patient	63	1.1	(0.2)	1	2	57	1.1	(0.2)	1	2
Gender										
Female	42	66.7%				36	63.2%			
Male	21	33.3%				21	36.8%			
Smoker										
Yes	21	33.3%				12	21.2%			
History of periodontitis										
Yes	42	66.7%				40	70.2%			
Diabetes										
Yes	3	4.8%				2	3.5%			
Age at surgery	63	60.1	(10.4)	35	79	57	61.7	(10.6)	34	78
Implant years	62	10.6	(5.8)	1	30	56	10.1	(5.1)	2	22
Surgery duration (minutes)	63	49.0	(16.7)	10	145	57	53.1	(13.7)	25	105
Supraconstruction										
Removed	45	71.4%				39	68.4%			
Access during surgery										
Full access	62	98.4%				56	98.2%			
Surgical assessment										
Fully satisfied	63	100.0%				57	100.0%			

TABLE A2a | Results of the logistic regression (all parameters) evaluating the outcome "disease recurrence."

Logistic regression					Number of obs = 87
					Wald chi^2 (11) = 28.40
					Prob > chi^2 = 0.0028
Log pseudolikelihood = −28.681465					Pseudo R^2 = 0.3534
(Std. err. adjusted for 84 clusters in id)					
Recurrence	**Odds ratio**	**Robust std. err.**	**z**	***P>z***	**[95% conf. interval]**
Group					
Test	1 (base)				
Control	0.1029593	0.1004646	−2.33	0.020	0.0152086, 0.6970158
Gender					
Female	1 (base)				
Male	2.236927	1.52045	1.18	0.236	0.59031828, 0.476517
Age at surgery	1.013305	0.0331036	0.40	0.686	0.95045641, 0.080309
Smoker					
No	1 (base)				
Yes	12.68025	12.16315	2.65	0.008	1.93481183, 0.10309
BOP_Y1	1.810197	0.5011556	2.14	0.0321	0.0521313, 0.114456
MBL3	1.604947	0.3912888	1.94	0.052	0.99525922, 0.588124
PL3	0.9903603	0.3291534	−0.03	0.977	0.51628581, 0.899749
KM3	1.246159	0.3853585	0.71	0.477	0.67975172, 0.284528
REC3	1.1197	0.3579708	0.35	0.724	0.59837082, 0.095235
Defect_Conf					
Open at buccal and lingual aspect	1 (base)				
Open at either buccal or lingual aspect	1.272106	1.205132	0.25	0.799	0.1986716, 8.145368
Contained	3.024687	2.910772	1.15	0.250	0.4587081, 19.94456
_cons	0.0017019	0.0049541	−2.19	0.028	5.67e-06, 0.5112856

Note: _cons estimates baseline odds; end of do-file.

TABLE A2b | Results of the logistic regression (selected parameters) evaluating the outcome "disease recurrence."

Logistic regression					Number of obs = 87
					Wald chi^2 (4) = 17.42
					Prob > chi^2 = 0.0016
Log pseudolikelihood = −29.985779					Pseudo R^2 = 0.3239
(Std. err. adjusted for 84 clusters in id)					
Recurrence	**Odds ratio**	**Robust std. err.**	**z**	***P>z***	**[95% conf. interval]**
Group					
Test	1 (base)				
Control	0.1389089	0.1230306	−2.33	0.026	0.0244809, 0.788194
Smoker					
No	1 (base)				
Yes	10.50875	9.720232	2.54	0.011	1.714819, 64.39963
BOP_Y1	1.678216	0.3959431	2.19	0.028	1.056874, 2.664849
MBL3	1.562092	0.304671	2.29	0.022	1.06583, 2.289419
_cons	0.0165172	0.0169013	−4.01	0.000	0.002223, 0.1227256

Note: _cons estimates baseline odds; Number of observations = 87; Area under ROC curve = 0.8752; Goodness-of-fit test after logistic model; Variable: recurrence; Number of observations = 87; Number of groups = 10; Hosmer–Lemeshow $chi^2(8)$ = 8.62; Prob > chi^2 = 0.3758.

TABLE A3 | Patient-reported outcomes at baseline and 3 years (baseline: not considering drop-outs; 3 years: only patients with target implant(s) in situ). Scores based on visual analog scales (100 mm).

	Control			**Test**			
	n	**Median**	**IQR**	***n***	**Median**	**IQR**	***p***
Baseline							
Pain	63	6.0	[27.0]	57	0.0	[13.0]	
Bad smell/taste	63	3.0	[20.0]	57	0.0	[13.0]	
Pain on brushing	63	5.0	[33.0]	57	0.0	[24.0]	
Pain on chewing	63	0.0	[12.0]	57	0.0	[0.0]	
Satisfied with esthetics	62	90.0	[30.0]	57	95.0	[35.0]	
Year 3							
Pain	49	0.0	[4.0]	53	0.0	[0.0]	0.466
Bad smell/taste	49	0.0	[0.0]	53	0.0	[0.0]	0.331
Pain on brushing	49	0.0	[5.0]	53	0.0	[0.0]	0.377
Pain on chewing	49	0.0	[1.0]	53	0.0	[0.0]	0.035
Satisfied with esthetics	47	90.0	[25.0]	49	100.0	[20.0]	0.075
Satisfaction with therapy	49	92.0	[20.0]	53	100.0	[20.0]	0.156

Note: *p*-value from Wilcoxon rank sum test.

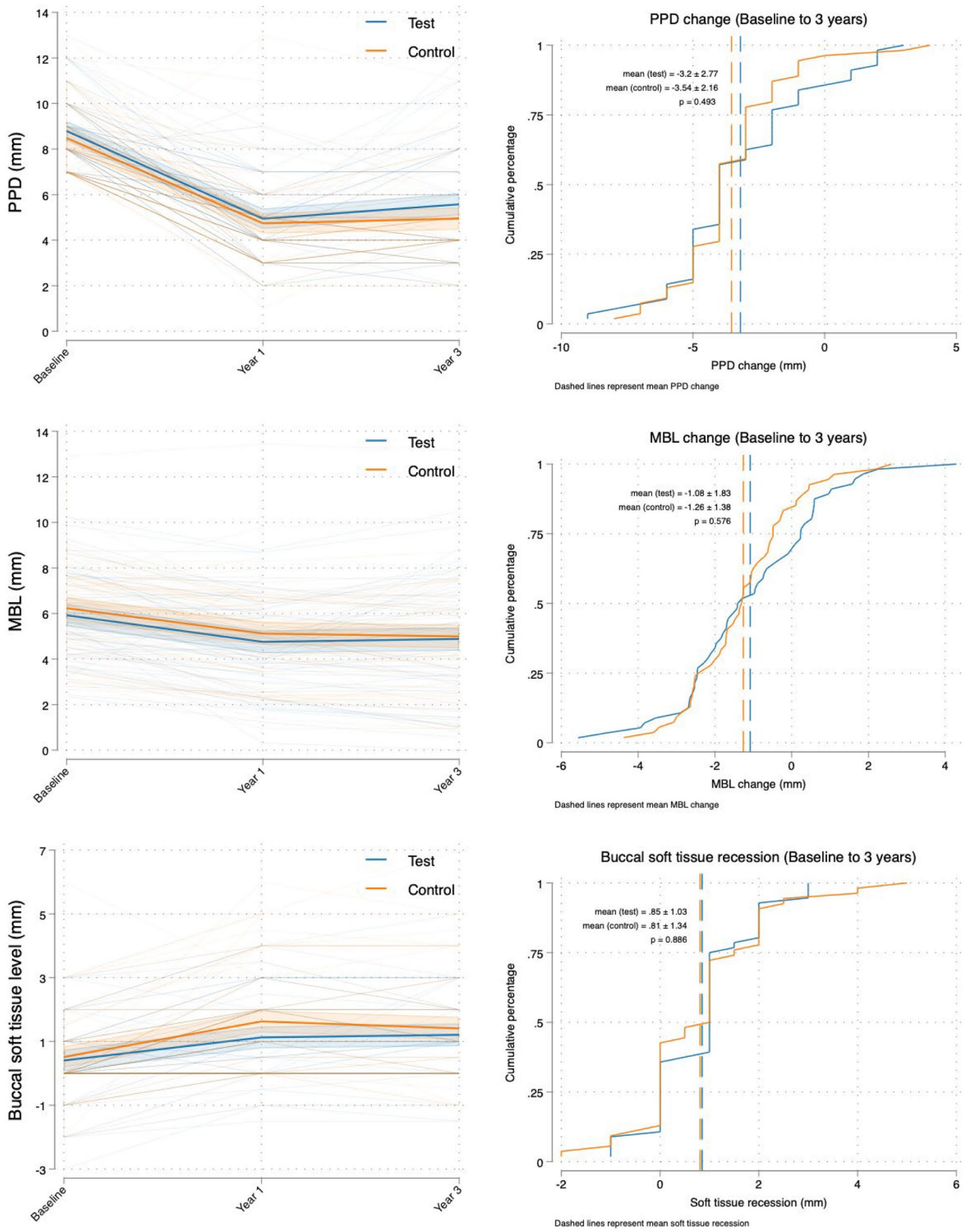

FIGURE A1 | Spaghetti plots and cumulative distribution curves illustrating alterations of probing pocket depth, marginal bone levels, and buccal soft tissue levels. The shaded lines represent single implants up to the latest observation. Group estimates and 95% CIs were generated by an unadjusted mixed-effects model using implant and time point as levels.

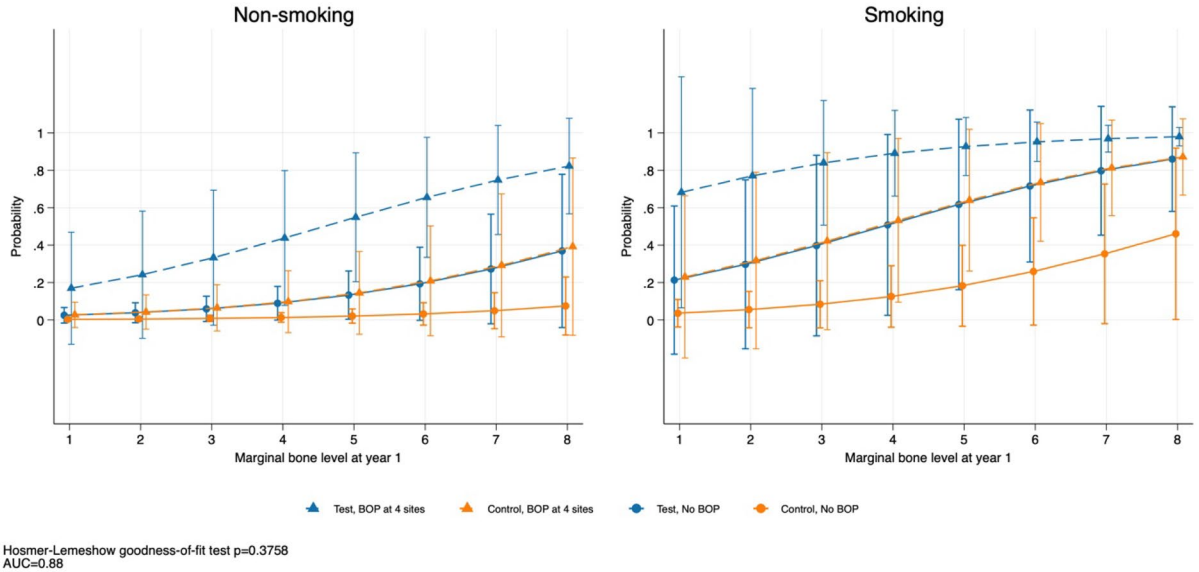

FIGURE A2 | Probability of recurrence at implant sites with a favorable outcome (PPD ≤ 5 mm) at year 1. Recurrence was defined as: PPD ≥ 6 mm, lost or re-surgery at/by year 3.